



## REVIEW

# Evidence on measures for the prevention of ventilator-associated pneumonia

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**ABSTRACT:** Ventilator-associated pneumonia (VAP) continues to be an important cause of morbidity and mortality in ventilated patients.

Evidence-based guidelines have been issued since 2001 by the European Task Force on ventilator-associated pneumonia, the Centers for Disease Control and Prevention, the Canadian Critical Care Society, and also by the American Thoracic Society and Infectious Diseases Society of America, which have produced a joint set of recommendations.

The present review article is based on a comparison of these guidelines, together with an update of further publications in the literature. The 100,000 Lives campaign, endorsed by leading US agencies and societies, states that all ventilated patients should receive a ventilator bundle to reduce the incidence of VAP.

The present review article is useful for identifying evidence-based processes that can be modified to improve patients' safety.

**KEYWORDS:** Ventilator-associated pneumonia

Ventilator-associated pneumonia (VAP) continues to be an important cause of morbidity and mortality in critically ill patients [1–3]. The present review article is based on a summary of the evidence from the literature and the guidelines for the prevention of VAP produced by the European Task Force (ETF) in 2001 [4], the Centers for Disease Control and Prevention (CDC) in 2004 [5], the Canadian Critical Care Society (CCCS) in 2004 [6] and the American Thoracic Society and Infectious Diseases Society of America (ATS-IDSA) in 2005 [7], focusing on the measures described in these guidelines. The measures to prevent VAP can be classified as pharmacological (table 1) and non-pharmacological (table 2).

### SEARCH STRATEGY

Medline searches of publications in English from 1966 to 2006 were carried out for the following major topic headings: "ventilator-associated pneumonia", "oro-tracheal intubation", "nasotracheal intubation", "endotracheal tube cuff pressure", "aspiration of subglottic secretions", "extubation", "re-intubation", "noninvasive ventilation", "tracheostomy", "respiratory filters", "change of breathing circuits", "heat and moisture exchanger", "heated humidifier", "closed

tracheal suctioning system", "open tracheal suctioning system", "change of closed tracheal suctioning system", "sterilization", "disinfection", "barrier measures", "kinetic bed", "semi-recumbent position", "supine position", "gastric feeding", "post-pyloric feeding", "selective digestive decontamination", "preventive intravenous antibiotics", "chlorhexidine oral rinse", "ranitidine", "sucralfate", "sedation", and "paralytic agents". In addition, Personal Reference Manager files were used as the database for the present review. References were selected on the basis of the bearing of their results on prevention of VAP.

### CATEGORISATION OF RECOMMENDATIONS

#### European Task Force

In the ETF guidelines [4], a panel of experts in the field of VAP from four European societies (the European Respiratory Society, the European Society of Intensive Care Medicine, the European Society of Clinical Microbiology and Infectious Diseases and the European Society of Anaesthesiology) provided an overview of the most important aspects under debate. Each section was classified according to the following categories: 1) what is not controversial; and 2) what is still controversial.

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### Centers for Disease Control and Prevention

In the CDC guidelines [5], each recommendation was categorised in accordance with the following classification: “category IA” if strongly recommended for implementation and firmly supported by well-designed experimental, clinical or epidemiological studies; “category IB” if strongly recommended for implementation and supported by certain clinical or epidemiological studies and by a sound theoretical rationale; “category IC” if required for implementation, as mandated by federal or state regulation or standard; “category II” if suggested for implementation and supported by suggestive clinical or epidemiological studies or by a strong theoretical rationale; “no recommendation; unresolved issue” in the case of practices for which insufficient evidence was available or if no consensus existed regarding their efficacy.

### Canadian Critical Care Society

In the CCCS guidelines [6], the recommendations were classified according to the following terms: “recommended” if there were no reservations about endorsing an intervention; “considered” if there was evidence supporting an intervention but there were minor uncertainties about the benefits, harms, or costs; “no recommendation” if evidence regarding an intervention was inadequate or if there were major uncertainties about the benefits, harms or costs.

### American Thoracic Society and Infectious Diseases Society of America

In the ATS-IDSA guidelines [7], the grading system for the evidence-based recommendations used was as follows: “level I”

when the evidence was from well-conducted, randomised controlled trials; “level II” when the evidence came from well-designed, controlled trials without randomisation (including cohort, patient series, and case-control studies); “level III” when it comes from case studies and expert opinion.

## NONPHARMACOLOGICAL MEASURES FOR PREVENTING VAP

### Orotracheal versus nasotracheal intubation

The use of nasotracheal intubation has been associated with a higher incidence of nosocomial sinusitis than orotracheal intubation [8–10], and sinusitis may predispose to VAP through the aspiration of infected secretions from the nasal sinuses, although causality between sinusitis and VAP has not been firmly established. Thus, orotracheal intubation should be chosen in patients who do not have contraindications for it.

