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Ventilator Associated Pneumonia in Critically Ill Patients: Prevention and Treatment

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Ventilator associated pneumonia (VAP) represents a major threat to the recovery of patients receiving mechanical ventilation, and is a difficult diagnostic and therapeutic challenge for critical care physicians. VAP occurs in 5-25% of all patients with different varieties of respiratory failure, and its incidence exceeds 70% in patients who die of adult respiratory distress syndrome (ARDS).

The microaspiration of bacteria from the oropharynx is an important step in the pathogenesis of VAP; colonization of a patient's oropharynx with multi-resistant nosocomial pathogens does not make the problem easier to solve. There are several endogenous and exogenous factors behind oropharyngeal colonization and despite several preventive measures and efforts to find a solution are continuing. Recent studies on VAP have demonstrated that *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, Enterobacter spp. and *Escherichia coli* are the leading pathogens but anaerobes have also been isolated in levels of up to 30%.

Conventional criteria for the diagnosis of VAP include: new or progressing pulmonary infiltrate findings as well as fever leukocytosis and purulent tracheal secretions. However, none of these signs are very sensitive or specific. Therefore, for the above reasons, prevention and therapy are considered essential (1).

I. Prevention

Because VAP has been associated with increased morbidity and mortality and greater costs, prevention remains an important goal for all intensivists.

Preventative strategies can be divided into five main categories:

Identification and "control" of risk factors

Classic infection control measures

Strategies aiming to limit airway colonization

Strategies that improve host defense mechanisms

Other measures

1. Identification and "control" of risk factors

Various risk factors for VAP have been identified. They include old age, severity of injury or illness, length of hospital stay prior to ICU admission, duration of mechanical ventilation or length of ICU stay, supine body position, and type of comorbidity. Underlying chronic cardiorespiratory disease, neurologic injury and trauma as well as prior administration of corticosteroids and prior inappropriate antibiotic treatment also predispose patients to VAP. Identification of potentially modifiable risk factors for VAP at the institutional level and development of strategies to modify or prevent the occurrence of these risk factors is a significant preventive measure. Although risk factors for acquiring VAP have been well defined, diagnosis of VAP remains controversial and its actual incidence appears to be unchanged over the past two decades (2-5). As a result, patients are often treated empirically with antibiotic regimens based on suspected pathogens.

2. Classic infection control measures

Prevention of VAP relies on basic infection control practices. General infection control measures remain the cornerstone of infection prevention in intensive care units. Furthermore, hand washing remains the cornerstone of ICU-acquired infection prevention, and it is a simple but very effective preventive measure. In addition, infection control programs employing combinations of interventions aimed at preventing both colonization of the aerodigestive tract with pathogenic bacteria and aspiration have been shown to be successful and cost effective.

3. Strategies limiting airway colonization

Colonization of the oropharynx with pathogens and ongoing aspiration seem to be required for the development of VAP. Oropharyngeal colonization is pivotal in the pathogenesis of VAP, while gastric and intestinal colonization appear to be less important than previously believed. Oropharyngeal colonization with several pathogens and micro-aspiration of colonized oropharyngeal secretions is a major cause of early-onset VAP. Prolonged mechanical ventilation (>5 days) and administration of broad-spectrum antibiotics increase the risk for late-onset VAP, which is more likely to be related to Gram-negative bacteria.

Realization that the pathogenesis of VAP requires aspiration of contaminated secretions, originating from the aerodigestive tract and ventilator circuit, helps highlight the role of cross-infection and the importance of standard infection control procedures.

Many specific strategies interfering with colonization have been studied. So far, only the use of topical non-absorbable antibiotics, either of the whole digestive tract or the oropharynx, has been proven successful in decreasing the incidence of VAP. However, the effect on patient survival was disappointing. In addition, there is risk of selecting antibiotic-resistant bacteria. For these reasons, the widespread use of these strategies is limited (6).

3.1 Subglottic secretion drainage

There are reports that the use of endotracheal tubes with the possibility of intermittent or continuous aspiration of subglottic secretions led to a significantly lower incidence of VAP in patients receiving prolonged (>72 h) mechanical ventilation (7,8). Unfortunately, the mortality rate and lengths of stay in the ICU and hospital did not appear to be significantly influenced by the use of this intervention.

