What's new in the prevention of ventilator-associated pneumonia?

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Purpose of the review
Ventilator-associated pneumonia (VAP) remains a frequent and severe complication in endotracheal intubated patients. Strict adherence to preventive measures reduces the risk of VAP. The objective of this paper is to review what has come forward in recent years in the non-pharmacologically prevention of VAP.

Recent findings
It seems advantageous to implement care bundles rather than single prevention measures. A solid basis of knowledge seems necessary to facilitate implementation and maintain a high adherence level. Continuous educational efforts have a beneficial effect on attitude towards VAP. Intermittent subglottic secretions drainage, continuous lateral rotation therapy, and poly-urethane cuffed endotracheal tubes decrease the risk of pneumonia. In an in vitro setting, an endotracheal tube with a tapered shaped cuff appear to better prevent fluid leakage compared to cylindrical poly-urethane or polyvinylchloride cuffed tubes. Cuff pressure control by means of an automatic device and multimodality chest physiotherapy need further investigation, as does some aspects of oral hygiene.

Summary
New devices and strategies are developed to prevent VAP. Some of these are promising but need further study. Besides this, more attention goes to factors that might facilitate the implementation process and the challenge to achieve high adherence rates.

Key words
Ventilator-associated pneumonia, prevention, endotracheal tube, bundle

Abbreviations

VAP ventilator-associated pneumonia

ICU intensive care unit

PU poly-urethane

PVC polyvinylchloride

CI confidence interval

OR odds ratio

Introduction

Despite many efforts taken in the field of prevention, healthcare-associated pneumonia remain among the most frequent complications associated with intensive care unit (ICU) admission. In a large European study including nearly 120,000 ICU patients, Lambert et al. found healthcare-associated pneumonia to be associated with an excess risk of death (adjusted hazard ratio) ranging from 1.7 (95% confidence interval [CI] 1.4–1.9) for methicillin-susceptible *Staphylococcus aureus* to 3.5 (2.9–4.2) for ceftazidime resistant *Pseudomonas aeruginosa* [1]. Most of these are ventilator-associated pneumonia (VAP). Several studies found VAP to be associated with a significant excess in morbidity and mortality, as well as a substantial economic burden [2, 3]. In order to limit the deleterious effect of severe infections, prevention remains the first step to take [4]. Unfortunately, VAP is not a rare complication. Recent surveillance data from a large initiative in which 173 ICUs from different continents were involved, estimated the pooled mean of VAP to be 13.6 per 1000 mechanical ventilation days (95% confidence interval: 13.3–14.0) [5]. Therefore in many infection prevention programs special emphasis is given to VAP. Many preventive measures can be taken to reduce the risk of VAP, either as a single measure or combined with others. Yet, the strength of evidence about some measures is often a matter of discussion as guidelines developed by distinct societies are frequently conflicting [6]. Also concerning strategies to facilitate implementation and adherence there exist no consensus [7]. The value of several newly developed measures remains controversial or need at least additional conformation in either larger clinical trials [8]. The objective of this review is to summarize which elements in the non-pharmacological prevention of VAP have come to the front in the past year.

Awareness, knowledge, and a positive attitude: prerequisites for successful implementation. In general, teams tend to be conservative in nature and often change will provoke resistance. Therefore it is essential to prepare the team for the upcoming modifications in policy. In order to facilitate the process of implementation and optimize adherence rates, the following elements should be taken into account [9]. First, the team must be aware of the problem and perceive VAP as a real problem that threatens the prognosis of patients. Second, basic knowledge of the pathogenesis is essential to understand the underlying concept of some preventive measures. Lack of profound insights frequently are the main reason for poor compliance. Third, knowledge of infection prevention in general, and VAP prevention in particular, are pivotal to have the prevention protocol adopted with at least some assurance of a long-term favorable effect. Recent data indicate that there exist a

substantial lack of knowledge among ICU clinicians concerning VAP prevention [10-12]. Based on a questionnaire Labeau et al. evaluated the knowledge about evidence-based guidelines for VAP prevention of 3329 ICU nurses from 22 European countries [13]. Overall, the results were disappointing with an average score of 45%.