### Monitoring endotracheal tube cuff pressure

The pressure of the endotracheal tube cuff should be sufficiently high to avoid the loss of gas from the lower respiratory tract and the leakage of bacterial pathogens around the cuff into the lower respiratory tract. In a study by RELLO *et al.* [11], 83 consecutive intubated patients were evaluated. There was a trend toward a higher risk of pneumonia (relative risk 2.57, 95% confidence interval (CI) 0.78–8.03) among patients with persistent intra-cuff pressures <20 cmH<sub>2</sub>O. Among intubated patients not receiving antibiotics, persistent intra-cuff pressure <20 cmH<sub>2</sub>O was independently associated with the development of pneumonia (relative risk 4.23, 95% CI 1.12–15.92). Moreover, this pressure should be maintained at

**TABLE 1** European Task Force (ETF), Centers for Disease Control and Prevention (CDC), Canadian Critical Care Society (CCCS) and American Thoracic Society and Infectious Diseases Society of America (ATS-IDSA) recommendations regarding nonpharmacological measures for ventilator-associated pneumonia

	ETF	CDC	CCCS	ATS-IDSA
[Ref.]	[4]	[5]	[6]	[7]
Publication yr	2001	2004	2004	2005
Oral intubation better than nasal	Not controversial	IB	Recommended	II
Optimal pressure of endotracheal tube cuff	Not controversial	NR	NR	II
Subglottic secretion drainage	Still controversial	II	Considered	I
Early extubation	NR	IB	NR	II
Avoid re-intubation	Not controversial	II	NR	I
Noninvasive ventilation	Still controversial	II	NR	I
Tracheostomy: early better than late	NR	NR	Insufficient evidence	NR
Respiratory filters	NR	Unresolved	NR	NR
Routine change of ventilator circuits	NO: Not controversial	NO: IA in HME/II in HH	NO	NO
HME better than HH	Still controversial	Unresolved	Recommended	I: is the same
Tracheal suctioning system: closed better than open	Still controversial	Unresolved	NR	NR
Routine change of closed tracheal suctioning system	Still controversial	Unresolved	NO	NR
Sterilisation or disinfection of respiratory devices	NR	IB	NR	NR
Barrier measures	Not controversial	IA	NR	I
Kinetic or standard beds	NR	Unresolved	Considered	NR
Semirecumbent position (30–45°)	Not controversial	II	Recommended	I
Feeding: post-pyloric better than gastric	Still controversial	Unresolved	NR	NR

HME: heat and moisture exchanger; HH: heated humidifier; IB: the evidence comes from certain clinical or epidemiological studies; II: the evidence comes from well-designed, controlled trials without randomisation; NR: the guideline did not review this issue; I: the evidence is from well-conducted, randomised controlled trials; NO: the recommendation is of no use; IA: the evidence comes from well-designed experimental, clinical or epidemiological studies.

**TABLE 2** European Task Force (ETF), Centers for Disease Control and Prevention (CDC), Canadian Critical Care Society (CCCS) and American Thoracic Society and Infectious Diseases Society of America (ATS-IDSa) recommendations regarding pharmacological measures for ventilator-associated pneumonia

	ETF	CDC	CCCS	ATS-IDSa
[Ref.]	[4]	[5]	[6]	[7]
Publication yr	2001	2004	2004	2005
Selective digestive decontamination	Not controversial in some patients	Unresolved	Insufficient evidence	I
Preventive intravenous antibiotics	Still controversial	Unresolved	Insufficient evidence	I at time of intubation
Chlorhexidine oral rinse	NR	II in cardiac surgery	NR	I in cardiac surgery
Sucralfate better than ranitidine	Still controversial	Unresolved	Insufficient evidence	I: is the same
Avoidance of deep sedation and paralytic agents	Not controversial	NR	NR	II

I: the evidence is from well-conducted, randomised controlled trials; NR: the guideline did not review this issue; II: the evidence is from well-designed, controlled trials without randomisation.

<30 cmH<sub>2</sub>O to prevent tracheal injury [12, 13]. Thus, the intra-cuff pressure should be persistently maintained at 20–30 cmH<sub>2</sub>O.

### Subglottic secretions drainage

Oropharyngeal secretions may descend into the trachea, accumulate above the endotracheal cuff and later progress to the lower respiratory tract, causing VAP. Investigators have attempted pre-emptively to remove these secretions with the goal of reducing microaspiration and the risk of VAP. Subglottic secretions drainage (SSD) is accomplished through use of a specially designed endotracheal or tracheostomy tube with a separate dorsal lumen that opens directly above the endotracheal or tracheostomy tube cuff. SSD has reduced the incidence of VAP in some studies [11, 14–16]; however, in other studies it has not been found to decrease the incidence of VAP [17, 18] or airway colonisation [19]. Maintaining the pressure of the endotracheal tube at >20 cmH<sub>2</sub>O and the concomitant role of antibiotics may explain these discrepancies.

