Advances in the prevention and management of ventilator-associated pneumonia

Emilio Bouza[a,b] and Almudena Burillo[c]

[a]Clinical Microbiology and Infectious Diseases Department, [b]Ciber de Enfermedades Respiratorias (CIBERES), Hospital General Universitario 'Gregorio Marañón', Universidad Complutense and [c]Clinical Microbiology Department, Hospital Universitario de Móstoles, Madrid, Spain

Correspondence to Emilio Bouza, MD, PhD, Servicio de Microbiología y E. Infecciosas, Hospital General Universitario Gregorio Marañón, Dr Esquerdo 46, 28007 Madrid, Spain
Tel: +34 915868452; fax: +34 913721721;
e-mail: ebouza@microb.net

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Purpose of review

Despite copious literature on ventilator-associated pneumonia (VAP), several aspects of this subject remain controversial. We review the current state of the prevention, diagnosis, and treatment of VAP, paying special attention to data reported over the past year.

Recent findings

The latest recommendations for VAP prevention stress the importance of implementing ventilator bundles and VAP-specific process measures such as hand hygiene in healthcare workers and regular oral care with a chlorhexidine antiseptic in patients. Isolated interventions such as aspirating subglottic secretions or the use of silver-coated endotracheal tubes have also achieved a reduction in the incidence of VAP. Improvement should be confirmed by active surveillance.

Summary

There is still no consensus as to the best microbiological diagnostic method for VAP, although an early, rapid, and accurate diagnosis should be pursued. Most recent improvements include the direct antibiogram using E-test strips. There is much clinical assessment work pending before biomarkers and molecular techniques become routine practice. The best treatment strategy consists of immediate antimicrobial treatment deescalated later according to clinical progress and culture results. Emphasis is placed on the need for timely short treatment courses to avoid the emergence of resistance.

Keywords

critical care, diagnosis, prevention, therapeutics, ventilator-associated pneumonia

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Introduction

Ventilator-associated pneumonia (VAP) is among the most common infections acquired by adults in ICUs. Preventive strategies, early suspicion of VAP, rapid diagnostic work-up, and immediate administration of adequate antimicrobial treatment active against the potential pathogens, followed by deescalation according to clinical progress and culture results are imperative [1•,2•,3••,4,5,6••, 7•,8•]. This review summarizes the recent literature on adult VAP (2008–2009) considered clinically most relevant.

Advances in prevention

The 2003 Centers for Disease Control and Prevention (CDC) Guideline for Preventing Healthcare Associated Pneumonia includes 208 recommended practices. Recent guidelines issued by several agencies and scientific societies offer priorities for prevention (Table 1) [3••,9••,10••,11•].

Pooling of secretions above the endotracheal tube (ETT) cuff may increase the volume of bacteria entering the airways. Continuous aspiration of these subglottic secretions (CASS) requires the use of a specialized ETT with a second lumen allowing the exit of a suction catheter proximal to the ETT cuff. Several randomized, controlled trials have examined the benefits of CASS with different results. In the largest trial to date [12••], CASS was able to reduce the incidence density of VAP, median length of ICU stay, and antibiotic use, and led to overall cost savings in the postoperative course of patients undergoing major surgery. The recent Canadian Critical Care Trials group guideline update on VAP prevention recommends subglottic secretion drainage in patients predicted to require more than 72 h of mechanical ventilation [9••]. However, given the difficulty in identifying target patients expected to require more than 48 h of mechanical ventilation, it could be advisable to adopt the universal use of this type of ETT, as recommended in recent UK guidelines [13••].

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A further intervention that has managed to reduce the incidence of VAP is the use of a silver-coated ETT [14••]. In a prospective, randomized, single-blind, controlled study conducted in 54 North American centers, lower rates of microbiologically confirmed VAP were reported in patients intubated with coated tubes for 24 h or longer (4.8 vs. 7.5%) with a relative risk reduction in VAP incidence of 35.9%. No significant differences were observed in the duration of intubation, ICU stay, hospital stay, mortality, and frequency and severity of adverse events. The benefit of the silver-coated ETT is independent of staffing conditions such that both CASS and the use of a silver-coated or antiseptic-coated ETT are recommended [1•].

Oral hygiene is of utmost importance to prevent VAP. In a prospective randomized trial performed in patients on mechanical ventilation, conventional oral care was compared with timed oral care involving an every 8-h toothbrushing regimen. This intervention caused a drop to zero in the VAP incidence within a week [15•].

Oral hygiene with chlorhexidine is presently recommended in all patients undergoing mechanical ventilation. In a recent randomized controlled trial (RCT) and meta-analysis, oral decontamination with 2% chlorhexidine solution achieved a significant decrease in the incidence density of VAP [16•].