Targeted education seems to be the key to increase awareness of the problem and the necessary knowledge to tackle it. As publication and distribution of guidelines on itself seems not to result in improved implementation, an interactive web-based 'crash course' in infection prevention is developed (http://www.evidenceproject.org/). The interactive course design might be helpful to more easily adopt and maintain knowledge about issues such as VAP prevention. To which extent this learning module is effective, is still a matter of study. An additional main beneficial effect of continuous education is a change in attitude towards the problem. The team should perceive VAP as a challenge in which it is possible to succeed, and not as a obstacle that simply cannot be prevented in some patients. There exists a relationship between hand hygiene compliance of nurses and a supportive, enthusiastic attitude in terms of self-efficacy [14]. Recent data by Bouadma L et al. demonstrated that a multifaceted educational program focused on VAP prevention gradually changed behavior over a one year period [15]. Positive perception was significantly associated with cognitive factors predicting behavior. Indeed, analogue with the educational program, these investigators demonstrated significantly increased compliance rates with an 8-item prevention program [16], as well as a decrease in VAP incidence by 43% (from 22.6 to 13.1 VAP per 1000 mechanical ventilation days)[17].

Intermittent subglottic secretions drainage

The most important element in the pathogenesis of VAP is micro-aspiration of subglottic secretions. Subglottic secretions drainage (SSD) by use of an endotracheal tube with a separate dorsal lumen that opens directly above the cuff, has been developed to avoid micro-aspiration. SSD can be performed either continuous or intermittent. However, concerns about injuries at the tracheal mucosa have been raised by the use of continuous SSD. Therefore Lacherade et al. performed a multicenter trial including 333 intubated patients expected to require mechanical ventilation >48 hours in which intermittent SSD was compared with a control group without SSD [18]. In the experimental group subglottic secretions were aspirated with 10 mL syringe each hour. Microbiologically confirmed VAP occurred in 14.8% of patients in the experimental group and 25.6% in the control group ($p=0.02$), which

corresponds with a relative risk reduction of 42.2% (95% confidence interval: 10.4 – 63.1%). This favorable effect was valid for early and late-onset VAP (using a 5-day threshold).

Endotracheal tube cuff material and cuff shape

Ultrathin poly-urethane (PU) cuffs have been developed to minimize the channel size within folds of an inflated cuff. In a randomized controlled trial by Poelaert et al., PU cuffed endotracheal tubes resulted in a significant reduction of early post-operative pneumonia in post-cardiac surgery patients (adjusted odds ratio 0.31, 95% confidence interval: 0.13 – 0.77) compared to conventional polyvinylchloride (PVC) cuffed endotracheal tubes [19]. Miller et al. evaluated the use of PU cuffed endotracheal tubes for the prevention of VAP in a retrospective, interrupted time-series analysis [20]. The rate of VAP was compared before, during and after the replacement of a conventional PVC cuffed tube by a PU cuffed tube. VAP rates decreased from 5.3/1000 ventilator days before the use of the PU cuffed tube to 2.8/1000 ventilator days during the intervention (p=0.013). During the first three months after the return to PVC cuffed tubes, the rate of VAP was 3.5/1000 ventilator days. In a regression analysis which controlled for confounding variables, the use of a PU cuffed tube was associated with a significant decrease in the risk of VAP (incidence risk ratio: 0.565, 95% CI 0.335-0.935). In a study by Lorente et al. PU cuffed endotracheal tubes were successfully combined with SSD [21]. Compared to conventional PVC cuffed endotracheal tubes without SSD, this tube demonstrated a significant reduction in early (3.6% vs. 10.7%; p=0.02) and late-onset VAP (9.5% vs. 26.7%; p=0.01). Because of the combination of both prevention aspects, it is uncertain which concept contributed the most in the reduction of VAP risk. Anyhow, the future of VAP prevention by means of innovative devices, lays probably by the combination of characteristics which all comprise a VAP prevention potential.

Another innovation developed to avoid micro-aspiration, concerns the cuff shape. Conventional endotracheal tubes have a cylindrical shaped cuff. As a consequence an inflated cuff will always have folds by which leakage is possible. Recently a nendotracheal tube with a tapered shaped cuff was developed. The promise of this cuff is that it better accommodates natural variations in the size of the tracheal. As such, at least at one point, the taper shaped cuff seals the trachea without fold formation. In an in vitro study by Dave et al. demonstrated that endotracheal tubes with taper shaped cuffs have superior sealing capacity compared to cylindrical shaped cuffs and are equally effective as cylindrical shaped PU cuffed endotracheal tubes [22]. However, the study design included the use of different sizes of artificial tracheas (16, 20, and 22 mm internal diameter) and in larger tracheal diameters, the

tapered shape cuff was more efficient in the prevention of fluid leakage compared with cylindrical shaped PU cuffs. To which extent the endotracheal tube with a tapered shaped cuff results in reduced VAP rates remains to be demonstrated.