The recommendation to use SSD was also supported by the results of a later meta-analysis developed by DEZFULIAN *et al.* [20], which evaluated 896 patients from five studies [14–18]. SSD appears to be effective in preventing VAP (relative risk 0.51, 95% CI 0.37–0.71) in patients expected to require >72 h of mechanical ventilation; primarily by reducing early-onset pneumonia. Thus, the use of an endotracheal or tracheostomy tube with SSD should be recommended in patients expected to require >72 h of mechanical ventilation.

### Avoiding delays in extubation

The presence of an endotracheal tube increases the probability of aspiration of pathogens from the oropharynx into the lower airways and the probability of developing nosocomial pneumonia. The risk of developing VAP increases over time in mechanical ventilation [21–23]. Thus, the present authors recommend removal of endotracheal tubes from patients as soon as the clinical situation allows; the duration of intubation can be reduced by protocols to improve the use of sedation and to accelerate weaning.

### Avoiding re-intubation

Re-intubation has been associated with the risk of VAP [24–26]. This fact may be due to an increased risk of aspiration of pathogens from the oropharynx by patients with subglottic dysfunction after several days of endotracheal intubation. Thus, re-intubation should be avoided as far as possible. The re-intubation rate can be reduced by the following measures: 1) improving planned extubations with the design of protocols to improve quality of weaning; 2) by the use of noninvasive mechanical ventilation; and 3) avoiding accidental removal of the endotracheal tube and monitoring the rate of accidental extubation, which according to the findings of several large series is 0.8–2.2 per 100 endotracheal tube-days [27–29].

### Noninvasive mechanical ventilation

In some studies [30–33], the use of noninvasive mechanical ventilation (NIMV) has been shown to reduce VAP incidence compared with invasive ventilation in patients who are in respiratory failure. The use of NIMV in weaning also reduced the VAP incidence in some studies [34–36], but not in another [37].

A recent meta-analysis published by BURNS *et al.* [38], which included 171 patients enrolled in five studies, analysed the 150 patients from four of the studies that reported the VAP rate [34–37]. BURNS *et al.* [38] found that in comparison with invasive ventilation, the noninvasive form decreased VAP (relative risk 0.28, 95% CI 0.09–0.85), mortality (relative risk 0.41, 95% CI 0.22–0.76) and duration of mechanical ventilation (weighted mean difference -7.33 days, 95% CI -11.45–-3.22 days).

Thus, NIMV has been shown to be an effective alternative in patients with respiratory failure due to cardiogenic pulmonary oedema or chronic obstructive pulmonary disease, and in weaning; however, its role in pneumonia, acute respiratory distress syndrome and asthma is less clear. Besides, it is assumed that in comatose patient, NIMV is not an option. Therefore, more research is necessary into the indications for and standards of NIMV.

### Early tracheostomy

Prolonged intubation has been associated with complications such as laryngeal injury and tracheal stenosis [39–42], and conversion to tracheostomy has been proposed when the use of prolonged intubation is anticipated to avoid these complications.

Some studies have found early tracheostomy to be more greatly associated with a lower incidence of VAP than late tracheostomy [43, 44], though other studies comparing early with late tracheostomy or prolonged intubation have found no such association [45–52].

In a more recent meta-analysis by GRIFFITHS *et al.* [53], which enrolled 382 patients from five studies [44–48], early tracheostomy did not significantly decrease the risk of pneumonia (relative risk 0.90, 95% CI 0.66–1.21) or mortality (relative risk 0.79, 95% CI 0.45–1.39). However, early tracheostomy significantly reduced the duration of artificial ventilation (mean difference -8.5 days, 95% CI -15.3– -1.7 days) and length of stay in intensive care (mean difference -15.3 days, 95% CI -24.6– -6.1 days). Thus, early tracheostomy should be performed in patients expected to require prolonged mechanical ventilation. Further studies are needed to clarify the timing of tracheostomy.

### Respiratory filters

From 1952 to 1972, outbreaks of nosocomial pneumonia were associated with contamination of anaesthesia machines [54–56]. To avoid VAP episodes linked to anaesthesia machine or to ventilator contamination, it was suggested that bacterial filters should be interposed in respiratory circuits, although it has not been proven that they diminish the incidence of VAP.

Contamination of the ventilator and the anaesthesia machine as the origin of nosocomial pneumonia is controversial. Some reports identify the anaesthesia circuit as a source of pneumonia [54–56], but none of them are conclusive, for a range of reasons. None presented a bacteriological demonstration of a cause-end-effect relationship; in addition, the study by TINNE *et al.* [55] reported that the same isolate of *Pseudomonas aeruginosa* responsible for an outbreak of post-operative pneumonia was cultured from the corrugated tubing of the anaesthesia machine and from manual ventilation bags. Also, in some studies [57–59], after the sterilisation of the anaesthesia machine and the anaesthesia circuit, the intentional contamination of the expiratory circuit was not followed by the contamination of the anaesthesia machine.

To avoid VAP due to the contamination of the ventilators, bacterial filters were inserted into the respiratory circuits. Previous studies have evaluated the effect of filters in circuits of anaesthesia machines and were unable to demonstrate that their use offered protection against the development of post-operative respiratory infection [60, 61]. The authors of both these studies believed that the anaesthesia machine was an unlikely source of infection.

