Review Article

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Prevention of ventilator-associated pneumonia in the intensive care unit: A review of the clinically relevant recent advancements

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Ventilator-associated pneumonia (VAP) is one of the most commonly encountered hospital-acquired infections in intensive care units and is associated with significant morbidity and high costs of care. The pathophysiology, epidemiology, treatment and prevention of VAP have been extensively studied for decades, but a clear prevention strategy has not yet emerged. In this article we will review recent literature pertaining to evidence-based VAP-prevention strategies that have resulted in clinically relevant outcomes. A multidisciplinary strategy for prevention of VAP is recommended. Those interventions that have been shown to have a clinical impact include the following: *(i)* Non-invasive positive pressure ventilation for able patients, especially in immunocompromised patients, with acute exacerbation of chronic obstructive pulmonary disease or pulmonary oedema, *(ii)* Sedation and weaning protocols for those patients who do require mechanical ventilation, *(iii)* Mechanical ventilation protocols including head of bed elevation above 30 degrees and oral care, and *(iv)* Removal of subglottic secretions. Other interventions, such as selective digestive tract decontamination, selective oropharyngeal decontamination and antimicrobial-coated endotracheal tubes, have been tested in different studies. However, the evidence for the efficacy of these measures to reduce VAP rates is not strong enough to recommend their use in clinical practice. In numerous studies, the implementation of VAP prevention bundles to clinical practice was associated with a significant reduction in VAP rates. Future research that considers clinical outcomes as primary endpoints will hopefully result in more detailed prevention strategies.

Key words Intensive care unit - mechanical ventilation - morbidity - non-invasive positive pressure ventilation - prevention - ventilator-associated pneumonia

Introduction

Ventilator-associated pneumonia (VAP) is one of the most commonly encountered hospital-acquired infections seen in the critical care setting and can be linked to several adverse clinical outcomes. Defined by the United States Centers for Disease Control and Prevention as pneumonia occurring 48 h after the initiation of mechanical ventilation, VAP is associated with increased rates of multidrug-resistant infections,

increased antibiotic use, prolonged mechanical ventilation time, increased ICU length of stay, and increased hospital length of stay[1]. Taken together, these factors increase the overall cost of care for patients with VAP, a cost that is increasingly not covered by insurers with the advent of pay-for-performance initiatives.

The association of VAP and increased mortality is somewhat more controversial[2,3]. It is unclear to date whether more patients die with VAP or because of VAP. However, despite this controversy, it is increasingly clear to patients, providers and health care systems the significant benefit that exists in the prevention of VAP.

This paper reviews the interventions currently available that have a clinical impact with regards to a reduction in the incidence of VAP. Interventions to be described include reducing the time patients spend mechanically ventilated, technical features of the endotracheal tube (ETT) and other mechanical considerations, and infection-control measures such as oral care and selective digestive decontamination. In order to fully understand these VAP-prevention strategies, the patient population at risk for development of VAP and the pathophysiology of VAP are also discussed.

How VAP happens

Patients at risk: Any patient who is mechanically ventilated is at risk for VAP. The rate of contracting VAP has been described as 3 per cent per day during the first week of mechanical ventilation, 2 per cent per day during week 2 and 1 per cent per day in the ensuing weeks[4]. The overall incidence of VAP ranges widely, from 5 to 67 per cent depending on the diagnostic criteria used[5].

Multiple additional risk factors have been shown to increase the rates of VAP. These are easily divided into non-modifiable and modifiable categories. Non-modifiable risk factors include male gender, increased age (over 60 yr), history of chronic obstructive pulmonary disease, presence of a tracheostomy or cranial trauma, recent neurologic surgery, acute respiratory distress syndrome, multiorgan system failure, and coma. Potentially modifiable risk factors include supine positioning, gastric overdistension, colonization of ventilator circuits, low pressure in the ETT cuff and repeated patient transfers[6,7].

Pathophysiology of VAP: In healthy individuals multiple mechanisms work together to fight off the development of pneumonia; unfortunately the presence of an ETT as well as the typical clinical circumstances of ICU patients (*i.e*. sedation, supine positioning, colonization of the oropharynx with pathogenic microorganisms) interfere with these native defense mechanisms and predispose intubated patients to the development of VAP. A clear understanding of the pathophysiology is important to understand the targets of VAP-prevention strategies.

