Intensive Care Med (2017) 43:1872–1874
DOI 10.1007/s00134-017-4863-4

EDITORIAL

Ventilator-associated pneumonia prevention: one good turn does not always deserve another

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Ventilator-associated pneumonia (VAP) is a frequent complication of patients undergoing invasive mechanical ventilation and its occurrence is associated with considerable morbidity and mortality [1–3]. The key factor in the pathogenesis of VAP is the endotracheal tube (ETT) [4]. Its presence compromises the natural anatomical barriers (larynx) and functional mechanisms (mucus clearance and cough), and it expedites the formation of biofilm as well as macro- and microaspiration of oropharyngeal secretions. As a result, several strategies have been successfully implemented, namely subglottic secretion drainage or cuff pressure control [3, 4].

One of the current recommendations for VAP prevention is elevation of the head of bed to 30–45° to prevent the reflux of colonized gastric contents that has a potential role in VAP pathogenesis. This strategy has been evaluated in three randomized controlled trials (RCT) enrolling 337 patients, one positive and two negatives [5–7], and in a meta-analysis pooling these three studies that found a significant impact on prevention [8]. However, the quality of evidence is low, being considered a basic practice because of its simplicity, ubiquity, low cost, and potential benefit [3].

Simultaneously, we can conceive that in a patient with an ETT, any position above horizontal increases the gravitational forces exerted by subglottic secretions above the cuff and, consequently, the risk of aspiration [9]. The results of several experimental studies challenged the recommendation of the semirecumbent position in VAP prevention. In animal models, the Trendelenburg position showed an increase in mucus clearance, decreasing aspiration and consequently VAP rates [9, 10]. With this rationale an RCT was designed to evaluate this hypothesis.

In the GRAVITY-VAP trial, recently published in *Intensive Care Medicine*, Li Bassi, Panigada, and co-workers performed a multicenter, multinational RCT to assess the impact of the lateral Trendelenburg position (LTP) vs. semi-recumbent position (SRP) in VAP incidence [11]. A total of 395 patients ($N = 194$ LTP; $N = 201$ SRP) were included. The trial was prematurely ended because of low incidence of VAP, lack of benefit in secondary outcomes, and serious adverse events (SAE). The incidence of microbiologically confirmed VAP was 0.5% in LTP and 4.0% in the SRP patients ($P = 0.04$); however, the rate of SAE was significantly higher in the LTP group, namely transient oxygen desaturation and hemodynamic instability. In addition, mortality (ICU, hospital, and day 28) was non-significantly higher in the LTP group, ranging from an absolute difference of 6.5% in ICU mortality to 4.5% in day 28 mortality. Moreover, in spite of the risk difference of −7.6% ($P = 0.02$) in microbiologically confirmed VAP in the LTP group, antibiotic consumption was similar in both groups. This may be due to the higher incidence of clinically suspected VAP in LTP patients with pulmonary infiltrates at the time of enrollment, encouraging BAL assessments, and empirical antibiotic prescription or to the fact that LTP patients had more ventilator-associated tracheobronchitis (VAT), promoting antibiotic treatment directed at this entity. As prevention of aspiration—a paramount mechanism for both VAP and VAT—is the rationale behind LTP, this strategy would be expected to reduce the incidence of both infections. In our opinion, consumption of antibiotics should be an important

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outcome variable for studies assessing new preventive strategies for healthcare-associated infections.

This is an example of a well-designed RCT, in which safety was carefully monitored. The apparent discrepancy between the lower incidence of VAP and higher incidence of SAE could explain the absence of clinical impact of this intervention. These results raise two methodological considerations that deserve to be discussed. First, the potential random nature of the reduced rate of microbiologically confirmed VAP in the intervention group as the study was stopped early. Although study interruption was not due to benefit, it is well known that trials stopped early, on average, overestimate the effect of an intervention and that the apparent overestimation is larger in smaller trials [12]. The high rate of SAE seems incompatible with a positive result, suggesting that the study is clearly underpowered. Also, the fragility of positive results regarding the main outcome—microbiologically documented VAP—appears to be high. Walsh et al. [13] published an interesting exercise creating a fragility index for clinical trials to identify the number of events required to change statistically significant results to non-significant results. In Li Bassi and Panigada's study, the fragility index is 1: only one event-change (microbiologically documented VAP) is required to change the significant result.

However, this trial brings new data that deserves to be further discussed. The lower incidence of VAP with LTP (eight times lower) reinforces the concept that macro- and microaspiration of oropharyngeal secretions have a key role in the pathogenesis of VAP [4].

There is also new data from the interpretation of the SAE, namely in two areas. The central nervous system seems to have been involved in some causes of death and was one of the reasons behind the decision to terminate the RCT early. This occurred in spite of the fact that patients with raised intracranial pressure (ICP) were excluded by the study protocol. However, LTP is always associated with a persistent non-quantifiable increase in ICP, with unpredictable consequences.

Secondly, the change in chest compliance and intrathoracic pressure as a consequence of LTP may be a problem, especially in the presence of raised intra-abdominal pressure (IAP). In the supine position, on average, 40% of the IAP is transmitted to the intrathoracic pressure and also changing chest wall compliance [14]. This effect can increase the risk of basal atelectasis, worsening of gas exchange, and arterial blood gases.

Finally, the incidence of delirium as a marker of acute brain dysfunction [15] was not evaluated. We all know that increased duration and degree of sedation, namely in LTP patients, in particular with benzodiazepines, is associated with increased risk of acute brain dysfunction, namely delirium, and this could potentially be associated with the observed poor outcomes.

In conclusion, we should pursue efforts and research to improve our knowledge of the pathophysiology of VAP as well as to design RCT to assess the safety and efficacy of new preventive strategies. But it seems that turning the head down is not a safe turn!

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Compliance with ethical standards

Conflicts of interest
The authors declare no conflict of interest related to this topic.

Received: 4 June 2017 Accepted: 7 June 2017
Published online: 22 September 2017

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