In a randomised clinical trial [62], no significant differences were found in VAP incidence either with or without filters in the ventilator circuit; the authors found no significant differences in VAP incidence in the patients ventilated with or without filters (24.5 *versus* 21.5%,  $p=0.58$ ). Thus, it can be

concluded that filters should not be used routinely. However, according to the CDC recommendation, they should be used in patients with suspected or confirmed bacillary pulmonary tuberculosis undergoing mechanical ventilation [63].

### Routine change of ventilator circuits

With the use of heated humidifiers (HH), condensed liquid may appear in the ventilator circuits due to the difference in temperature between the inspiratory phase gas and the ambient air. This condensed liquid may become contaminated with microorganisms *via* different routes, either directly by a manipulation of the airway, or with the respiratory secretions of the patient. This contaminated liquid can enter the tracheobronchial tree *via* manipulations, such as respiratory secretion aspiration, change of the respirator location or patient bathing, and it may be associated with VAP.

Periodic changing of the ventilator circuits has been proposed as a way of avoiding VAP due to this condensed liquid, but the usefulness of the measure has been questioned over the years. In 1983, the CDC proposed changing of the ventilator circuit every 24 h [64] and, in 1994, they recommended extending the period to 48 h [65]. Later studies suggested that the period should be extended still further [66–71].

In all these studies the humidification was generated with an HH. However, the effectiveness of the periodic changing of ventilator circuits in decreasing VAP incidence is even more doubtful when the humidification system used is a heat and moisture exchanger (HME), because this instrument avoids the condensation of liquid in ventilator circuits. Recently, a randomised study analysed VAP incidence in patients using a HME exclusively with and without periodic changing of ventilator circuits [72], finding no significant differences in VAP incidence (23.0 *versus* 22.9%,  $p=0.98$ ), which suggested that routine circuit change when using a HME is also unnecessary. Thus, the ventilator circuits should not be changed routinely, only for a new patient or if they become soiled.

### Heat and moisture exchangers or heated humidifiers

The use of mechanical ventilation with an artificial airway requires conditioning of the inspired gas. This is because medicinal gases are cold and dry, and when the upper airway is bypassed it cannot contribute to the natural heat and moisture exchange process of inspired gases. At low levels of inspired humidity, water is removed from the mucus and periciliary fluid by evaporation, causing a decrease in mucus clearance.

Artificial humidification of medicinal gases may be active or passive. In active humidifiers, called HHs, the inspired gas passes across or over a heated water bath. Passive humidifiers, called artificial noses or HMEs, trap heat and humidity from the patient's exhaled gas and return some of it to the patient on the subsequent inhalation.

There is controversy about what constitutes the optimal humidity level of the inspired gas and about the appropriate humidification system. Some authors have advocated absolute humidity levels of 26–32 mg of water vapour per litre of gas and recommend the use of HMEs because these devices provide these levels. However, others advocate an absolute

humidity level of 44 mg of water vapour per litre of gas and recommend the use of HHs because they can condition inspired gas to this humidity level (programmed to deliver medicinal gas at a temperature of 37°C and a relative humidity of 100%).

In the review by WILLIAMS *et al.* [73], the data from 200 relevant studies on respiratory tract physiology and humidification were plotted on a humidity exposure map. This review reveals that there have been few studies with human subjects and that the duration of most of them was only 12 h. The trend of the map data suggests that mucociliary dysfunction can occur after 24–48 h with an absolute humidity level of <32 mg water vapour per litre, and that the optimal humidification model of inspired medicinal gas should be at body temperature and 100% relative humidity, containing ~44 mg water vapour per litre of gas; however, further research with exposure times >24 h is needed to verify this proposition fully.

A randomised study conducted by HURNI *et al.* [74] evaluated the morphological integrity of the respiratory epithelium of 41 patients receiving mechanical ventilation for ≥5 days using either an HH at 32°C and a relative humidity of 100% or an HME as the humidification system. The group with HME showed a trend towards a greater damage of the respiratory epithelium than with HH; however, it would be of interest to observe the result with a bigger sample size and using HH with a temperature of 37°C and a relative humidity of 100% (which would ensure the delivery of ~44 mg of water per litre of gas).

There is also controversy concerning the possible influence of these systems on the incidence of VAP. While one study reported a lower incidence of VAP associated with the use of HME [75], several studies found no significant differences between the two systems [74–85], and three studies found a lower incidence of VAP associated with HH [86–88].

A recent meta-analysis by KOLA *et al.* [89], which enrolled 1,378 patients from nine trials [74–82], found that the use of HME decreased the VAP rate (relative risk 0.7, 95% CI 0.50–0.94). However, only one of the studies included in the meta-analysis by KOLA *et al.* [89], the study by KIRTON *et al.* [75], reported a significantly lower incidence of VAP with HME compared with HH. In addition, these meta-analyses did not include the nonrandomised studies by COHEN *et al.* [86] and BLIN *et al.* [87], which found significantly decreased VAP rates using HH compared with HME.