Despite the large volume of extant literature, many questions remain unanswered. Which patients benefit from continuous subglottic suctioning? Do certain surgical procedures predispose patients to VAP more than others? Furthermore, much research has generally been in the form of single reports that need to be replicated in larger multicenter trials. For this reason, further studies are warranted to confirm the efficacy of this system.

3.2 Pharmacologic strategies aiming to reduce colonization of the aerodigestive tract with pathogenic bacteria

Aerosolized antibiotics

Wood et al. administered aerosolized ceftazidime (250 mg every 12 hours) or placebo (normal saline) for up to 7 days. The frequency of VAP in patients receiving aerosolized ceftazidime was 73% lower than that in patients receiving placebo at ICU day 14 (15% vs. 55%, P = 0.02), and 54% lower for the entire ICU stay (30% vs. 65%, P = 0.02) (9).

Biofilm formation routinely occurs on endotracheal tubes and is considered an important factor promoting the occurrence of VAP. Unfortunately, there are no current interventions that have the ability to prevent biofilm development on the endotracheal tube as well as within the airways of patients receiving mechanical ventilation.

Adair et al. compared the efficacy of nebulized gentamycin (80 mg in 4 ml of normal saline every 8 h), with that of parenteral cefotaxime or cefuroxime in preventing the formation of endotracheal tube (ET) biofilm. Nebulized gentamycin attained high concentrations in the ET lumen and was more effective in preventing the formation of biofilm than any parenterally administered cephalosporin and therefore may be effective in preventing VAP in mechanically ventilated patients (10).

Chemicals aimed at blocking gene products from bacteria forming biofilms, antibodies blocking adhesion of bacteria, via fibronectin-binding protein, and the use of specialized coatings blocking bacterial adherence may offer the possibility to block biofilm formation in the endotracheal tubes in mechanically ventilated patients and reduce the incidence of VAP.

In a recent study, mechanically ventilated trauma patients who selectively received local decontamination for the subglottic area, using a continuous infusion of a suspension containing three non-absorbable antibiotics (polymyxin, tobramycin, and amphotericin B), developed VAP at a lower rate compared to controls (11).

4. Strategies that improve host defense mechanisms

Early nutrition is the most important strategy aiming to improve host defense mechanisms. Immunostimulatory therapies, such as interferon and granulocyte colony stimulating factor, require further research to confirm their role in the prevention and/or management of VAP (12).

5. Other preventive measures

5.1 Chest physiotherapy

Chest physiotherapy in ventilated patients is independently associated with a lower incidence of VAP. This suggested benefit of physiotherapy in the prevention of VAP requires confirmation by a larger randomized controlled trial (13).

5.2 Stericath closed suctioning system

There are reports that the use of Stericath reduced the incidence of VAP without demonstrating any adverse effects (14).

5.3 Strategies attempting to decrease the occurrence of aspiration: Positioning of patients in a semirecumbent position

When possible, patients receiving ventilation should be positioned at a 45° head-up angle to decrease the risk of the aspiration of gastric contents.

5.4 Kinetic beds

Modalities, such as rotating or kinetic beds, early bronchoscopy, and changes in ventilator management, have not been shown to be useful (15). In addition, studies of "early" tracheostomy have been unable to define both the optimal timing of tracheostomy and its effect in decreasing VAP.

5.5 Circuits - humidifiers

Several studies have reported no change in VAP rates when circuits are only changed on an at-needed basis. There is also evidence that passive humidifiers and closed suction catheters do not need to be changed on a daily basis.

5.6 Selective digestive decontamination (SDD)

Selective digestive decontamination is associated with a reduction in the incidence of VAP, but the mortality rate remains largely unaffected, while the selection of antibiotic-resistant pathogens is a potential disadvantage. SDD remains controversial despite more than 30 prospective randomized trials and 6 meta-analyses. Routine SDD in ICU is discouraged. SDD is contraindicated in ICUs with endemic resistant strains, while decontamination of the oropharynx appears to be equally effective (16).

5.7 Stress ulcer prophylaxis

In a recent study, no difference in the incidence of VAP, macroscopic stress ulcer bleeding or mortality was found between mechanically ventilated pediatric patients treated with ranitidine, omeprazole or sucralfate for stress ulcer prophylaxis and other subjects not receiving the same treatment (17).

