# In the name of ventilator-associated pneumonia prevention: lung microbiota blown away by colistin!

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**Negative RCT results and harmful effects on lung microbiota mean inhaled antimicrobials cannot be used to prevent VAP** http://ow.ly/T1kZS

Whilst ventilator-associated pneumonia (VAP) incidence has decreased during the last decade [1], this infection is still associated with increased duration of mechanical ventilation [2], high mortality rates and additional cost [3]. As VAP incidence is considered as an indicator of quality of care provided to the critically ill patient, preventing this infection has become a major public health issue in the intensive care unit (ICU) [4]. After several years of debate on the best diagnosis method for VAP, and in the absence of new therapeutic options, research has moved towards better understanding of pathophysiology of VAP in order to improve preventive strategies [5].

In patients receiving invasive mechanical ventilation, colonisation of the lower respiratory tract occurs rapidly after intubation. The pathogens colonising the lower respiratory tract are mainly endogenous, coming from contaminated oropharyngeal secretions and gastric contents. However, the exogenous route has also been described, resulting from contamination during tracheal suctioning, fiberoptic bronchoscopy, or ventilator circuit disconnection for aerosols or patient transport [6, 7]. Microaspiration of contaminated secretions from the subglottic area, above the tracheal cuff, to the lower respiratory tract is common. Several factors increase microaspiration in intubated critically ill patients, including the tracheal tube, ventilator settings, enteral nutrition, and other patient-related factors [8].

A recent multicentre study was performed in 604 intubated patients to determine the best cuff material and shape in preventing tracheobronchial colonisation [9]. The results of this study provide valuable information on the incidence of colonisation of lower respiratory tract, which was diagnosed ($10^3$ CFU·mL$^{-1}$) at day 2 after intubation, regardless of randomisation group, in approximately two thirds of study patients. However, only 14.4% of study patients developed subsequent VAP. Previous studies suggested a continuum between lower respiratory tract colonisation and subsequent ventilator-associated lower respiratory tract infections [10, 11]. Progression from colonisation to ventilator-associated tracheobronchitis (VAT) and VAP is related to quantity and virulence of bacteria [12]. In addition, local and general host defence also play an important role in the development of VAT and VAP in colonised patients. Bacterial biofilm formation on the tracheal tube has also been investigated as a risk factor for VAP, related to multidrug resistant bacteria, and recurrence of this infection [13].

Based on pathophysiology of VAP, preventive measures could be classified into three categories: 1) measures aiming at avoiding intubation and/or reducing its duration, 2) measures to prevent lower respiratory tract colonisation, and 3) measures to prevent progression from colonisation to VAT and VAP. Recently, the Society Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of

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America (IDSA) published their updated recommendations on strategies to prevent VAP in acute hospitals [14]. Among the 24 discussed preventive measures, nine measures were recommended in basic practices, including only five with high level of evidence.

Duration of invasive mechanical ventilation is the strongest predictor of VAP, since the tracheal tube is the main route of entry of bacteria into the lower respiratory tract. All measures aiming at avoiding intubation or reducing its duration, such as noninvasive mechanical ventilation in selected populations, management of patients without sedation, daily interruption of sedation when required, assessment of readiness to extubate daily, are recommended to reduce the risk for VAP [15–17].

Several measures aiming at preventing heavy colonisation of the lower respiratory tract have been studied. Subglottic secretion drainage [18] and head-of-bed elevation to 30–45° [19] are both recommended, although the level of evidence for head-of bed elevation is low. Other measures such as selective oral or digestive decontamination, prophylactic antibiotics, oral care with chlorehexidine, prophylactic probiotics, mechanical tooth brushing, ultrathin polyurethane or tapered cuffs, continuous control of tracheal cuff pressure, and saline instillation before tracheal suctioning are not recommended in routine [14]. The insufficient data on possible risks, and/or on their impact on duration of mechanical ventilation, length of stay, or mortality explain why these measures are still under investigation.

In case of failure of the measures discussed earlier, colonisation of the lower respiratory tract appears and other preventive measures such as antibiotic treatment, improvement of host defence, or virulence directed therapies could be useful. Systemic antimicrobial treatment has been suggested in colonised patients. However, because of the increased risk for multidrug resistant bacteria, this strategy is discouraged [20, 21]. Recent data coming from observational studies and two small randomised controlled trials suggested beneficial effects of systemic or inhaled antibiotics to prevent progression from VAT to VAP [22–24]. However, further studies are required to confirm these results.