After the meta-analysis, two randomised studies found no significant differences in VAP rates associated with the use of HH or HME [84, 85]; in a randomised study of 104 patients requiring mechanical ventilation for >5 days, a lower incidence of VAP was found with the use of HH than with HME (15.69 versus 39.62%;  $p=0.006$ ) [88].

In addition to VAP, there are other important issues that must be considered when a passive humidifier is used. In one study, a lower incidence of tube occlusion, thick bronchial secretions and atelectasis was reported with HH than with HME [86]. Besides, the use of HME has been associated with increased airway resistance and dead space, thus HME could entail increased work-of-breathing [90–93].

Thus, more research is necessary to establish the optimal humidification level and system; however, the present authors recommend the use of HME in patients who are expected to need mechanical ventilation for 24–48 h, and HH in patients expected requiring more prolonged ventilation.

### **Closed tracheal suctioning system versus open tracheal suctioning system**

The suction of respiratory secretions is necessary in patients with an artificial airway (endotracheal intubation or tracheostomy) to remove respiratory secretions and to maintain the airway's permeability.

There are two kinds of respiratory secretion suctioning systems: 1) the open tracheal suctioning system (OTSS), which uses single-use suctioning catheters and must be disconnected from the respiratory circuit; and 2) the closed tracheal suctioning system (CTSS), which uses reusable suctioning catheters and does not require disconnection of the respiratory circuit. For these reasons, CTSS is presumed to offer advantages over OTSS, such as lower gasometric and haemodynamic impairment during the suction of respiratory secretions, which has been found in several studies [94–97], and a protective effect against VAP, although this latter finding is controversial because only one study has reported a lower incidence of VAP using CTSS [98]. Several other studies have not found significant differences in the incidence of VAP between the systems [99–105].

In two recent meta-analyses by VONBERG *et al.* [106] and JONGERDEN *et al.* [107], no significant difference was found in the incidence of VAP using either a CTSS or an OTSS.

One of the potential advantages of CTSS is that these systems can reduce exogenous VAP, that is, those infections caused by microorganisms that were not colonising the throat at the moment of diagnosis and reached the patient airway directly through the endotracheal tube. This decrease in the exogenous pneumonia rate could be due to the fact that CTSS avoids direct manipulations of the aspiration catheter, as it is protected by a plastic envelope. Nevertheless, in two recent randomised studies, no significant differences were found between the patients suctioning with CTSS or OTSS in terms of either total VAP incidence or exogenous VAP incidence [104, 105]. Thus, the evidence does not support the routine use of CTSS for prevention of VAP.

### **Routine change of closed tracheal suctioning system**

The main restriction on the use of CTSS is its higher cost [94, 95, 100, 101, 104], since the manufacturer recommends that the system should be changed completely each day. However, the need for this complete daily change has not been demonstrated.

VAP incidence did not increase in two studies [108, 109] in which the period for the change of CTSS was prolonged. KOLLEF *et al.* [108] did not report significant differences in VAP incidence between patients with and without routine 24-hourly change of CTSS. Nor were there significant differences in VAP incidence between patients with CTSS change every 48 or 24 h in the study by DARVAS and HAWKINS [109].

A randomised study recently evaluated the incidence of VAP and the suctioning cost, comparing OTSS and CTSS without daily change [105]. The CTSS used had two parts: 1) a suction catheter (enveloped in a protective plastic); with 2) a suction valve, detachable from the elbow and equipped with a rotating patient access valve (bronchoscope valve). This division into two parts means that the suctioning catheter and its protective plastic envelope can be disconnected and changed without changing the whole system (a partial change). The closed system that was used was not routinely changed unless it presented mechanical failure (e.g. valve dysfunction with air entering the protective catheter envelope or protective envelope breakage) or soiling (with blood or vomit), or when the patient needed re-intubation. On re-intubation or valve dysfunction, a total change of the system was performed. When the protective envelope became torn or soiled, a partial change of the system was performed (only the suctioning catheter and the protective envelope). When patients needed to be moved for a surgical or radiological procedure, they continued to use the same system. The authors found no differences in VAP incidence between the CTSS without complete daily change (13.9%) and OTSS patients (14.1%,  $p=0.99$ ); nor did tracheal suctioning costs differ significantly per patient-day between CTSS and OTSS ( $\text{€}2.3 \pm 3.7$  versus  $\text{€}2.4 \pm 0.5$ ,  $p=0.96$ ); when length of mechanical ventilation was  $>4$  days, costs were lower with CTSS than with OTSS ( $\text{€}1.6 \pm 2.8$  versus  $\text{€}2.5 \pm 0.5$ ,  $p<0.001$ ). Some types of CTSS allow the possibility of partially changing the system (only the suctioning catheter and the protective envelope). With other types of CTSS, this partial change cannot be made and, in this case, the cost of each aspiration may not be lower. Thus, CTSS should not be routinely changed, only for a new patient or if it becomes soiled or spoiled.