5.8 Non-invasive ventilation

Several studies have demonstrated that non-invasive ventilation reduces the incidence of nosocomial infections, including VAP, and antibiotic use, compared to conventional mechanical ventilation (18,19). Non-invasive ventilation comes closest to accomplishing prevention of both colonization of the aerodigestive tract with pathogenic bacteria and aspiration.

II. Treatment

Once VAP develops, treatment is usually supportive along with the administration of antibiotics.

Antibiotic Therapy of Ventilator-Associated Pneumonia Initial empiric therapy

Several studies have emphasized the importance of early antibiotic therapy in the management of patients with clinically suspected VAP (20,21). Other studies have shown that patients who are initially treated inadequately had poorer outcomes than did those receiving adequate therapy at the beginning. Clinicians, therefore, are faced with the following options: first, to treat all patients with suspected VAP early, preferably with a combination of broad-spectrum antibiotics at high doses, in order to cover the most likely causative microorganisms and overcome potential resistance problems. Alternatively, a

more conservative policy can be followed at the risk of exposing some ICU patients to a delay in therapy or inadequate treatment.

There are actually two challenges for intensivists: first, to decide when and which patient should be treated, and second to select which antibiotics to prescribe empirically. For the first challenge, Singh et al. propose a strategy by which all patients with suspected VAP are treated empirically with one antibiotic (e.g., ciprofloxacin) (22). After 3 days of therapy, it is withdrawn in all patients with a low likelihood of pneumonia, as assessed by the clinical pulmonary infection score (score <6). This approach, while treating all patients with suspected VAP, has the merit of limiting the administration of unnecessary antibiotic therapy. A more sophisticated approach of administering antibiotics in a patient with suspected VAP is to combine clinical data (fever and purulent tracheal secretions) and laboratory data (pulmonary infiltrates, leucocytosis and hypoxemia) with the results of direct examinations (Gram stain) from bronchial secretions or from bronchoalveolar lavage samples.

For the second challenge, the selection of initial appropriate antibiotic therapy appears to be an important determinant of clinical outcomes. However, there is a critical question: how should the selection of empiric antibiotic therapy proceed? Although ciprofloxacin was effective in the study performed by Singh et al., this choice can be questioned. Although ciprofloxacin is usually effective against enterobacteriaceae, Haemophilus influenza, and some Staphylococcus spp., it is ineffective against streptococci, *Pseudomonas aeruginosa* and Acinetobacter.

In a recent study, Fowler et al. suggested that piperacillin-tazobactam could be the most appropriate empiric therapy for suspected VAP. The favorable results associated with piperacillin-tazobactam (possibly in combination with an aminoglycoside), especially in patients with suspected late-onset pneumonia, have been due to its broad spectrum of activity, or to a lower level of resistance emergence and superinfection during or after therapy. However, the authors did not demonstrate improved outcomes associated with appropriate vs. inappropriate therapy, or with combination therapy vs. monotherapy (23). Evidence-based guidelines suggest that piperacillin-tazobactam may be the most effective single agent for the empiric treatment of VAP (24).

Several clinical trials compared piperacillin-tazobactam with ceftazidime (both in combination with an aminoglycoside) and found that the former was at least as effective as the latter (25,26). Thus, could piperacillin-tazobactam be considered a standard therapy for all patients with clinical suspicion of VAP? Or, is it better to follow an individualized antibiotic strategy according to the specific condition and risk factors in combination with specific institutional epidemiological surveillance and resistance patterns?

According to the guidelines of the American Thoracic Society, the initial antibiotic therapy should be based on specific risk factors that influence the spectrum of causative microorganisms in patients with VAP (27). In patients with a high probability of infection due to multiresistant bacteria, such as in late-onset pneumonia, in those who have received prior antibiotic treatment, or in those who have had prolonged ICU stay before developing VAP, a combination antimicrobial therapy is recommended with antibiotics active against *Pseudomonas aeruginosa*, Acinetobacter spp., and possibly methicillin-resistant *Staphylococcus aureus* (MRSA). Some patients may be changed to monotherapy, based on clinical response and the results of pertinent cultures available at days 2 and 3.