As with any pneumonia, VAP occurs when the bacteria are introduced into the normally sterile lower respiratory tract and overwhelm the host's typical defense mechanisms against infection. Two mechanisms have been described for the entry of disease-causing organisms into the lower respiratory tract: most significant is microaspiration of pathogenic organisms from the upper respiratory tract/ gastrointestinal tract around the ETT, and the second is biofilm production on the ETT itself.

The upper respiratory tract of the majority of mechanically-ventilated patient is colonized with potentially pathogenic microorganisms. This was first established in a study in 1969 that reported the presence of enteric Gram-negative bacteria in the oropharynx of 75 per cent of critically ill patients[8]. A proposed explanation is bacterial overgrowth of the upper gastrointestinal tract and retrograde movement. Aspiration of secretions containing these pathogens provides a means for infection of the sterile bronchial tree. Another study published in 2007 confirmed the presence of similar pathogenic microorganisms in the lower respiratory tract of intubated patients by comparing DNA samples from bacteria on the tongue and obtained from bronchoalveolar lavage (BAL)[9].

The second potential source of introduction of bacteria into the lower respiratory tract can be attributed to the ETT itself. Biofilms, a network of secretions and microorganisms that develop along the ETT cuff and inside the lumen of the ETT, and are easily transferred to the lower respiratory tract and subsequently may cause infection.

VAP prevention: Reducing the time at risk

As discussed above, any intubated patient is at risk for development of VAP and the longer the duration of mechanical ventilation, the higher the risk. Thus, prevention of VAP must begin with avoiding or limiting time of mechanical ventilation whenever possible. Several strategies have been described to achieve this goal: non-invasive positive pressure ventilation (NPPV), sedation holidays, weaning trials, avoiding re-intubation, and early tracheostomy have all been

studied as methods to decrease time of mechanical ventilation and therefore, decrease the risk of VAP.

Non-invasive positive pressure ventilation: The use of NPPV has been shown to significantly lower the risk of VAP and has also demonstrated a mortality benefit in randomized studies conducted using patients with a variety of illnesses[10]. A meta-analysis including 12 studies of over 800 patients, confirmed these findings[11]. Additionally, prior studies have shown that NPPV is particularly useful in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) and patients with pulmonary oedema[12,13]. Therefore, it is recommended that NPPV be used when possible to prevent endotracheal intubation.

Daily weaning trials and sedation holidays: When the decision is made to intubate a patient, a strategy to liberate the patient from mechanical ventilation must also be considered. Daily weaning trials and sedation holidays have been repeatedly described and validated as strategies that limit the time of mechanical ventilation[14,15]. As the risk of VAP is related to the duration of mechanical ventilation[7], limiting this duration makes physiologic sense though no randomized trials have shown a benefit with regards to reduction in VAP rates.

Re-intubation: Re-intubation is associated with a higher risk of VAP due to higher rates of aspiration[16]. Adequate ICU staffing should be maintained to minimize unplanned extubations necessitating re-intubation[17], and planned extubations should be carefully considered. As clinicians postulate weaning, they must be mindful of and balance the risks associated with re-intubation and the cumulative time of mechanical ventilation.

Early tracheostomy: It was previously thought that early tracheostomy might lead to better outcomes[18]. However, a recently published meta-analysis of studies comparing early tracheostomy (performed within 7 days of intubation) and either prolonged endotracheal intubation or prolonged endotracheal intubation followed by tracheostomy found that the timing of tracheostomy was not associated with a significant reduction in short-term mortality, long-term mortality, the incidence of VAP, duration of mechanical ventilation, duration of sedation, duration of ICU or hospital stay, or other complications[19].

VAP prevention: Targeting endotracheal tube colonization and microaspiration

The presence of the endotracheal tube contributes to VAP via two mechanisms: first through micro-aspiration of secretions that contain pathogenic microorganisms, and secondly through formation of a biofilm. Prevention strategies directed towards interrupting these mechanisms, including removal of subglottic secretions, head of bed elevation, and use of antimicrobial-coated endotracheal tubes, have had varied success.

Subglottic suctioning endotracheal tubes: It has been postulated that intermittently or continuously removing the secretions that pool above the ETT cuff may reduce the risk for aspiration and subsequent development of VAP. ETTs have therefore, been designed to accomplish this task through application of negative pressure to a separate port that opens above the ETT cuff[20]. Outcomes of the initial trials evaluating these tubes showed mixed results, however, a meta-analysis of 13 randomized controlled trials (RCTs) including 2,442 patients provided strong support for this strategy[21]. In this meta-analysis, subglottic suctioning was associated with lower rates of VAP in patients requiring more than 24 h of mechanical ventilation as well as an increase in time to first VAP episode, decrease in time of mechanical ventilation and decrease in ICU length of stay. However, no mortality benefit was seen. Another recent meta-analysis evaluating 10 RCTs with 2,213 patients reported a significantly reduced incidence of VAP and early-onset VAP with subglottic secretion drainage (SSD)[22]. Moreover, SSD was associated with shortened ventilation duration and prolonged time to VAP. No significant differences were observed regarding incidence of late-onset VAP, overall mortality, or length of ICU or hospital stay.

