Ventilator-associated pneumonia

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Purpose of review

Ventilator-associated pneumonia (VAP) is the main nosocomial infection in patients receiving mechanical ventilation. Despite numerous advances in the understanding of this disorder, the incidence rate continues in an unacceptable range. In this review, we discuss some important findings of recently published studies on diagnosis, prevention and treatment.

Recent findings

The microbiological sampling of the lower airways may be performed by invasive or noninvasive methods. The use of blind techniques to sample the lower respiratory tree has gained wide acceptance within the critical care setting. The use of cytological parameters such as the percentage of infected cells (cells containing phagocytised bacteria) may add objectivity to the unspecific clinical suspicion of VAP. A lot of information on the subject of prevention of VAP has been published recently that evaluates several preventive measures including new antiseptic-coated endotracheal tubes, new cuff shape and meta-analysis of known techniques. However, the clinicians must choose a bundle of measures and implement them in their intensive care units. The effectiveness of the bundles must be documented. New studies emphasize the key role of an appropriate empirical treatment. The de-escalation strategy increases the reduction of antimicrobials without worsening the outcome of VAP patients. The efficacy of monotherapy in the treatment of this infectious disease has been evaluated in new studies with controversial results. The diagnostic approach and therapy of the VAP patients are clarified with these studies.

Summary

In the last year, numerous articles have been published on diagnosis, treatment and prevention of VAP. In this review, we have selected those articles that potentially could lead to changes in clinical practice: Use of noninvasive techniques for diagnosis, new methods and strategies for prevention, and, finally, the efficacy of monotherapy and de-escalation in the treatment of VAP.

Keywords

diagnosis, pneumonia, prevention, treatment

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Introduction

Ventilator-associated pneumonia (VAP) is the main nosocomial infection in patients receiving mechanical ventilation [1]. Actually, it is not 'associated' with the ventilators but with the artificial airways (endotracheal tubes and tracheostomies cannulae). VAP is related with an increased duration of mechanical ventilation, ICU and hospital length-of-stay; and increased healthcare costs [2,3]. Additionally, patients who develop VAP may have an increased attributable mortality around 30% [2]. This variable is not decreasing despite many advances in this field and the incidence rate of this infection continues in unacceptable values. We will discuss some of the most important recent findings on the diagnosis, prevention and treatment of VAP published lately.

Diagnosis

The first step in the diagnosis of VAP is clinical suspicion. The most accepted clinical definition for suspicion of pneumonia is currently the presence of a pulmonary infiltrate on chest radiograph plus two of the following three criteria: leukocytosis or leukopenia, purulent respiratory secretions and fever or hypothermia [4]. Unfortunately, this approach has good sensitivity but poor specificity. The next step is to obtain samples of the lower respiratory tract for microbiological tests. For several

years now, the superiority of invasive (bronchoscopic) vs. noninvasive (endotracheal aspirate) sampling techniques in the diagnostic yield of patients with suspected VAP and the utility of quantitative vs. qualitative cultures have been under debate [5]. An interesting article published by the Canadian Critical Care Trials Group evaluated the optimal diagnostic approach in these patients [6]. They performed a multicenter trial randomizing 740 patients to undergo either bronchoalveolar lavage (BAL) with quantitative cultures or endotracheal aspiration with nonquantitative culture of the aspirate. The most important result was that they did not find significant differences in the primary outcome (28-day mortality rate) between the two groups (18.9 and 18.4%, respectively; $P = 0.94$). The rates of targeted therapy were also similar in both groups (74.2 and 74.6%, respectively; $P = 0.90$), so were days alive without antibiotics and maximum organ-dysfunction scores. The two groups also did not differ significantly in the length of ICU or hospital stay. The time from clinical suspicion of VAP to initiation of AB was slightly longer in the BAL group. However, this trial had important drawbacks that deserve consideration. It has a lot of exclusion criteria. This population may not be representative of the current critical care patient. And mainly, they excluded patients infected or colonized with *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus*.