Cuff pressure monitoring

No cuff seals unless it is sufficiently inflated. On the other hand, excessive cuff pressure (above 30 cm H_2O) impose tracheal damage. A recent survey by Labeau et al. evaluated both daily practice and knowledge about cuff pressure management in 591 ICU nurses [23]. Respondents were well aware of the importance of optimal cuff pressures and of the consequences of either insufficient or excessive pressures. Nevertheless, in the absence of a specific indication (e.g. audible leakage), 53% checks pressure only every 8 hours and frequently this is done by means of finger palpation of the pilot balloon. Recently Liu et al. showed that cuff pressure estimates by finger palpation results in excessive cuff pressure and that monitoring the cuff with a manometer results in fewer post-intubation complications [24]. In order to guarantee optimal cuff pressure monitoring and regulation an automatic device has been developed. This device proved to decrease the risk of insufficient cuff pressure (defined as <20 cm H_2O), but no decrease in VAP was observed [25].

Continuous lateral rotation therapy

The value of kinetic beds to reduce the risk of VAP have been confirmed earlier but because of the high cost associated with this approach and the lack of benefits in terms of survival, most guidelines are rather cautious to recommend its routine use in ventilated patients [6]. A recent randomized clinical trial in three ICUs, however, again showed the preventive capacity of continuous lateral rotation therapy [26]. Rotation therapy over an arc of 90° was performed continuously in a specialized designed bed. Patients in the experimental group experienced significantly less VAP compared to the control group (11% vs. 23%; p=0.048). Also, rotation therapy led to shorter ventilation time and length of stay. The latter observation may be subject of an economic analysis in which the use of expensive kinetic beds are balanced with the gains originating from a reduced length of hospitalization. Anyway, in the existence of much cheaper and effective ways to prevent VAP the routine use of kinetic beds is probably doomed to remain a matter of controversy.

Saline instillation prior to endotracheal suctioning

Besides kinetic beds there is also renewed interest in saline instillation before tracheal suctioning. This practice may be beneficial because greater amounts of secretions may be removed, it stimulates coughing, and may decrease biofilm formation in the endotracheal tube [8]. On the other hand saline instillation may promote VAP development by dislodging more bacterial colonies from the tube resulting in contamination of the lower airways. In a recent study by Caruso et al. patients randomized to the saline group experienced less microbiologically confirmed VAP (10.8% vs. 23.5%; p=0.008) [27]. Given, however, the potential harm associated with saline instillation, and the specific subset of oncologic patients in this study, more data are needed to make a strong recommendation [8].

Multimodality chest physiotherapy

Various combinations of chest physiotherapy have beneficial effects on arterial oxygenation, hemodynamic ventilator effects, and changes in total lung/thorax compliance. In a randomized study Pattanshetty and Gaude evaluated the value of multimodality chest physiotherapy in the prevention of VAP [28]. Patients in the control group received twice daily chest physiotherapy by manual hyperinflation and suctioning, while patients in the experimental group received additional chest wall vibrations and patient positioning. Study outcomes showed more successful weaning (62% vs. 31%; p=0.007) and a greater reduction in clinical pulmonary infection scores in the study group (average scores reduction: 3.4 vs. 1.9; p<0.001). From this observation the authors suggest a potential in terms of VAP prevention but – without questioning the value of chest physiotherapy for other indications – we believe it is much too hasty to make this conclusion.

Oral hygiene

Poor oral health is a risk factor for pneumonia in critically ill patients. Although oral rinse with chlorhexidine has generally accepted as an effective measure to reduce the risk of VAP, it remains unclear which concentration to use, what the exposure time should be, and how frequently it should be performed [29, 30]. Also the issue of teeth brushing remains controversial. Only one randomized controlled study evaluated the effect of dental brushing in mechanical ventilated ICU patients [31]. In this study twice daily electric tooth brushing combined with chlorhexidine-based oral rinse vs. oral rinse without dental brushing did not result in a reduction of the risk of either suspected VAP (odds ratio [OR] 0.78, 95%CI 0.36 to 1.68) or documented VAP (OR 1.14, 95% CI 0.46 to 2.81). However, these results do not indicate futility of teeth brushing in intubated patients. While brushing teeth may not

necessarily lead to reduced VAP rates, it contributes to the prevention of dental plaque, stomatitis, gingivitis, subgingivitis, and periodontitis. An additional problem is that oral care is perceived as a difficult and unpleasant task; moreover, most nurses give to understand they lack training and efficient equipment to care for the oral cavity [32]. Therefore, investments in training and appropriate equipment are pivotal.