One of the promising therapeutic perspectives is the identification of specific *Pseudomonas aeruginosa* targets for specific monoclonal antibody (mAb) development. François *et al.* [25] reported interesting results in a phase II trial that tested a pre-emptive mAb therapeutic approach targeting PcrV in critically ill patients colonised with *P. aeruginosa*. In addition, given their complementary roles, a combination of the anti-Psl and anti-PcrV mAbs (MEDI3902; MedImmune, AstraZeneca, Gaithersburg, MD, USA) (www.ClinicalTrials.gov, identifier: NCT02255760) could increase the benefit in a pre-emptive VAP approach against *P. aeruginosa*. A similar pre-emptive approach targeting *Staphylococcus aureus* alpha toxin with a long half-life mAb (MEDI4893; MedImmune, AstraZeneca) (www.ClinicalTrials.gov, identifier: NCT0229630) is currently evaluated in a European randomised controlled multicentre study.

The idea of sterilising the respiratory tract using inhaled antibiotics is old, and could be classified with those methods aiming at preventing colonisation in intubated critically ill patients. Two randomised controlled trials were published during the 1970s on the usefulness of inhaled polymixin B in preventing pneumonia. In their small randomised controlled trial (n=58), Greenfield *et al.* [26] found no significant difference in pneumonia rate between patients treated with aerosolised polymixin and control group. In contrast, Klick *et al.* [27] reported a significant decrease in VAP rates in patients who received inhaled polymixin (n=335) compared with those who received placebo (n=337). In an observational study, Rouby *et al.* [28] reported significantly lower VAP rates in patients receiving prophylactic colistin instilled compared with control group.

Falagas *et al.* [29] performed a meta-analysis of eight comparative trials (five randomised controlled and three observational trials) studying gentamycin (three trials), polymixin (three trials), tobramycin (one trial) and ceftazidine (one trial) that studied 1877 patients to determine the impact of antibiotics administered *via* the respiratory tract for prevention of ICU-acquired pneumonia. They found ICU-acquired pneumonia to be less frequent in patients who received antibiotic prophylaxis, compared with controls (odds ratio (OR) 0.49, 95% CI 0.32–0.76). However, no significant impact of inhaled antibiotics was found on mortality (OR 0.86, 95% CI 0.55–1.32). Further, multidrug resistant bacteria emergence was not evaluated, different medications were investigated, and some included patients were not receiving mechanical ventilation.

In this issue of the *European Respiratory Journal*, Karvouniaris *et al.* [30] report the results of a single centre, randomised-controlled, unblinded trial aiming to determine the impact of inhaled colistin on the incidence of VAP. 168 patients were randomised to receive inhaled colistin (500 000 units) or normal saline three times daily for the first 10 days in ICU or until extubation. No significant difference was found in the rate VAP between the two groups (16.7 *versus* 29.8%, in colistin and saline groups, respectively; p=0.07). However, significantly lower incidence density of VAP, incidence of VAP related to Gram-negative bacilli, or to multidrug resistant bacteria were found in patients who received colistin compared with those who received normal saline. Similar rates of multidrug resistant bacteria were found in the two study groups.

The authors should be congratulated for having conducted such an interesting study with straightforward methodology and important results. The strengths of this trial are the randomised controlled design, the careful evaluation of patients for different outcomes, and the quantitative microbiological assessment of patients with suspected pneumonia.

However, some drawbacks should be outlined. The study was unblinded, and is probably underpowered to detect a significant impact of inhaled colistin on VAP incidence, as the expected incidence of VAP was higher than the one reported in the study. Further, the impact of colistin on emergence of multidrug resistant bacteria was probably underestimated, given the absence of routine screening for these bacteria. A recent randomised placebo-controlled double-blind study reported that aerosolised antibiotics effectively eradicated multidrug resistant bacteria in intubated patients, without promoting new resistance [31]. However, a small number of patients (n=42) were included and no follow-up cultures were performed, suggesting that these results could simply reflect the *in vitro* suppression of bacterial growth by high concentrations of antibiotics in the sputum.

Recent studies highlighted the importance of lung microbiota in critically ill patients receiving invasive mechanical ventilation, suggesting a strong relationship between bacterial DNA within exhaled breath condensate fluid and bronchoalveolar lavage in patients with suspected pneumonia [32]. Further, changes in the lung microbial community occurred over the period of mechanical ventilation and preceded the development of VAP. Results from serial sample analyses of heat and moisture exchangers of a small number of patients who developed VAP suggested that derangement in lung microbiota might precede the clinical suspicion of pneumonia. Therefore, one could argue that preventive strategies aiming at reducing microaspiration and subsequent colonisation should be preferred to those aiming at modifying lung microbiota, such as inhaled antimicrobials.

Based on the results of the study by Karvouniaris *et al*. [30] and the possible negative impact of inhaled colistin on lung microbiota, we do not recommend using this strategy for VAP prevention in critically ill patients. By contrast, inhaled antibiotics are probably an interesting option to reduce transition from VAT to VAP. Further, inhaled antimicrobial combined with *i.v.* antibiotic treatment could be beneficial in patients with VAP related to multidrug resistant pathogen, or in patients with severe pneumonia (www.ClinicalTrials.gov, identifier: NCT00805168). However, further randomised controlled studies are required before recommending their use for these indications.

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