#### **Sterilisation or disinfection of reusable respiratory devices**

Several outbreaks of nosocomial pneumonia have been reported due to various respiratory devices, such as nebulisers [110], resuscitation bags [111], respirometers [112], ventilator thermometers [113] and bronchoscopes [114]. Thus, reusable respiratory devices should be sterilised or disinfected for use in different patients to avoid cross-contamination and the development of VAP.

#### **Barrier measures**

Colonisation of the hands is a concern in healthcare workers [115–117], since it increases the risk of nosocomial infection by cross-colonisation with procedures, such as tracheal suctioning, manipulation of ventilatory circuits and bronchoscopy. The risk of cross-contamination can be reduced by using adequate barrier measures, such as hand washing, gloves, aprons and masks, to avoid contact with patients' secretions [118, 119]. Thus, adequate barrier measures should be used for contact with the secretions of the patients.

#### **Kinetic beds**

Mechanically ventilated patients are often cared for in the supine position for extended periods of time. In this position, the functional residual capacity is decreased because of alveolar closure in dependent lung regions. Immobility may impair mucociliary clearance, with the accumulation of mucus in dependent lung zones. This can lead to atelectasis and

respiratory infection of dependent lung regions. As standard practice, mechanically ventilated patients are usually turned every 2 h by the nursing staff. The potential benefits of kinetic beds are that they accomplish continuous turning of a patient to at least  $40^\circ$  on each side and, in addition, can provide percussion and vibration therapy, with the goal of optimising mucociliary clearance and avoiding the accumulation of mucus in dependent lung zones.

The use of kinetic beds in place of standard beds was found to decrease VAP incidence in some studies [120–122], but not in others [123–129]. In the recent meta-analysis by DELANEY *et al.* [130], which included 1,169 patients from 15 trials, analysis of the 967 patients from the 10 studies that reported VAP rate [120–129] found that kinetic bed therapy reduced VAP incidence (odds ratio 0.38, 95% CI 0.28–0.53). However, kinetic bed therapy did not reduce mortality rate (odds ratio 0.96, 95% CI 0.66–1.14), duration of mechanical ventilation (pooled standardised mean difference  $-0.14$  days, 95% CI  $-0.29$ – $0.02$  days), duration of intensive care unit stay (pooled standardised mean difference  $-0.064$  days, 95% CI  $-0.21$ – $0.086$  days) or duration of hospital stay (pooled standardised mean difference 0.05 days, 95% CI  $-0.18$ – $0.27$  days). Besides this, most of the VAP diagnoses in kinetic bed therapy studies were made only on a clinical basis without microbiological cultures. In addition, the potential benefit of kinetic beds to decrease the incidence of atelectasis was not analysed. Additionally, many of the patients undergoing kinetic bed therapy showed complications, such as intolerance, unplanned extubation, loss of vascular lines, cardiac arrest, arrhythmia, problems with skeletal traction, and increased intracranial pressure. Thus, given the lack of consistent benefit and the poor methodological quality of the studies, it is not possible to make a definitive recommendation regarding its use.

#### **Semirecumbent position (30–45°)**

Some studies have found the semirecumbent position to be associated with lower levels of aspiration into the lower airways [131–133] and lower VAP incidence than the supine position [134–136]. A recent study by VAN NIEUWENHOVEN *et al.* [137] questioned the efficacy of this measure and its feasibility for daily practice. VAN NIEUWENHOVEN *et al.* [137] randomised 221 patients to a semirecumbent (with a backrest of  $45^\circ$ ) or supine position (backrest of  $10^\circ$ ), finding that the targeted semirecumbent position was not achieved in the conditions of the study and that the difference attained in the treatment position ( $28$  versus  $10^\circ$ ) did not reduce VAP incidence. The influence of enteral nutrition [134] might explain the discrepancies between authors regarding effectiveness. In the study by DRAKULOVIC *et al.* [134], the semirecumbent position reduced the incidence of VAP, especially in patients who receive enteral nutrition. Thus, the patients should remain in the semirecumbent position, mainly in patients receiving enteral nutrition. It is noteworthy that the position of the upper body of the patient should not be  $<10^\circ$  at any time (including during basic care or transport).

#### **Gastric compared with post-pyloric feeding**

Gastro-oesophageal reflux may contribute to aspiration to lower airways and thus the risk of VAP. It was suggested that

placement of a post-pyloric tube can reduce the risk of aspiration and VAP.

In some studies, there were not significant differences in VAP and mortality rates between patients with gastric or post-pyloric feeding [138–144]. In the meta-analysis by MARIK and ZALOGA [145], which enrolled 522 patients from nine studies, analysis of the 422 patients from seven studies that reported the VAP rate [138–144] found that gastric feeding showed a trend to higher incidences of VAP (odds ratio 1.44, 95% CI 0.84–2.46) and mortality (odds ratio 1.08, 95% CI 0.69–1.68) than post-pyloric feeding; however, the differences were not statistically significant.