Another protective measure against the development of VAP is the instillation of 8 ml of isotonic saline before tracheal suctioning. This simple measure rendered a significant decrease in VAP incidence when compared with aspiration without saline [17••].

Other preventive strategies evaluated in appropriate trials over the last year include the utilization of positive-end expiratory pressure (PEEP), the prone position during mechanical ventilation, and the use of closed rather than open endotracheal suction systems. PEEP (5–8 cmH_2O) in nonhypoxemic ventilated patients was shown to reduce VAP incidence (PEEP group 9.4%, control patients 25.4%) [18••]. Two recent meta-analyses suggest that the prone position during mechanical ventilation does not reduce mortality or duration of ventilation and should not be used routinely for acute hypoxemic respiratory failure. The two reports are, nevertheless, contradictory in their appreciation of the VAP incidence reduction [19••,20••]. The available evidence regarding closed tracheal suction systems (TSSs) suggests that closed as opposed to open TSS provides no beneficial effects on VAP incidence, mortality, or ICU stay. Suctioning with closed systems was even associated with longer mechanical ventilation duration and higher colonization of the respiratory tract [21•].

A multicenter crossover trial has just been published [22••] in which the authors examined through cluster randomization the effects of selective digestive tract decontamination (SDD) and selective oropharyngeal decontamination (SOD) on mortality in ICU patients. The 13 participating ICUs, all in The Netherlands, varied in size and teaching status. All eligible patients were assigned to one of three regimens (SDD, SOD, and standard care) over the course of 6 months. SOD involved oropharyngeal administration of tobramycin, colistin, and amphotericin B, whereas SDD involved topical application of the same antibiotics to the oropharynx and intravenous cefotaxime. Approximately, 2000 patients were enrolled in each of the trial's three arms. In a random-effects logistic-regression model with pertinent factors introduced as covariates, absolute reductions in mortality of 3.5 and 2.9% (relative reductions of 13 and 11%) were observed on day 28 for SDD and SOD, respectively, compared with 27.5% for the standard-care group. This was related to needed-to-treat numbers of 29 and 34 to prevent one casualty on day 28 for SDD and SOD, respectively. SDD and SOD showed a trend toward diminishing mechanical ventilation, ICU stay, and hospital stay, but the authors do not mention a reduction in the incidence of VAP.

A need has also been identified to standardize VAP surveillance and data collection allowing for longitudinal assessment of the care process. The uniform implementation of guidelines and accountability is also a firm recommendation [23–25,26•,27•].

Advances in diagnosis

There is scarce correlation between a clinical diagnosis of VAP based on clinical criteria and true VAP. Optimal diagnostic performance requires both clinical and microbiological data [28••].

Invasive strategies for sampling lower respiratory tract specimens have not returned better results than noninvasive strategies. The same can be said of quantitative vs. semiquantitative cultures in the etiological diagnosis or outcome of VAP. There is no evidence that the use of quantitative cultures of respiratory secretions reduces mortality, shortens ICU stay or time of mechanical ventilation, or leads to higher rates of antibiotic change when compared with qualitative cultures [29••,30••]. Notwithstanding, the main advantage of using quantitative cultures is that fewer patients may be treated with unnecessary antibiotics because it is possible to differentiate colonizing pathogens from infecting ones [31].

The 2008 Canadian guideline on the diagnosis and treatment of VAP recommends nonquantitative cultures on endotracheal aspirates as the initial diagnostic strategy

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Table 1 List of recommendations for ventilator-associated pneumonia prevention grouped as priority modules recently issued by the US Department of Health & Human Services

Priority module 1. Recommendations for routine care of patients requiring mechanical ventilation
Use noninvasive ventilation whenever possible
Use orotracheal rather than nasotracheal intubation when possible
Minimize the duration of ventilation; perform daily assessments of readiness to wean from ventilation
Prevent aspiration by maintaining patients in a semirecumbent position (30–45° elevation of head of bed) unless otherwise contraindicated
Use a cuffed endotracheal tube with an endotracheal cuff pressure of at least 20 cmH_2O and in-line or subglottic suctioning
Perform regular oral care with an antiseptic solution
Priority module 2. Recommendations for appropriate cleaning, disinfection, and sterilization of ventilator equipment
Whenever possible, use steam sterilization (by autoclaving) or high-level disinfection by wet heat pasteurization at >158°F (>70°C) for 30 min for reprocessing semicritical equipment or devices that are not sensitive to heat and moisture (category 1A)
Use low-temperature sterilization methods for equipment or devices that are heat-sensitive or moisture-sensitive (category 1A)
After disinfection, proceed with appropriate rinsing, drying, and packaging, taking care not to contaminate the disinfected items in the process (category 1A)
Priority module 3. Recommendations for appropriate maintenance of ventilator circuit and associated devices
Drain and discard any condensate that collects in the tubing of a mechanical ventilator, taking precautions not to allow condensate to drain toward the patient (category 1B)
Use only sterile fluid for nebulization and dispense the fluid into the nebulizer aseptically (category 1A)
Use only sterile (not distilled, nonsterile) water to fill reservoirs of devices used for nebulization (category 1A)

Adapted from [11•].