Concerns have been raised about the use of subglottic suctioning devices experiencing mechanical failure due to blockage of the subglottic suction port by tracheal mucosa or causing injury to the tracheal mucosa[23]. However, changes in design of the tubes have reduced these complications at the expense of higher cost of the tubes[24]. Additionally, as there is no difference in VAP reduction rates between continuous and intermittent subglottic suctioning techniques[21], intermittent suctioning should be considered, as there may be less risk of associated tracheal injury. Further studies are needed to confirm this recommendation.

Head of bed elevation: Elevation of the head of the bed is attempted to reduce aspiration of gastric content. The basis for this intervention comes from studies using radiolabelled enteral feeding solutions which have shown that aspiration of gastric contents occurs to a greater extent in supine patients than in patients

in a semirecumbent position[25,26]. The first RCT to test this hypothesis compared a group of patients who were completely supine with a group of patients whose heads were elevated to 45 degrees and found a significant reduction in rates of VAP[27]. A second RCT also targeted head elevation of 45 degrees in the intervention group and compared these patients to usual practice[28]. The most significant finding in this study was the difficulty in achieving a constant mean head of the bed elevation in the intervention group of close to 30 degrees. In addition, there was not an associated reduction of the rate of VAP among semi-recumbent positioned patients when compared to supine positioned patients (10 degrees). In summary, while it is clear that supine positioning should be avoided in intubated patients, the exact degree the head should be elevated remains to be resolved. Clinical practice guidelines recommend keeping the head elevated above 30 degrees in order to prevent aspiration.

Antimicrobial-coated endotracheal tubes: ETTs coated with antimicrobial substances have been studied as a means to decrease bacterial colonization and prevent biofilm production with the ultimate hope of reducing VAP rates. It is hypothesized that microorganisms reach the ETT either as a consequence of a contaminated oropharynx or reflux of gastric secretions[29]. Once they reach the ETT surface, microorganisms produce biofilms, which provide an ideal environment for growth and proliferation protected from the host's natural defenses. When biofilms subsequently become dislodged, either spontaneously or iatrogenically due to suctioning or bronchoscopy, there is significant risk for development of late-onset VAP.

The use of a silver-coated ETT has been proposed as a method to reduce biofilm production[30]. It is well known that silver has broad-spectrum antimicrobial activity, decreases bacterial adhesion *in vitro* and blocks biofilm formation in animal models and, therefore, silver-coated tubes, such as urinary catheters, have been widely studied[31,32]. Based on these successes, silver-coated ETTs were studied in the North American Silver-Coated Endotracheal Tube (NASCENT) study and found to be associated with a lower rate of microbiologically confirmed VAP and a delay in VAP occurrence when compared to conventional tubes[33]. However, this study had several limitations and failed to show a significant difference in mortality, duration of mechanical ventilation, and ICU or hospital length of stay. Further investigation is needed to understand the potential impact of silver-coated ETTs but preliminary investigations show that despite their relative expense ($90 vs. $2 for a standard ETT) the use of silver-coated ETTs may result in cost savings[34].

Other coating materials including chlorhexidine with and without sulphadiazine, and "gendine" (gentian violet and chlorhexidine) have also been evaluated in animal models and *in vitro* studies; clinical trials are needed to evaluate their clinical utility[35].

VAP prevention: Infection control in the ICU

The goal of infection control is to prevent cross transmission of pathogens, which has been shown to play an important role in the development of nosocomial infections including VAP. An effective strategy should target infection control from several vantage points: education of the medical team, universal hand hygiene, use of personal protective equipment and a protocol for microbiological surveillance[36].

All healthcare providers involved in the care of patients requiring mechanical ventilation should be educated about and take an active role in VAP prevention, as multidisciplinary teams, who are well educated about infection control measures, are more successful in VAP prevention[37,38]. However, the translation of decades of research showing the effectiveness of VAP-prevention strategies into clinical practice has proven to be challenging. Studies conducted amongst ICU physicians and nurses reveal that only 37 and 22.3 per cent of these care providers respectively follow published recommendations for prevention of VAP[39,40]. Care bundles have been proposed to address this gap in implementation of guidelines but studies to date have been inconclusive.