In regard to invasive techniques, some authors have suggested sampling both lungs to increase the accuracy of BAL. Jackson *et al.* [7•] assessed this topic in patients with clinical suspicion of VAP performing bilateral BAL. Samples were concordant if the organism(s) and the thresholds from both lungs were diagnostically consistent and results with an increase above the threshold in one lung and under the threshold in the other were considered false-negative samples. They found that 64% of VAP patients had concordant samples. An important finding was that the sole use of unilateral samples to guide treatment inappropriately directed antibiotic avoidance or discontinuation in 25% of VAP patients or both. It is important to remember that some evidence has shown that VAP is a multifocal disease and frequently affects both lungs. One limitation of this approach may be the possibility of inoculating a healthy lung with the bronchoscope after sampling the infected lung.

Nowadays, the use of blind techniques to sample the lower respiratory tree has gained wide acceptance within the critical care setting [8]. Leo *et al.* [9•] performed a prospective study to compare the results of blind lavage vs. bronchoscopic-guided BAL for the etiologic diagnosis of VAP. They included 25 patients and performed the blind sampling with a modified nasogastric tube. Paired comparison of quantitative cultures was made in 21 patients with only two patients having discordant cultures. The correlation coefficient between the number of colonies was very high, being $r = 0.90$ ($P = 0.0001$). This study confirms that the diagnostic yield of blind BAL is as bronchoscopic-guided lavage [10]. There are currently several catheters that have been validated to perform blind sampling and may be directed to a specific lung to thereby increase the diagnostic yield. These techniques are very valuable in an ICU without a bronchoscopist available around the clock.

On performing the sampling of lower respiratory tract secretions for cytological and microbiological diagnosis of patients with VAP, it is very important to take the introduction of new antibiotics within the previous 72 h into account, as this may affect the diagnostic yield of these tests. In this regard, the study published by Linssen *et al.* [11•] involving 335 episodes of clinically suspected VAP showed that the introduction of antibiotic therapy 72 h prior to BAL did not influence the predictive value of several BAL fluid cytological parameters such as total cell count per millilitre, differential cell count and the percentage of infected cells (cells containing phagocytised bacteria). The AUC for the percentage of infected cells in diagnosing VAP was 0.90 and this value did not increase when combined with other cytological parameters. The percentage of intracellular organisms, with a cut-off varying between 2 and 5%, has a high specificity for the diagnosis of VAP [12], and this study provides more validity of this test on demonstrating that it is not affected by the use of previous antibiotics such as in what occurs with bacteriologic tests.

Clinical suspicion of VAP is currently considered a good starting point but requires more precise confirmation to avoid the abuse of antibiotics or delays in treating VAP. At present, it does not seem to be necessary to perform invasive techniques in all patients to obtain samples of lower respiratory tract secretions, as the endotracheal aspirate or blind techniques provide a similar diagnostic yield, mortality and use of antibiotics. However, precaution should be the rule in patients in whom colonization or infection by potentially multiresistant microorganisms is probable. The aid of cytological parameters such as intracellular organism count to achieve the diagnosis is useful and has the advantage of being little influenced by the previous use of antibiotics in contrast to what occurs with other microbiologic techniques.

Prevention

In a disease with such a high incidence and with such an important impact on the mortality and morbidity of patients such as VAP, measures aimed at prevention provide a great advantage in comparison with treatment. In the last years, many trials have assessed several measures of VAP prevention that may be grouped into

pharmacological and nonpharmacological measures. However, the strategies to improve airway care have gained a major development due to their efficacy, feasibility and low cost. Passive humidifiers (heat and moisture exchangers) have gained wide acceptance in the current critical care clinical practice; however, there is no consensus on their superiority in terms of VAP prevention, length of stay and mortality compared with active humidifiers (heated humidifiers) [13]. A meta-analysis published a few months ago including 13 randomized controlled trials and studying 2580 patients evaluated this topic [14••]. The authors did not find any significant differences in terms of VAP incidence [odds ratio (OR) 0.85, 95% confidence interval (CI) 0.62–1.16], mortality (OR 0.98), length of ICU stay or duration of mechanical ventilation or episodes of airway obstruction. Although these data are now available, we prefer the passive system to humidify the airway of mechanically ventilated patients due to the relative low cost, technical ease and the absence of condensates in the circuits. Heated humidifiers may be preferable in patients with copious respiratory secretions, abundant hemoptysis or in those with a tendency to atelectasias.