Care bundles to prevent VAP

Especially in units with an already high standard in infection prevention, single preventive measures will generally insufficient to further decrease the rate of VAP. The concept of implementing a package of measures is therefore attractive as it is more likely to make a difference. A recent review stated that a care bundle is an effective method to prevent VAP [33]. However, the effect of care bundles is generally evaluated by means of before-after designs which are prone to bias, such as natural fluctuations in infection rates. This makes interpretation of the study results difficult. In addition, it seems important which items to include. Some preventive measures will be adopted more easy than others. Crucial is the willingness of the team to change their routine practice. In this regard, it is important to involve the whole team in the process of developing a care bundle.

Rello et al. developed care bundle based on a multi-criteria decision analysis [34]. In this way the a formalized methodology was used to end up with a set of preventive measures for which there exists a broad willingness to support its implementation. The selected items are showed in Table 1. Finally, as mentioned by Kollef, the work is not accomplished by implementing a care bundle [35]. Implementation of a care bundle should be accompanied by a surveillance program to closely monitor VAP rates. Adjustments must be made according to the occurrence rate of VAP, and the care bundle should be integrated in other quality improvement programs.

Conclusion

A wide range of measures to prevent VAP have been developed. Among them innovative endotracheal tubes to minimize micro-aspiration of subglottic secretions, cuff pressure control devices, aspects of oral hygiene and chest physiotherapy. While some of these measures are well established and generally accepted as effective in the prevention of VAP, some need additional confirmation. Besides the prevention measure as such, more attention must be given to aspects of team dynamics. Awareness and knowledge can be enhanced through

targeted education. The implementation process can be facilitated by involving the team in the development of the quality improvement program.

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Bullet points.

- Implementation of care bundles is to be preferred above single prevention measures.
- Education is of key importance as it positively affect knowledge, awareness and attitude.
- Intermittent subglottic secretions drainage, continuous lateral rotation therapy, and poly-urethane cuffed endotracheal tubes decrease the risk of pneumonia.
- Endotracheal tubes with a tapered shaped cuff appear to better prevent fluid leakage.

Table 1 – European care bundle developed for the prevention of ventilator-associated pneumonia [33].

Note to editor: "original table"

Preventive measure
No ventilator circuit tube changes unless specifically indicated
Strict hand hygiene practice with use of alcohol-based hand rub
Appropriately educated and trained staff
Sedation vacation and weaning protocol
Oral care with use of chlorhexidine

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

*Of special interest

**Of outstanding interest

1. Lambert ML, Suetens C, Savey A et al: Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: a cohort study. Lancet Infect Dis 2010, DOI:10.1016/S1473-3099(10)70258-9. This is the largest epidemiological cohort study about healthcare-associated pneumonia and bloodstream infections in intensive care unit patients including 119,699 patients.

** The study was focused on the four most frequent pathogens. Infection resulted in significant excess of death. The deleterious impact of antimicrobial resistance was significant for pneumonia but not for bloodstream infections.

2. Nguile-Makao M, Zahar JR, Francais A et al: Attributable mortality of ventilator-associated pneumonia: respective impact of main characteristics at ICU admission and VAP onset using conditional logistic regression and multi-state models. Intensive Care Med 2010, 36:781-789.
3. Restrepo MI, Anzueto A, Arroliga AC et al: Economic burden of ventilator-associated pneumonia based on total resource utilization. Infect Control Hosp Epidemiol 2010, 31:509-515.
4. Blot S: Limiting the attributable mortality of nosocomial infection and multidrug resistance in intensive care units. Clin Microbiol Infect 2008, 14:5-13.
5. Rosenthal VD, Maki DG, Jamulitrat S et al: International Nosocomial Infection Control Consortium (INICC) report, data summary for 2003-2008, issued June 2009. Am J Infect Control 2010, 38:95-104 e102.