[29••]. However, the 2008 UK guideline warns against using endotracheal aspirates due to their low specificity [13••]. Our personal approach to the etiologic diagnosis of VAP is either endotracheal secretion aspiration followed by semiquantitative culture, with a cut-off value of at least 10^4 colony forming units (CFU)/ml or telescopic brush sampling and quantitative culture with a cut-off value of at least 10^3 CFU/ml. We concur, however, that the most recommendable diagnostic method for VAP is that which can be most rapidly performed and with which experience is greatest at each center.

Recent Society for Healthcare Epidemiology of America/Infectious Diseases Society of America (SHEA/IDSA) guidelines recommend Gram staining of endotracheal secretions [3••]. In our experience, Gram staining of endotracheal secretions in patients with suspected VAP is of high etiologic diagnostic value and is a good guide for its timely treatment. Notwithstanding, the medical literature is packed with variable data regarding the sensitivity (57–95%), specificity (48–87%), positive predictive value (47–78%), negative predictive value (69–96%), and accuracy (60–88%) of the Gram stain in managing the patient with VAP. In the Canadian study [32•], a retrospective correlation of endotracheal or bronchoalveolar lavage fluid Gram stains and final culture results was very poor.

Whether surveillance cultures can be used to predict future VAP episodes or to anticipate cause, allowing empirical therapy to be tailored, is uncertain. Studies both in favor and against the utility of surveillance cultures exist [33•,34•,35•,36•,37]. In a retrospective analysis of a RCT of different diagnostic and antibiotic strategies, there was poor agreement between cultures taken 1 to 3 days before suspicion of VAP and enrolment cultures performed on the day of suspicion of VAP [34•]. In our experience, surveillance cultures in patients undergoing heart surgery failed to predict VAP and we do not recommend their routine use [37]. Current European recommendations state that prior cultures should not be used to narrow the spectrum of empirically given antibiotics [6••].

The importance of a microbiological diagnosis of VAP lies not only in determining whether the patient has pneumonia, but also in optimizing antimicrobial treatment [6••]. To allow narrowing or deescalation of the initially prescribed antimicrobial agents, antimicrobial susceptibility data should be available as soon as possible. For this purpose, E-test strips applied directly to respiratory tract samples have proved both reliable and effective and expedite the availability of antimicrobial susceptibility data by more than 48 h [4,5].

The use of biomarkers is still an area in which much research work is needed. C-reactive protein (CRP) has been proposed as a diagnostic and prognostic marker and to assess the appropriateness of antibiotic therapy. Lisboa *et al.* [38•] found that a CRP ratio of 0.8 at 96 h of starting antimicrobial treatment is a useful indicator of antibiotic therapy appropriateness.

Treatment outcomes of VAP will be affected by the susceptibilities of infecting organisms and the time to first dose of antimicrobials [39•,40••]. Hence, the rapid detection of antibiotic-resistant bacteria should be pursued.

There is a real need for scores to predict VAP severity and mortality. One such score is the VAP PIRO system (Predisposition, Insult, Response, Organ dysfunction), based on four variables independently associated with mortality (presence of comorbidities, bacteremia, shock, and acute respiratory distress syndrome). One point is given for each of these features and higher scores allow stratification of patients according to the severity of their VAP episode [41•].

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Advances in treatment

At the time of writing this review (2009), treatment recommendations for hospital-acquired pneumonia including VAP have been issued by different organizations around the world [29••,42••].

Inappropriate antimicrobial treatment has been associated with excess mortality from pneumonia [8•,40••,43–45]. The choice of empirical antibiotic therapy in an individual unit should be based on knowledge of the nature and susceptibility patterns of prevalent pathogens and should also take into account variables such as length of hospital stay, recent administration of antibiotic therapy, and comorbidities [13••]. Defined risk factors for given pathogens and resistance patterns include age, structural lung disease, prior tracheobronchial colonization, and pneumonia severity [6••]. In the empirical treatment phase, the risk of a resistant Gram-negative bacillus suggests the use of combinations of anti-Gram negative drugs until the antimicrobial susceptibility of the microorganism is known [46,47••].

During guided therapy, current recommendations lean toward the use of an appropriate single agent for each potential pathogen [13••,29••,48••].