VAP prevention: Reducing colonization

Prevention of colonization of the upper airway and gastrointestinal tracts has also been targeted as a means to prevent VAP. Here we discuss the relative utility of oral decontamination, selective digestive decontamination, and the use of probiotics.

Selective digestive tract decontamination: Selective digestive tract decontamination (SDD) and selective oropharyngeal decontamination (SOD) are measures in which antibiotic therapy is used to eradicate potentially pathogenic microorganisms in oral, gastric, and intestinal flora. Antibiotics are typically non-absorbable, topical preparations of antibiotics with broad-spectrum activity administered either orally, enterally and/or in conjunction with parenteral antibiotics. These techniques have been studied for decades and have

been the subjects of reviews and meta-analysis showing modest reductions in mortality[41,42].

The largest study to date of SDD was conducted in 13 ICUs in the Netherlands and showed a 28-day mortality reduction with the use of SDD and SOD of 3.5 and 2.9 per cent, respectively[43]. In this trial, SDD consisted of four days of intravenous cefotaxime and topical application of tobramycin, colistin and amphotericin B in the oropharynx and stomach. SOD consisted of oropharyngeal application only of the same antibiotics.While rigorous, a significant limitation to this study was that it did not address the impact of antibiotic resistance. A follow up study was, therefore, conducted and showed that bacterial resistance in fact increased in the ICUs that used SDD/SOD[44]. At this time, despite repeated and rigorous studies, SDD/SOD cannot be recommended for the prevention of VAP due to concern for emergence of antibiotic-resistant pathogens.

Oral decontamination: Chlorhexidine is the oral antiseptic most rigorously studied with regards to VAP[45]; its use has been associated with a reduction in the rates of VAP in recent systematic reviews and meta-analysis[46-48]. This effect was most pronounced in patients undergoing cardiac surgery and is highly dependent upon both frequency of administration and the concentration of chlorhexidine (2% is more effective than 0.12 or 0.2%)[49,50]. Unfortunately, the results in non cardiac patients were not as clear and there was no benefit in terms of mortality, number of mechanical ventilation days, or other outcomes.

Iseganan and povidone iodine have also been investigated for oral decontamination. Iseganan is a topical antimicrobial with activity against Gram-positive and Gram-negative bacteria, and yeast. However, topical oropharyngial administration failed to show any reduction in VAP when compared to placebo in a multicenter randomized trial[51]. Povidone iodine has demonstrated a benefit in VAP rates in patients with severe head trauma, but this has yet to be investigated in other patient populations[52].

Probiotics: Probiotics are living microorganisms that confer a health benefit when administered in adequate dosages. A 2010 pilot study found that critically ill patients at high risk for VAP who received *Lactobacillus rhamnosus* had significantly fewer microbiologically confirmed cases of VAP and significantly fewer episodes of *Clostridium difficile*-associated diarrhoea compared to patients who did not receive the probiotics[53]. However, larger multi-center trials with more liberal inclusion criteria are needed to evaluate the generalizability of this finding.

Bundles of care: VAP-prevention strategies have recently been grouped together into care bundles with hopes that routine, co-ordinated practice of a select number of interventions in concert will result in better outcomes than any intervention in isolation. Improvements in VAP rates have been reported by several authors through the use of bundles that include measures such as head of bed elevation, oral cleansing with chlorhexidine, sedation holidays, weaning protocols, and care provider education[54-61]. However, it has yet to be clearly shown which interventions are most crucial to include in such bundles and precisely how to go about implementation so has to improve clinical outcomes. There are no well-designed, controlled trials addressing this question to date.

Conclusions

VAP continues to be a commonly encountered challenge amongst critically ill patients and carries significant burdens of morbidity, antibiotic utilization and cost. Studies on prevention strategies directed towards the pathophysiologic mechanisms of VAP have shown variable success. However, certain measures as described in this review have been shown to improve patient outcomes and, therefore, we recommend care providers consider a multidisciplinary strategy incorporating the following: NPPV when able; sedation and weaning protocols for those patients who do require mechanical ventilation; mechanical ventilation protocols including head of bed elevation and oral care; and removal of subglottic secretions. Future research that considers clinical outcomes as primary endpoints will hopefully result in more detailed prevention strategies.

Disclosure statement

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