*Results of large epidemiological surveillance initiative in 173 intensive care units from 25 countries in Latin-America, Africa, Asia, and Europe. Occurrence rates for distinct device-associated infections are described per type of ICU. Impact of infections is expressed in terms of excess length of stay and risk of death.

6. Lorente L, Blot S, Rello J: Evidence on measures for the prevention of ventilator-associated pneumonia. Eur Respir J 2007, 30:1193-1207.
7. Zilberberg MD, Shorr AF, Kollef MH: Implementing quality improvements in the intensive care unit: ventilator bundle as an example. Crit Care Med 2009, 37:305-309.
8. Lorente L, Blot S, Rello J: New issues and controversies in the prevention of ventilator-associated pneumonia. Am J Respir Crit Care Med 2010, 182:870-876.

** Clinically oriented review with special emphasis on controversial or until now insufficiently studied issues in the prevention of VAP. Based on the available data from literature the authors make suggestions for clinical practice.

9. Labeau S, Vandijck D, Blot S. Strategies for implementation of evidence-based guidelines for prevention of healthcare-associated infection. In: Vincent JL, ed. *Yearbook of intensive care and emergency medicine*. Berlin: Springer-Verlag; 2010:244-256.

* This book chapter reviews essential elements of the implementation process. Barriers as well as facilitators are outlined.

10. Blot SI, Labeau S, Vandijck D, Van Aken P, Claes B: Evidence-based guidelines for the prevention of ventilator-associated pneumonia: results of a knowledge test among intensive care nurses. Intensive Care Med 2007, 33:1463-1467.
11. Labeau S, Vandijck DM, Claes B, Van Aken P, Blot SI: Critical care nurses' knowledge of evidence-based guidelines for preventing ventilator-associated pneumonia: an evaluation questionnaire. Am J Crit Care 2007, 16:371-377.
12. El-Khatib MF, Zeineldine S, Ayoub C, Husari A, Bou-Khalil PK: Critical care clinicians' knowledge of evidence-based guidelines for preventing ventilator-associated pneumonia. Am J Crit Care 2010, 19:272-276.
13. Labeau S, Vandijck D, Rello J et al: Evidence-based guidelines for the prevention of ventilator-associated pneumonia: results of a knowledge test among European intensive care nurses. J Hosp Infect 2008, 70:180-185.
14. De Wandel D, Maes L, Labeau S, Vereecken C, Blot S: Behavioral determinants of hand hygiene compliance in intensive care units. Am J Crit Care 2010, 19:230-239.

* Qualitative research study that aimed to assess relationships between hand hygiene compliance and behavior by means of questionnaires and factor analysis. ICU nurses reporting a poor self-efficacy or a poor attitude towards time-related barriers appear to be less compliant.

15. Bouadma L, Mourvillier B, Deiler V et al: Changes in knowledge, beliefs, and perceptions throughout a multifaceted behavioral program aimed at preventing ventilator-associated pneumonia. Intensive Care Med 2010, 36:1341-1347.

** A study that assessed the change of individual behavioral factors throughout a multifaceted VAP prevention program. Behavior changed gradually throughout the program and was especially pronounced for healthcare workers with the lowest baseline cognitive profiles.

16. Bouadma L, Mourvillier B, Deiler V et al: A multifaceted program to prevent ventilator-associated pneumonia: impact on compliance with preventive measures. Crit Care Med 2010, 38:789-796.
17. Bouadma L, Deslandes E, Lolom I et al: Long-term impact of a multifaceted prevention program on ventilator-associated pneumonia in a medical intensive care unit. Clin Infect Dis 2010, 51:1115-1122.
18. Lacherade JC, De Jonghe B, Guezennec P et al: Intermittent subglottic secretion drainage and ventilator-associated pneumonia: a multicenter trial. Am J Respir Crit Care Med 2010, 182:910-917.

** Randomized controlled trial demonstrating that intermittent (once per hour) subglottic secretions drainage significantly reduce the occurrence rate of VAP. In contrast with continuous drainage this technique potentially reduce the risk of tracheal mucosal injury.

19. Poelaert J, Depuydt P, De Wolf A, Van de Velde S, Herck I, Blot S: Polyurethane cuffed endotracheal tubes to prevent early postoperative pneumonia after cardiac surgery: a pilot study. J Thorac Cardiovasc Surg 2008, 135:771-776.
20. Miller MA, Arndt JL, Konkle MA et al: A polyurethane cuffed endotracheal tube is associated with decreased rates of ventilator-associated pneumonia. J Crit Care 2010, DOI: 10.1016/j.jcrc.2010.05.035.
21. Lorente L, Lecuona M, Jimenez A, Mora ML, Sierra A: Influence of an endotracheal tube with polyurethane cuff and subglottic secretion drainage on pneumonia. Am J Respir Crit Care Med 2007, 176:1079-1083.