This last year was very productive regarding the use of antimicrobial agents in VAP. The effect of adding intravenous clarithromycin (intravenously once daily for 3 consecutive days) to the treatment regimen of patients with VAP and sepsis was assessed by Giamarellos-Bourboulis *et al.* [49••]. The clarithromycin group showed a shorter median time to VAP resolution and of weaning from mechanical ventilation compared with placebo-treated patients. The mortality rate at day 28 was unaltered. The mechanism of action of clarithromycin is unclear.

Pharmacokinetic and pharmacodynamic parameters for piperacillin/tazobactam suggest that a continuous daily dose of 16/2 g achieves serum concentrations above the 35–40 mg/l required for optimal efficacy and adequate alveolar levels in patients with normal renal function [50•].

Data also suggest that imipenem is more appropriately administered as a 2 h infusion of 0.5–1 g every 6 h rather than a bolus to obtain plasma concentrations above its minimum inhibitory concentration (MIC) of 4 mg/l for 60% of a 6 h interval [51•].

Doripenem, a new carbapenem with broad-spectrum activity against bacterial pathogens commonly responsible for VAP, was shown in two prospective clinical trials to be noninferior to piperacillin/tazobactam and imipenem, respectively, in the treatment of VAP [52•,53••]. Resource utilization comparing doripenem and imipenem favored doripenem [54•].

In a retrospective analysis of two prospective, double-blind, randomized studies of nosocomial pneumonia, linezolid (LZD) was associated with higher cure and survival rates than vancomycin (VAN) in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia [55–58]. A recently published prospective, open-label, multicenter clinical trial compares the efficacy of LZD and VAN in terms of the microbiological response observed in patients with MRSA VAP. The results of this trial indicate neither a significantly better microbiological outcome among patients treated with LZD for VAP compared with VAN nor differences favoring LZD therapy in all secondary clinical outcomes such as clinical response rates, time alive not receiving mechanical ventilation, or mortality [59•].

The safety of 'targeted therapy' (defined as the tailoring of antibiotics to the specific pathogens identified in the index culture or stopping antibiotics when index cultures are reported as negative) [60••] has been recently reinforced by Joffe *et al.* [7•] as part of a secondary analysis of data from a multicenter trial of 740 patients with suspected VAP. Thus, results for the targeted therapy group indicated more days alive and off broad-spectrum antibiotics, fewer mechanical ventilation days, and similar mortality compared with patients who did not receive targeted therapy.

Ventilator-associated tracheobronchitis (VAT) has been associated with an increased duration of mechanical ventilation. In a prospective, randomized, multicenter study, Nseir *et al.* [61••] showed that an 8-day course of antibiotics in patients with VAT significantly reduced the incidence of VAP and ICU mortality. However, antibiotic treatment had no significant impact on total duration of mechanical ventilation. In our own experience, untreated patients with VAT progress to VAP more frequently than those who receive early antibiotic therapy [37].

The use of aerosolized antibiotics in VAT patients was compared with aerosolized saline placebo for 14 days or until extubation. The antibiotics group showed reduced VAP incidence and Clinical Pulmonary Infection Score (CPIS), a lower white blood cell count on day 14, reduced bacterial resistance, and use of systemic antibiotics and increased weaning [62•].

Clinical trials have demonstrated that treatment duration can be safely shortened from the traditional 2-week courses [63], that antibiotic management protocols improve outcomes [60••,64], and that antibiotic discontinuation based on objective criteria reduces antibiotic

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use without adversely affecting clinical outcomes [65]. An 8-day regimen is nowadays probably standard for patients with VAP. Exceptions to this recommendation include pneumonia due to *Pseudomonas aeruginosa* or *S. aureus* (especially MRSA), immunosuppressed patients, those given inappropriate empirical antibiotic therapy, and patients with an infection caused by very difficult-to-treat microorganisms showing no improvement in clinical signs of infection [6••,39•,66,67]. Preliminary data suggest that in well documented VAP cases, 7 days of antimicrobial therapy may not be inferior to 10 days [68].

Finally, a failure to respond to initial antibiotic treatment in VAP is a serious event associated with excess adverse outcomes that should prompt an invasive diagnostic procedure to rule out multidrug-resistant pathogens. The results of a recent study in patients with VAP indicated that failure of the PaO_2/FiO_2 ratio and fever to improve by day 3 of treatment is independently associated with clinical failure [69•].

Conclusion

Approaches to preventing VAP rely on evidence-based strategies that minimize intubation, the duration of mechanical ventilation, and the risk of aspiration of oropharyngeal pathogens. Current recommendations are being reviewed to help acute care hospitals prioritize efforts to implement and monitor the most effective prevention measures. This review highlights the current gaps in our knowledge of VAP that need to be targeted by future research efforts, such as the role of ETT composition, the lack of a gold standard diagnostic technique, and the benefits and costs of universally adopting preventive measures such as subglottic suction or antiseptic-coated ETTs.

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

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 410–412).

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