In regard to the system to suction the airway secretions in mechanically ventilated patients (open vs. closed tracheal suction system), a meta-analysis of randomized controlled trials found no difference in the incidence of VAP between patients managed with closed or open tracheal suction systems (OR 0.96, 95% CI 0.72–1.28) [15•]. Similar results were found with respect to mortality or length of ICU stay. These data confirm results of a previous Cochrane database review in which the authors found no significant difference between these suction systems either [16]. The influence of these suction systems in maintaining lung volume and episodes of lung derecruitment remains to be defined. Previous studies have found a possible advantage of the closed system in terms of derecruitment [17]. Additionally, the closed suction system may be useful in patients infected with multidrug resistant respiratory pathogens such as MRSA or *Mycobacterium tuberculosis*.

In relation to the physiopathology of VAP, microaspiration of contaminated subglottic respiratory secretions around the endotracheal tube cuff plays a very important role. These secretions have a high bacterial load and consequently their access to the pulmonary parenchyma could cause pneumonia. To avoid this event, continuous or intermittent subglottic secretion suction systems have been developed [18]. Nonetheless, although these systems seem to be effective in preventing mainly early-onset VAP, they may not prevent late-onset pneumonia [19]. Likewise, new materials have been developed for the endotracheal tube cuff. One of these materials is *polyurethane, which on being thinner than the polyvinyl* cuff, avoids the leakage of secretions along the cuff [20,21]. An elegant study published by Lorente *et al.* [22••] assessed the efficacy of an endotracheal tube with polyurethane cuff and subglottic secretion suction (Seal-Guard Evac endotracheal tube; Mallinckrodt Medical, Athlone, Ireland) vs. a conventional endotracheal tube with a polyvinyl cuff and without subglottic suction in patients expected to require mechanical ventilation longer than 24 h. They randomized 140 patients in each arm and the diagnosis of VAP was established with quantitative culture of tracheal aspirates. VAP was found in 31 of 140 (22.1%) patients in the conventional cuff group and in 11 of 140 (7.9%) patients in the polyurethane cuff and subglottic secretion suction group ($P=0.001$). Cox regression analysis showed that conventional tubes were a risk factor for global VAP [hazard ratio (HR) 3.3; $P=0.001$], early-onset VAP (HR 3.3; $P=0.02$) and late-onset VAP (HR 3.5; $P=0.01$). This topic deserves several considerations: the cost of these new tubes, which would make them the first choice in patients with high risk. It remains unclear whether the best way to perform subglottic suction is in the continuous or intermittent form as undertaken in this study [18,23]. The systems of suction may dysfunction due to aspiration of tracheal mucosa or occlusion of the system [24]. In any case, it seems to be an effective preventive measure that combines two airway care techniques but which should be validated in other studies.

We know that bacterial colonization and biofilm formation on the inner surface of the tracheal tubes is a risk factor for VAP [25]. Coating an endotracheal tube with silver is a modification to the classical endotracheal tubes. Silver has broad-spectrum antimicrobial activity *in vitro*, reduces bacterial adhesion to devices *in vitro* and blocks biofilm formation on the device in animal models. Kollef *et al.* [26••] performed a multiple-center, prospective, randomized, single-blind, controlled study to determine whether a silver-coated endotracheal tube would reduce the incidence of microbiologically confirmed VAP. They randomized a total of 2003 patients expected to require mechanical ventilation for 24 h or longer. Among patients intubated for 24 h or longer, rates of microbiologically confirmed VAP were 4.8% (37/766 patients) in the group receiving the silver-coated tube and 7.5% (56/743) ($P=0.03$) in the group receiving the uncoated tube, with a relative risk reduction of 35.9%, an absolute risk reduction of 2.7%. The silver-coated endotracheal tube was associated with delayed occurrence of VAP ($P=0.005$). No statistically significant between-group differences were observed in durations of intubation, ICU and hospital stay, mortality, and frequency and severity of adverse events. Coated surfaces are used in different clinical scenarios to decrease device-related infections as in endovascular catheters and have demonstrated their efficacy [27]. This study had *some limitations: first, the low incidence of VAP in the*

included population; second, the investigators were not blind; and finally, the uncoated group has a statistically significant higher proportion of patients with preexisting chronic obstructive pulmonary disease. Again, this measure may be recommended for the subset of patients at a very high risk of developing VAP. The benefits for patients requiring prolonged mechanical ventilation are not clear.

