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EDITORIAL

# The zero-VAP sophistry and controversies surrounding prevention of ventilator-associated pneumonia

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In critically ill mechanically ventilated patients, ventilator-associated pneumonia (VAP) is the most common iatrogenic pulmonary infection. Diagnosis of VAP is challenging, potentially leading to delayed treatment or overuse of antimicrobials [1]. The impact of VAP on clinical outcomes has been thoroughly investigated [2], but remains a matter of controversy. Indeed, various trials that showed reduction of VAP failed to demonstrate improved clinical outcomes. In addition, the association between VAP and mortality is uncertain, since risk of VAP is time-dependent and patient needs to survive at least until VAP onset, limiting clear extrapolation of mortality risks. Studies attempting to control for these confounding biases have demonstrated VAP attributable mortality slightly higher than 10% [3]. Irrespective of methodological limitations, substantial body of evidence has been produced in this field and a questionable drive to achieve zero-VAP rates has grown in the past decade. This editorial provides a critical viewpoint on the zero-VAP contradiction, and summarizes controversies surrounding pharmacological and non-pharmacological interventions to reduce VAP rates.

## Zero-VAP

VAP has been increasingly considered as a fully preventable iatrogenic complication and used for benchmark and quality measure, in the context of pay-for-performance programs. This has led to overemphasized reduction in VAP incidence, specifically in North America. Indeed, in the latest National Healthcare Safety Network report, VAP rates between 0 and 4 per 1000 ventilation-days were described [4], while around the same period, Europeans were reporting an incidence density higher than 8 [5]. International administrators and healthcare policy makers strongly endorsed the "zero-VAP" approach, motivating nation-wide efforts [6], but overlooking its fundamental limitations. First, several promising interventions that reduced VAP risks, did not concurrently curtail secondary outcomes or even use of antibiotics (Table 1), questioning their clinical impact. Second, reliable and accurate diagnostic methods are crucial to corroborate eradication of a preventable disease. To date, a gold-standard to diagnose VAP is still inaccessible and we rely on multiple unspecific assays to score the risk of VAP. The newly proposed definitions of VAP, namely infection-related ventilator condition [8], did not noticeably improve accuracy of VAP diagnosis [7]. This results in easy manipulation of surveillance figures [8], specifically when quality standards or accreditations are needed. More importantly, diagnostic hurdles raise legitimate concerns on the overall evidence in this field of investigation. Indeed, substantial reduction of VAP has been frequently demonstrated by single-centre studies, using before–after designs, heterogeneous diagnostic methods and lacking concealment of interventions [9]. Finally, long-term implementation of strategies to avoid VAP is challenging, requires frequent monitoring of adherence and reinforcements, but even when methodically strategized, adherence rates not greater than 80% have been achieved [10], implying that sizeable compliance could be an unfeasible goal.

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**Table 1** **Evidence-based measures to prevent ventilator-associated pneumonia**

**Table 1. Evidence-based measures to prevent ventilator-associated pneumonia**

| *Non-pharmacological strategies* | | | |
|---|---|---|---|
| **Interventions** | **Preventive mechanisms** | **Main Effect** | **Additional Benefits/Limitations** |
| Daily sedation vacation and spontaneous breathing trials | Reduce length of mechanical ventilation and associated risks | Approximately 3-day reduction in duration of mechanical ventilation [13] | Strong additional effect on survival and ICU-acquired weakness |
| Semi-recumbent position >30° | Reduction of gastro-pulmonary aspiration of pathogens | Reduction in clinically suspected VAP [15] | Evidence is limited with a high risk of bias. No concomitant reduction in other major outcomes |
| ETTs compromising subglottic scretions drainage | Reduction of aspiration of bacteria-laden oropharyngeal secretions across ETT cuff | Reduction in clinically/microbiologically confirmed VAP [risk ratio 0.58, 95% CI 0.51-0.67] [17] | No concomitant reduction in other major outcomes |
| Continuous control ETT cuff pressure | Reduction of aspiration of bacteria-laden oropharyngeal secretions across ETT cuff | Reduction in clinically/microbiologically confirmed VAP [risk ratio 0.47, 95% CI 0.31-0.71] [18] | Heterogeneous applied methods. No concomitant reduction in other major outcomes |
| *Pharmacological strategies* | | | |
| **Interventions** | **Preventive mechanisms** | **Main Effect** | **Additional Benefits/Limitations** |
| Alcohol-based hand hygiene | Broad spectrum activity against pathogens present on healthcare providers' hands | Reduction of cross-contamination between patients | Achieving and maintaining optimal hand hygiene practices continue to be a challenge [20] |
| Oropharyngeal decontamination with chlorhexidine | Broad-spectrum activity against oropharyngeal pathogens | Reduction in VAP incidence up to 40% [20] | Intervention mostly advantageous for cardiac surgery patients. No concomitant reduction in other major outcomes |
| Selective oropharyngeal decontamination | Selective eradication of aerobic gram-negative bacilli, methicillin-sensitive *Staphylococcus aureus*, and yeasts | Strong reduction in respiratory infections [21] and mortality | Effective in Dutch ICUs with low level of antimicrobial resistance |