Thus, a definitive recommendation regarding the routine use of post-pyloric feeding is not possible; however, there are some patients who may benefit from post-pyloric feeding, such as patients who are unlikely to tolerate gastric feeding (those with severe head injuries with high intracranial pressure or severe respiratory failure requiring prone ventilation, or who have major burns) or those with high nutritional requirements (those who are severely malnourished or have major burns).

## PHARMACOLOGICAL MEASURES FOR PREVENTING VAP

### Selective digestive decontamination

Oropharyngeal colonisation has been identified as an independent risk factor of VAP. Modulation of oropharyngeal colonisation has been proposed by the use of selective digestive decontamination (SDD), which consists of the administration of nonabsorbable oral antibiotics (usually polymyxin, tobramycin and amphotericin B) applied topically to the oropharynx and stomach, together with the intravenous administration of cefotaxime.

Several large meta-analyses report that SDD decreases the rates of VAP and mortality [146–151]. Two meta-analyses have shown that this effect on the rate of VAP and mortality is greater in surgical and trauma than in medical patients [147, 148]. However, despite the measure's proven clinical benefits, its use has not been generalised worldwide. There are a number of possible explanations: many physicians are still unfamiliar with the practice; emerging antimicrobial resistance has been reported in some studies [152–154]; proper application is complex and requires bacteriological monitoring (since the use of SDD should be carefully monitored as a potential stimulus for further antimicrobial resistance); and its cost-effectiveness is unclear. It is controversial whether the benefit is due to the concomitant parenteral administration of antibiotics within the first days of the regimen.

Afterwards, several randomised studies have found a lower incidence of VAP with SDD [155–158]; however, a lower mortality rate was not found in some studies [157, 158].

Failure to prevent VAP using iseganan [159] raises additional concerns in implementing SDD. Iseganan is a topical antimicrobial peptide active against Gram-positive bacteria, Gram-negative bacteria and yeasts. In the randomised study [159], the topical administration of iseganan did not reduce the incidence of VAP. Thus, given the lack of consistent benefit and the unclear cost-effectiveness, it is not possible to make a definitive recommendation regarding its use.

### Preventive administration of intravenous antibiotics

The administration of antibiotic peri-intubation showed a protective effect of early VAP in a randomised trial and in at least one observational study [160, 161]; however, in other studies, the prolonged administration of antibiotics has been associated with a higher risk of VAP [136, 162, 163]. Thus, due to this and concerns of resistance development, the present authors do not recommend the preventive administration of intravenous antibiotics.

### Oral cleaning and decontamination

In some studies, oral chlorhexidine decreased VAP incidence [164–166], but not in others [167]. In the study by FOURRIER *et al.* [164], 60 patients in a multidisciplinary intensive care unit were randomised to receive oral chlorhexidine or placebo; the VAP incidence was found to be lower in the treated group (odds ratio 0.27; 95% CI 0.07–0.96). In the study by HOUSTON *et al.* [165], 561 patients undergoing cardiac surgery were randomised to receive chlorhexidine gluconate oral rinse or phenolic mixture; although the overall rate of VAP was not significantly lower in the chlorhexidine group (1.4 *versus* 3.0%,  $p=0.21$ ), in patients intubated for >24 h, the decrease in VAP incidence in the chlorhexidine group was statistically significant (20 *versus* 70%;  $p=0.02$ ). In the study by DERISO *et al.* [166], 353 patients undergoing cardiac surgery were randomised to receive chlorhexidine gluconate oral rinse or phenolic mixture; again, the VAP incidence was lower in the treated group (2.9 *versus* 9.4%,  $p<0.05$ ).

A recent meta-analysis by PINEDA *et al.* [168], which included 1,202 patients from four studies [164–167], reported that the use of oral decontamination with chlorhexidine did not significantly decrease either the incidence of VAP (odds ratio 0.42, 95% CI 0.16–1.06) or the mortality rate (odds ratio 0.77, 95% CI 0.28–2.11).

At about the same time, in a study by KOEMAN *et al.* [169], 385 patients needing mechanical ventilation for  $\geq 48$  h were randomised to oral decontamination with chlorhexidine, chlorhexidine–colistin or placebo. The daily risk of VAP was reduced in both treatment groups compared with placebo, as follows: chlorhexidine–placebo (hazard ratio 0.35, 95% CI 0.16–0.79) and with chlorhexidine–colistin–placebo (hazard ratio 0.45, 95% CI 0.22–0.92).

Again at a similar time, a study by MORI *et al.* [170] was published, which showed that the incidence of VAP in a group of 1,252 patients who received oral care (povidone–iodine solution in combination with a toothbrush) was lower than in a group of 414 patients who did not receive it.

Thus, it seems that chemical decontamination with chlorhexidine as a solitary intervention may be insufficient to decrease the risk of pneumonia in a significant way, and that thorough mechanical cleaning is necessary. Thus, the present authors recommend the use of chlorhexidine oral rinse in combination with thorough mechanical cleaning of the oral cavity. A survey of oral care practices in 59 European intensive care units has recently been published [171], which shows that oral care is considered very important.

