

## WHAT'S NEW IN INTENSIVE CARE



# Ten ineffective interventions to prevent ventilator-associated pneumonia

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In spite of important progress in the field of ventilator-associated pneumonia (VAP) pathophysiology and prevention, this infection is still commonly diagnosed in critically ill patients requiring invasive mechanical ventilation. Recognizing ineffective measures for VAP prevention is helpful to avoid side effects of these interventions and to reduce associated costs and workload in the intensive care unit (ICU).

### 1. Residual gastric volume measurement

A recent randomized, noninferiority, open-label, multicenter trial was performed in 449 adults requiring invasive mechanical ventilation and compared absence of residual gastric volume monitoring vs measurement of gastric volume every 6 h [1]. VAP rate was similar in intervention (16.7%) and control group (15.8%) (difference 0.9%, 90% CI -4.8% to 6.7%). In addition, the proportion of patients receiving 100% of their target calorie intake was higher in the intervention group (odds ratio 1.77, 90% CI 1.25–2.51;  $p = 0.008$ ), suggesting that this measurement should not be performed.

### 2. Parenteral nutrition

Enteral feeding carries a risk for microaspiration of gastrointestinal content and could increase the incidence of VAP. On the other hand, parenteral feeding can provide adequate caloric intake and carries no risk of aspiration. Yet, the impact of different nutrition modalities in reducing VAP rates is questionable because of the scarcity of available data. A small randomized study found no impact of parenteral feeding on VAP rates [2]. Further, a recent large prospective database study, which included over 3000 patients, reported that early enteral feeding

was not significantly associated with increased risk for VAP [3]. Interestingly, early nutrition was associated with reduced 28-day mortality irrespective of the route of feeding [3].

### 3. Stress ulcer prophylaxis

The recent Surviving Sepsis Campaign 2016 guideline issued a strong recommendation to use stress ulcer prophylaxis in critically ill patients at high risk for bleeding. However, this recommendation is based on low-quality evidence. In addition, side effects of stress ulcer prophylaxis, such as infection related to *Clostridium difficile*, pneumonia, and cardiovascular events preclude its use in routine [4]. Although several bundles for VAP prevention included stress ulcer prophylaxis, recent guidelines from the Infectious Disease Society of America and the Society of Hospital Epidemiology of America recommend not using stress ulcer prophylaxis for VAP prevention. Proton pump inhibitors and anti-histamine-2-receptor antagonists modify gastric pH and increase bacterial proliferation in gastric contents. Previous studies reported higher rates of VAP in patients receiving enteral nutrition and stress ulcer prophylaxis. A recent meta-analysis of randomized trials found no significant impact of proton pump inhibitors on pneumonia rate in critically ill patients [5].

### 4. Systemic or inhaled antibiotic therapy

Few studies have assessed antibiotics as preemptive therapy for VAP aiming either to suppress colonization or to treat ventilator-associated tracheobronchitis (VAT), which is considered to be a condition that may lead to VAP [6]. Systemic use of short courses of antibiotics early after intubation, or later at VAT diagnosis, or the local application of antibiotics in the tracheobronchial tree showed promising results for reducing VAP prevalence [6, 7]. However, available studies are small, observational,

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**Table 1 Selected studies on ineffective measures to prevent ventilator-associated pneumonia**