*ETT* endotracheal tube, *VAP* ventilator-associated pneumonia, *ICU* intensive care unit, *CI* confidence interval

## Preventive bundles

Various individual measures have proven efficacy in the prevention of VAP (Table 1), but when these measures are concomitantly applied, risks of VAP are further reduced. Meta-analyses on the implementation of VAP bundles showed that simple interventions, applied in a coordinated way as a part of a ventilator bundle care not only reduce VAP, but might also improve survival [11]. Nonetheless, as mentioned in previous paragraphs, those studies often applied inadequate methods and overlooked potential confounding factors, such as secular temporal trends in VAP incidence or regression to the mean. In addition, disagreement still exists on the most efficient and feasible bundle, since previous studies differed in the number and types of interventions, while it is known that individual components unequally impact outcomes [12].

## Non-pharmacological measures

Endotracheal intubation is a main risk factor for VAP, since patients aspirate orogastric pathogens across the endotracheal tube (ETT) cuff, specifically when they are placed in the supine horizontal position. Therefore, reducing the time of intubation, through daily sedation vacation [13] and spontaneous breathing trials [14] are tenable preventive measures. Positioning the patient with the head of the bed elevated > 30° reduces aspiration and clinically confirmed VAP [15], but quality of evidence supporting this intervention is poor, and the optimal

angulation of the head of the bed is still uncertain. The Gravity-VAP trial showed that the lateral-Trendelenburg position (LTP) could further reduce VAP, specifically in patients with healthy lungs upon intubation, but LTP feasibility appeared challenging [16]. To date, only ETTs comprising aspiration of subglottic secretions [17] reduced VAP by more than 50%, but substantial benefits were mostly corroborated in cardiac surgery patients. Avoiding ETT cuff deflation could further decrease pulmonary infections, as demonstrated by the use of devices that continuously control cuff pressure [18]; however, diverse machines have been used across available studies and consistent lack of benefits in secondary outcomes has been reported.

## Pharmacological measures

It is firmly established that contact precautions, including hand hygiene with alcohol-based solutions, are pivotal in reducing transmission of drug-resistant pathogens [19]. These measures are endorsed by the most prominent international health agencies to reduce incidence of all nosocomial infections. Following endotracheal intubation, oropharyngeal flora shifts to a predominance of aerobic Gram-negative pathogens and *Staphylococcus aureus*. Thus, modulation of orogastric colonization has been a central strategy in the prevention of VAP. Various concentrations of chlorhexidine, up to 2%, have been used to hinder oropharyngeal growth of pathogens [20], specifically in cardiac surgery ICU patients. Importantly, in recent years, arguments have been raised against the use of chlorhexidine, due to associated increased mortality. These findings could be anecdotal or imply extensive pulmonary aspiration of chlorhexidine, specifically in patients in the semi-recumbent position; thus, experimental/clinical corroboration is needed. Several investigators have also recommended selective digestive or oropharyngeal decontamination (SDD/SOD) to maximize eradication of gastrointestinal Gram-negative bacteria. SDD/SOD have been principally applied in Dutch ICUs, with lower prevalence of multi-drug resistant pathogens. In those settings, SDD/SOD have consistently reduced incidence of respiratory infections [21] and mortality. Potential rebound colonization and increased antibiotic resistance have been a serious concern. Indeed, even in Dutch ICUs, rising ceftazidime resistance was documented. Interestingly, a recent study [22] evaluating SDD/SOD effects on bloodstream infections was conducted in ICUs with high prevalence of antibiotic-resistance. Mortality was not affected by the interventions, while antibiotic resistance did not vary throughout the study periods.

In conclusion, although a variety of studies have demonstrated reduction in VAP, certainty of evidence in this field of investigation is still limited, due to the lack of reliable diagnostic methods, disagreement on VAP burden and substantial inconsistency, heterogeneity and risk of bias of available studies. In conclusion, we call attention to the crucial need of innovative diagnostic markers and application of improved research methods to advance this field and precisely corroborate efficacy of interventions in reducing VAP.

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**Compliance with ethical standards**

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