Nowadays, the use of 'bundles' (group of measures) to improve several healthcare procedures is very common. In this sense, the 'VAP prevention bundle' should include some basic preventive measures to decrease the rate of VAP. These measures could include (but not limited) semi-recumbent position, oropharyngeal decontamination with disinfectants, control of the endotracheal cuff pressure, hand hygiene, staff education, adequate nurse/patient staffing ratios, microbiological surveillance and antibiotic control policies, no change of ventilator circuits and standardized protocols for sedation and weaning. These measures are not expensive and most could be easily applied in the intensive care unit. It should be remarked that the benefit of this bundle is not in the short term. Effective prevention programs need constant effort, may increase the initial costs, but they will bring a higher healthcare quality and a reduction in the costs.

Treatment

The success in the overall management of VAP requires an appropriate diagnosis and treatment strategies. The key actions for diagnosis and treatment are as follows:

(1) Use clinical parameters to suspect VAP
(2) Obtain lower airways secretions for stains and cultures before antibiotic treatment
(3) Do not delay antimicrobial therapy to perform sampling techniques
(4) Use bronchoscopic or noninvasive techniques to sample the airways
(5) Quantitative or semi-quantitative cultures are useful to distinguish colonization from infection
(6) Biomarkers (C-reactive protein, procalcitonin) may help in the diagnosis and follow-up
(7) Initiate early and appropriate empirical antimicrobial therapy
(8) Apply de-escalation strategies
(9) Short course of antimicrobial therapy (most patients)
(10) Consider mono-antimicrobial therapy

One of the aspects of greatest importance in the treatment of VAP is currently the need to initiate empiric treatment early with adequate and appropriate antibiotics. This has been associated with a significant reduction in the mortality and rate of complications [28,29]. To this respect, Kuti *et al.* [30•] performed a meta-analysis of VAP studies using unadjusted and adjusted data and found that inappropriate therapy significantly increased the odds of mortality (OR 2.34, $P=0.0001$; OR 3.03, $P=0.0292$, respectively). This study reaffirms the importance of an early appropriate empirical antimicrobial treatment. This isolation of *P. aeruginosa* or multidrug-resistant microorganisms reduces the probabilities of a patient receiving adequate treatment in comparison with those in whom these pathogens are not isolated [31].

The practical implications involved in ensuring adequate and appropriate treatment at the beginning are the need to use broad-spectrum antibiotics and combinations of these in the empiric therapy. Carrying out surveillance cultures and the results of cultures prior to the suspicion of VAP may aid in predicting the presence of multidrug-resistant organisms or in guiding the antibiotic regimen to be used in a patient. It should, however, be taken into account that the concordance between the previous cultures and those performed on suspicion of VAP varies between 55 and 71%, and thus, does not ensure 100% adequate coverage of the empiric treatment [32,33•]. However, these schemes could lead to overuse of and resistance to the antimicrobials.

De-escalation therapy is a strategy developed to decrease the use of antibiotics without worsening the outcome of the patients. It consists in the shortening of the spectrum, decreasing the number, limiting the duration or the discontinuation of antibiotic therapy based on the results of microbiological cultures. Joffe *et al.* [34••] performed a study to determine the safety of targeted antibiotic therapy (TT) in VAP (de-escalation strategy). This was a secondary analysis from a multicenter trial of 740 patients with suspected VAP randomized to bronchoscopy or endotracheal aspirate cultures; all received empirical broad-spectrum antibiotics. Patients were grouped by whether they received TT, defined as tailoring or discontinuing antibiotics in response to enrolment culture results. For patients with a positive culture ($n=412$), baseline demographics, clinical progression of infection and multiple organ dysfunction scores (MODSs), and mortality were similar for those on TT ($n=320$) or those who did not receive TT (NoTT) ($n=92$). The TT group had more days alive and off broad-spectrum antibiotics (14.5 vs. 13.2, $P=0.04$). In patients with a negative culture ($n=327$), those on TT had similar baseline demographics, less frequent final adjudicated diagnosis of VAP (63.0 vs. 76.3%, $P=0.02$), and less severe clinical progression of infection and MODSs compared with NoTT. The TT group had more days alive and off broad-spectrum antibiotics, lower delta MODSs, fewer mechanical ventilation days, and similar

mortality compared to NoTT. Several aspects such as the protocol to follow in patients with negative cultures or those with an infection by nonfermentative Gram-negative bacteria (GNB), such as *P. aeruginosa*, remain to be defined in the de-escalation strategy. Another method of de-escalating the treatment is limiting the duration of this treatment, which may be reduced to 8 days in most patients [35].