Intervention	First author/year of publication	Type of study/number of included patients	Main results	Comment
1. Residual gastric volume measurement	Reignier/2013	RCT multicenter open label/449	Similar rates of VAP in intervention (16.7%) and control (15.8) group. Difference 0.9% (90% CI -4.8% to 6.7%)	Proportion of patients receiving 100% of their target calorie intake significantly higher in intervention group
2. Parenteral nutrition	Altintas/2011	RCT single-center open label/71	Similar rates of VAP in intervention (16.7%) and control (26.8%) group, $p = 0.311$	No significant impact on mortality
3. Stress ulcer prophylaxis	Reignier/2015	Prospective observational multicenter cohort/1668	Non-significant association between enteral nutrition and VAP risk (HR 1.17, 95% CI 1.00-1.38, $P = 0.006$ )	Comparing patients who received only enteral nutrition to patients who received only parenteral nutrition
4. Systemic antimicrobials	Alshamsi/2016	Meta analysis/1571	No significant impact of proton pump inhibitors on pneumonia rate in the critically ill (RR 1.12, 95% CI 0.86-1.46)	Overt upper gastrointestinal bleeding significantly reduced in proton pump inhibitor group (RR 0.48, 95% CI 0.34-0.66)
Inhaled antimicrobials	Bouza/2013	RCT single-center open label/78	Similar rates of VAP in intervention (17.5%) and control (21.1%) group, $P = 0.69$	Patients requiring invasive mechanical ventilation after major heart surgery
5. Statins	Karvouniaris/2015	RCT single-center open label/168	Lower, but not significant ( $p = 0.07$ ), rate of VAP in intervention (16.7%), compared with control (29.8%) group	Significantly ( $p = 0.03$ ) lower Gram-negative bacteria VAP in intervention (10.7%), compared with control (17.9%) group
6. Closed endotracheal suctioning system	Makris/2011	RCT two-center open label/152	Similar VAP rates in intervention (22.5%) and control group (34.5%), $p = 0.11$	Increased probability of being free from VAP during the 30-day treatment period in the pravastatin group compared to the control group ( $p = 0.06$ )
7. Improved tracheal cuff	Kuriyama/2014	Meta-analysis/1929	Compared with open tracheal suctioning system, closed tracheal suctioning system was associated with a reduced incidence of VAP (RR 0.69, 95% CI 0.54-0.87, $I^2 = 46.4%$ )	Trial sequential analysis suggested a lack of firm evidence for 20% RR reduction in the incidence of VAP. Low quality of the included trials
8. Early tracheostomy	Philippart/2015	RCT multicenter open label/621	Similar rates of VAP in patients intubated with tapered-PU, tapered-PVC, cylindrical-PU, and cylindrical-PVC cuff ( $p = 0.28$ )	VAP was a secondary outcome. No significant difference ( $p = 0.55$ ) in rate of patients with tracheobronchial colonization at day 3 (primary outcome)
9. Kinetic beds	Jaillette/2017	RCT multicenter cluster open label/326	Similar rates of VAP in patients intubated with tapered-PVC (20.4%), compared with standard-PVC (23.3%) cuff ( $p = 0.54$ )	VAP was a secondary outcome. No significant difference in rates of patients with abundant microaspiration of gastric contents
10. Prone positioning	Meng/2016	Meta analysis of RCTs/1141	No significant impact of early tracheostomy on VAP rate (RR 0.84, 95% CI 0.66-1.08)	High heterogeneity, $I^2 = 82%$
	Delaney/2006	Meta-analysis/1169	Significant reduction in the incidence of nosocomial pneumonia (OR 0.38, 95% CI 0.28-0.53)	Lack of consistent benefit and poor methodological quality of the trials included in this analysis
	Ayzac/2016	Ancillary study of a multicenter RCT/466	incidence rate for VAP similar ( $p = 0.1$ ) in prone (11.8/1000 MV days) and supine (15.4/1000 MD days) groups	Patients with acute respiratory distress syndrome

CI confidence interval, HR hazard ratio, MV mechanical ventilation, RCT randomized controlled trial, RR relative risk, VAP ventilator-associated pneumonia

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or performed in specific populations such as patients with neurologic failure. Moreover, there is still skepticism about the emergence of multidrug-resistant bacteria following the implementation of such strategies.

A recent single-center randomized controlled trial (RCT) evaluated the impact of inhaled colistin on VAP incidence [8]. Although the rate of VAP was lower in intervention compared with control group, the difference did not reach statistical significance.