22. Dave MH, Frotzler A, Spielmann N, Madjdpour C, Weiss M: Effect of tracheal tube cuff shape on fluid leakage across the cuff: an in vitro study. Br J Anaesth 2010, 105:538-543.
** In vitro experiment demonstrating the effect of cuff shape and cuff material on subglottic fluid leakage aside the cuff. Tapered poly-urethane cuffs were as effective as a cylindrical poly-urethane cuffs in smaller tracheal diameters and were more efficient than the cylindrical poly-urethane cuffs in larger tracheal diameters. Polyvinylchloride tube cuffs leaked much more and faster than poly-urethane cuffs.

23. Labeau S, Bleiman M, Rello J, Vandijck D, Claes B, Blot S: Intensive Care Nurses' knowledge and management of tracheal tube cuffs. Intensive Care Med 2009, 35:0786.
24. Liu J, Zhang X, Gong W et al: Correlations between controlled endotracheal tube cuff pressure and postprocedural complications: a multicenter study. Anesth Analg 2010, 111:1133-1137.
** Clinical study demonstrating that – compared to finger palpation – the use of a manometer to control intracuff pressure results in less postprocedural respiratory complications such as cough, sore throat, hoarseness, and blood-streaked expectoration even in procedures of short duration (1-3 hours).

25. Valencia M, Ferrer M, Farre R et al: Automatic control of tracheal tube cuff pressure in ventilated patients in semirecumbent position: a randomized trial. Crit Care Med 2007, 35:1543-1549.
26. Staudinger T, Bojic A, Holzinger U et al: Continuous lateral rotation therapy to prevent ventilator-associated pneumonia. Crit Care Med 2010, 38:486-490.
* Randomized controlled trial putting renewed interest in continuous lateral rotation therapy for mechanically ventilated patients. VAP was significantly reduced in the experimental group.

27. Caruso P, Denari S, Ruiz SA, Demarzo SE, Deheinzelin D: Saline instillation before tracheal suctioning decreases the incidence of ventilator-associated pneumonia. Crit Care Med 2009, 37:32-38.
28. Pattanshetty RB, Gaude GS: Effect of multimodality chest physiotherapy in prevention of ventilator-associated pneumonia: A randomized clinical trial. Indian J Crit Care Med 2010, 14:70-76.
29. Van de Vyver K, Labeau S, Brusselaers N, Vogelaers D, Blot S: Impact of antiseptic based oral care on rates of ventilator-associated pneumonia in intensive care unit patients: a meta-analysis. Clin Microbiol Infect 2010, 16:S112.
30. Carvajal C, Pobo A, Diaz E, Lisboa T, Llaurado M, Rello J: [Oral hygiene with chlorhexidine on the prevention of ventilator-associated pneumonia in intubated patients: a systematic review of randomized clinical trials]. Med Clin (Barc) 2010, 135:491-497.
31. Pobo A, Lisboa T, Rodriguez A et al: A randomized trial of dental brushing for preventing ventilator-associated pneumonia. Chest 2009, 136:433-439.
* First randomized controlled trial to assess the effect of teeth brushin on the occurrence rate of VAP. In a protocol that also involved chlorhexidine oral rinse, additional teeth brushing with use of electrical brushes did not reduce the risk of VAP.

32. Rello J, Koulenti D, Blot S et al: Oral care practices in intensive care units: a survey of 59 European ICUs. Intensive Care Med 2007, 33:1066-1070.
33. Wip C, Napolitano L: Bundles to prevent ventilator-associated pneumonia: how valuable are they? Curr Opin Infect Dis 2009, 22:159-166.

34. Rello J, Lode H, Cornaglia G, Masterton R: A European care bundle for prevention of ventilator-associated pneumonia. Intensive Care Med 2010, 36:773-780.
* This article proposes a care bundle developed by means of a formalized methodology to assess supporting data, based on multi-criteria decision analysis.

35. Kollef MH: Prevention of Nosocomial Pneumonia in the Intensive Care Unit: Beyond the Use of Bundles. Surg Infect (Larchmt) 2010.