On the contrary, we now have some evidence showing that de-escalation therapy rates rise higher by bronchoalveolar lavage than by tracheal aspirate. Giantsou *et al.* [36] assessed this issue in 143 patients who were assigned to de-escalation therapy by BAL or tracheal aspirate. Of the 81 patients assigned to tracheal aspirate, 17 were de-escalated in comparison with 41 of 62 patients assigned to BAL.

The treatment guidelines of scientific societies have traditionally recommended an initial empiric therapy scheme that includes combination therapy against potentially multiresistant GNB (*P. aeruginosa*, *Acinetobacter baumanii*, etc.). One meta-analysis did not find any benefits with combined therapy in patients with bacteraemia, but it was based on studies with old antibiotics, suboptimal use of aminoglucosides [twice daily (b.i.d.) vs. once a day] and comparison with different beta-lactams in each arm [37]. A Spanish multicenter study performed to evaluate whether one antibiotic achieves equal outcomes compared with combination antibiotic therapy in patients with VAP analyzed a total of 183 episodes of monomicrobial *P. aeruginosa* pneumonia [38•]. Monotherapy alone was used empirically in 67 episodes, being significantly associated with inappropriate therapy (56.7 vs. 90.5%, $P < 0.001$). The use of monotherapy or combination therapy in the definitive regimen did not influence mortality, length of stay, development of resistance to the definitive treatment or the appearance of recurrences. In a Cox proportional hazard regression analysis, effective monotherapy was not associated with increased mortality after adjustment for disease severity compared with effective combination therapy (adjusted HR 1). The objective of a study by the Canadian Critical Care Trials Group [39••] was to compare a strategy of combination therapy with a strategy of monotherapy with broad-spectrum antibiotics for suspected late VAP, but they excluded patients known to be colonized or infected by *Pseudomonas* or methicillin-resistant *S. aureus*. As the initial unblinded therapy, patients were allocated to receive meropenem (1 g every 8 h) and ciprofloxacin (400 mg every 12 h) or meropenem alone. There was no difference in 28-day mortality between the combination and monotherapy groups (relative risk = 1.05, $P = 0.74$). Duration of ICU and hospital stay, clinical and microbiological treatment response, emergence of antibiotic-resistant bacteria, isolation of *Clostridium difficile* in stool and fungal colonization were also similar in the two groups. However, in a subgroup of patients with infection due to *Pseudomonas* spp., *Acinetobacter* spp. and multidrug-resistant Gram-negative bacilli at enrollment ($n = 56$), the adequacy of initial antibiotics (84.2 vs. 18.8%, $P < 0.001$) and microbiological eradication of infecting organisms (64.1 vs. 29.4%, $P = 0.05$) was higher in the combination group than in the monotherapy group, but there were no differences in clinical outcomes. Until more convincing data are available, we advocate for the initial use of combination therapy against potentially multidrug-resistant microorganisms, especially *P. aeruginosa*. This combination may be switched to monotherapy after 5 days of treatment.

Conclusion

VAP is a very important infection in patients admitted to the ICU. The diagnosis of this entity continues being very worrisome. We do not have any gold standard yet. The new data enable us to use invasive or noninvasive diagnostic methods to sampling the lower airways. Indeed, the blind methods like mini-BAL may have similar diagnostic yield like bronchoscopic techniques. However, the diagnostic technique must no delay the initiation of the empirical AB therapy. We encourage using quantitative cultures of respiratory secretions instead of qualitative because they may discriminate better between colonization and infection. The prevention of VAP is a key factor in the current critical care practice. There are a lot of measures evaluated lately. In our opinion, every ICU must implement bundles to decrease the incidence of VAP based on actual literature. The effectiveness of the bundles must be documented. Therefore, epidemiological surveillance plays a key role. We recommend initiating an early empirical antibiotic treatment in patients suspected of VAP. The mortality of VAP patients is related to the appropriateness of the treatment. Hence, every effort should be done to keep under surveillance the microbiology of the ICU. The de-escalation therapy is a useful strategy to limit the antibiotic use without compromising the security of patients. Until more convincing data are available, we advocate for the initial use of combination therapy against potentially multidrug-resistant microorganisms, especially *P. aeruginosa*.

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. 71–72).

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