## 5. Statins

Statins (reductase inhibitors) present anti-inflammatory immunomodulatory properties besides their ability to affect cholesterol composition and it has been hypothesized that they might be useful in improving the outcome or the incidence of various diseases, including pneumonia and acute respiratory distress syndrome. However, data from national registries or post hoc analysis of data from randomized studies reported conflicting results for the impact of the use of statins on the risk of pneumonia. A randomized study in critical care patients, without previous use of statins, reported that the prophylactic use of a 30-day treatment with pravastatin did not significantly modify the risk of VAP [9].

## 6. Closed tracheal suctioning system

Closed tracheal suctioning system (CTSS) might reduce exogenous tracheobronchial colonization via fewer manipulations by healthcare workers. However, three large RCTs did not report significant benefit of this system in reducing VAP incidence. By contrast, a recent meta-analysis of 15 RCTs reported significant reduction in VAP rate using CTSS, compared with open tracheal suctioning system (OTSS) (RR 0.69, 95% CI 0.54–0.87) [10]. However, heterogeneity was high ( $I^2 = 46.4\%$ ), and sensitivity analyses, including trial sequential analysis, suggested the scarcity of high-quality trials.

## 7. Improved tracheal cuff

In vitro and observational studies suggested reduced microaspiration and VAP rates using tracheal tubes with tapered and/or polyurethane cuffs. However, the large multicenter randomized controlled TOPCUFF study [11] carefully evaluated the impact of tapered vs tapered shape and polyurethane vs polyvinyl chloride cuffs in 621 patients receiving mechanical ventilation for more than 48 h. No significant impact of these interventions was found on tracheobronchial colonization or VAP rates. Recently, the multicenter cluster randomized controlled BestCuff trial [12] evaluated the impact of tapered cuff on microaspiration in 342 critically ill patients. No significant impact was found on microaspiration of gastric contents or oropharyngeal secretions. VAP and

ventilator-associated events rates were also similar in intervention and control groups.

## 8. Early tracheostomy

Early tracheostomy was suggested as a preventive measure for VAP, because this procedure might reduce duration of invasive mechanical ventilation. In addition, tracheostomy allows liberation of vocal cords and reduction of microaspiration of contaminated secretions. Further, biofilm formation is counterbalanced by the routine change of tracheostomy cannula. However, one large multicenter RCT and three recent meta-analyses of RCTs found no impact of early tracheostomy on VAP rate (RR 0.84, 95% CI 0.66–1.08) [13].

## 9. Kinetic beds

Delaney et al. performed a meta-analysis of 15 prospective studies and reported a significant reduction of nosocomial pneumonia incidence (OR 0.38, 95% CI 0.28–0.53) in patients with kinetic beds, compared with controls [14]. However, as recognized by the authors, there was a lack of consistent benefit and poor methodological quality of the trials. Further, safety of this procedure was not correctly evaluated. Therefore, recent Infectious Diseases Society of America (IDSA)/Society for Healthcare Epidemiology of America (SHAE) guidelines recommend not using this measure to prevent VAP in critically ill patients [15].

## 10. Prone positioning

Improved respiratory secretions drainage, and reduced atelectasis rate in prone position, compared with supine, could result in lower VAP rates in mechanically ventilated patients. Observational studies and one meta-analysis reported significant reduction of VAP rates, using prone positioning in critically ill patients. However, a recent ancillary study of the multicenter PROSEVA RCT found no significant impact of prone positioning on VAP rates [11.8 (95% CI 0.86–1.6) vs 15.4 (1.15–2.02) VAP per 1000 mechanical ventilation days, in prone and supine groups, respectively;  $p = 0.10$ ] [16].

## Conclusion

On the basis of the current literature, the measures discussed above are not effective and should not be used for VAP prevention (Table 1). However, some measures, such as inhaled antimicrobials, closed tracheal suctioning system, and kinetic beds should be further investigated to draw definite conclusions. In addition, some ineffective measures, such as prone positioning or closed tracheal suctioning system, could be used in the critically ill patients for purposes other than VAP prevention.

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## Compliance with ethical standards

## Conflicts of interest

SN has received speaker fees from Medtronic and MSD, and is member of advisory boards for Bayer and CielMedical. Other authors (DM, and CL) have not declared any conflict of interest.

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