### Stress ulcer prophylaxis

The controversy concerning the use of ranitidine or sucralfate for stress ulcer prophylaxis remains unresolved. In the study by COOK *et al.* [172], 1,200 critically ill patients who required mechanical ventilation were randomised to receive sucralfate or ranitidine. Clinically important gastrointestinal bleeding was lower in the patients receiving ranitidine (relative risk 0.44, 95% CI 0.21–0.92), but there were no significant differences between the groups in VAP rate, mortality rate, or duration of the ICU stay. However, in some studies, the use of ranitidine was associated with a higher risk of VAP than sucralfate [173–175], though not in other studies [172, 176–179]. In the meta-analysis by MESSORI *et al.* [180], analysis of the 1,825 patients from eight studies that reported VAP rate [172–179] showed that the use of ranitidine to prevent gastrointestinal bleeding increased the VAP incidence in comparison with sucralfate (odds ratio 1.35, 95% CI 1.07–1.70); however, this meta-analysis was full of ill-designed and under-powered studies. Later, a prospective cohort study, published by BORSTAIN *et al.* [181], of 747 patients undergoing mechanical ventilation found that sucralfate use was associated with a higher risk of early onset VAP (odds ratio 1.81, 95% CI 1.01–3.26).

Other possible agents for stress ulcer prophylaxis are proton-pump inhibitors. Limited data exist on its clinical efficacy; however, available data indicate that proton-pump inhibitors can be efficacious [182–186]. In two prospective series of patients receiving omeprazole oral suspension [182, 183], with sizes of 75 and 60 patients, respectively, clinically significant gastrointestinal bleeding was not experienced. In a randomised trial with 67 patients, a greater rate of clinically important bleeding (31 *versus* 6%,  $p < 0.05$ ), and a trend to a greater rate of VAP patients (14 *versus* 3%) was found in the patients given ranitidine intravenously *versus* omeprazole orally [184]. In a randomised clinical trial of 160 paediatric critically ill patients, there were no significant differences in the incidence of VAP and macroscopic stress ulcer bleeding using orally administered sucralfate oral, and *i.v.* administered ranitidine and omeprazole [185]. In a recent randomised trial with 359 patients, no significant differences were observed in the rate of clinically significant bleeding between the patients who received omeprazole oral suspension and *i.v.* cimetidine [186]. Thus, the present authors believe that stress bleeding prophylaxis can be obtained without increasing the risk of VAP with use of histamine-2 receptor antagonists, sucralfate or proton-pump inhibitors.

### Avoidance of sedation and paralytic agents

The influence of sedation as a risk factor for VAP has been documented in some studies [11, 135, 187]. In the study by KRESS *et al.* [187], in which 128 adult patients receiving mechanical ventilation were randomised either to daily interruption of sedative drug infusions until they were awake or were interrupted only at the discretion of the clinician, the daily interruption group had shorter duration of mechanical ventilation ( $p < 0.01$ ) and length of intensive care unit stay ( $p = 0.02$ ) than the latter group. In a prospective cohort study by COOK *et al.* [21] of 1,014 mechanically ventilated patients, the use of paralytic agents was associated with VAP (risk ratio = 1.57, 95% CI = 1.03–2.39). Thus, the present authors

recommend avoidance of deep sedation and relaxation if the incidence of VAP is to be reduced.

### Conclusion

Discrepancies between guidelines are probably due to the following two main reasons: 1) the clinical trials that are revised in each guideline; and 2) disagreement with the interpretation of clinical trials. In clinical practice, the implementation of evidence-based guidelines for VAP is very variable [188]. Main nonadherence reasons to recommendations of guidelines between physicians were disagreement with the interpretation of clinical trials and unavailability of resources [189, 190]; between nurses, the main nonadherence reasons were unavailability of resources and patient discomfort [191].

Clearly, the effect of these measures varies between institutions and case mixes. The 100,000 Lives campaign [192], endorsed by leading US agencies and societies, establishes that all ventilated patients should receive a ventilator bundle to reduce the incidence of ventilator-associated pneumonia and other adverse events, accompanied by the following four services: 1) elevation of the head of the bed to 30–45°; 2) daily “sedation vacation” and daily assessment of readiness for extubation; 3) peptic ulcer disease prophylaxis; and 4) deep vein thrombosis prophylaxis. Tables 1 and 2 summarise the recommendations of the European Task Force, Centers for Disease Control and Prevention, Canadian Critical Care Society, American Thoracic Society and Infectious Diseases Society of America, and the present authors’ recommendations. In recent years, there has been a rapid increase in the number of country-specific ventilator-associated pneumonia guidelines in Europe, which vary in their coverage of different disease aspects and in their overall recommendations; the development of pan-European ventilator-associated pneumonia guidelines would rationalise the conflicting proposals [193]. These data would be useful to design a ventilator-associated pneumonia care bundle to be implemented in European institutions.

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