Several other approaches have been proposed, mainly based on the use of specific diagnostic techniques, resulting in the treatment of fewer patients with clinically suspected VAP (28). The selection of antibiotic regimen is mainly based on the timing of VAP onset in reference to the start of mechanical ventilation, prior antibiotic use during the current hospitalization, results of appropriate diagnostic tests, as well as the most common bacterial pathogens isolated, and the antimicrobial resistance pattern of the specific ICU (29). Prescribing an initial broad-spectrum antibiotic regimen in order to cover all likely pathogens may result in improved clinical outcome. Initial combinational antimicrobial therapy, particularly aimed against antibiotic-resistant Gram-negative bacteria (e.g., *Pseudomonas aeruginosa* and Acinetobacter spp.) and MRSA, offers the greatest likelihood of providing adequate initial treatment. However, unless supported by appropriate cultures, such broad-spectrum antibiotic regimens should not be administered unnecessarily for a prolonged period in order to avoid the emergence of antibiotic-resistant infections.

Some authorities suggest that it is necessary to keep unit-specific microbiological data to guide the empiric therapy of suspected VAP. The use of unit-specific microbiological information can potentially influence antibiotic prescriptions in order to reduce the administration of inadequate or ineffective antimicrobial treatment. Thorough knowledge of ICU antibiotic resistance patterns should be available and applicable when choosing empiric therapy and awaiting culture results. If initial broad-spectrum therapy is to be instituted, its de-escalation is also imperative once microbiological and clinical response data become available (30).

If empiric therapy is administered by means of highly effective bactericidal agents, the emergence of resistance could theoretically be minimized. The Center for Disease Control and Prevention suggested that the optimization of antibiotic use can be enhanced by education about appropriate antibiotic use and by providing data to physicians about the resistant organisms seen in their own ICU, as part of an ongoing surveillance program, aimed to minimize the risk of antibiotic resistance.

Distinction of VAP

There are three important determinants that can be used to guide the selection of empirical therapy in patients with suspected VAP: the timing of onset of VAP relative to hospital admission (early vs. late VAP); the prior administration of antibiotics; and specific institutional epidemiological data. The distinction between early VAP (within the first 5 ICU days) and late-onset pneumonia is a major determinant of the etiology, provided that the patient has no recent hospitalization. According to a recent American Thoracic Society consensus statement, the pathogens usually involved in early-onset VAP are Haemophilus influenza, methicillin - sensitive *Staphylococcus aureus* (MSSA), and Streptococcus pneumoniae, and anaerobes (in selected circumstances). In this situation, a second-generation cephalosporin or a combination of ampicillin or amoxycillin with a β-lactamase inhibitor will suffice.

If the patient develops late-onset VAP or has received broad-spectrum antibiotics, the most likely pathogens are Klebsiella, Enterobacter, Acinetobacter, *Pseudomonas aeruginosa* or MRSA, all of which are likely to be resistant to most antibiotics administered (31). In this instance, it is very difficult to predict the microorganisms that may be involved and their susceptibility profile. For this reason, a combination of one antipseudomonal penicillin plus a β-lactamase inhibitor, or aztreonam with an aminoglycoside or fluoroquinolone, or a three-agent combination empiric therapy with a β-lactam, an aminoglycoside, and vancomycin or teicoplanin for severely ill patients with suspected MRSA infection is commonly prescribed pending culture results, unless a more targeted approach can be guided by the direct examination of bronchial secretions showing a single pathogen.

Directing antimicrobial therapy toward the most common pathogens with certain antibiotic regimens may improve survival, and reduce the emergence of resistance (32,33). Although most clinicians direct empiric therapy toward Gram-negative aerobic bacteria and staphylococci, the most commonly isolated microbes, there is a considerable variation in management of cases with a high suspicion of VAP. Aminoglycosides are also recommended in the initial empiric treatment of VAP. Aggressive aminoglycoside administration within the first days has been associated with high peak serum levels and higher alveolar levels that result in an earlier resolution of VAP (34).

Difficulties in VAP diagnosis

One of the most difficult issues involving the investigation of VAP is the confirmation of diagnosis. Although directed sampling procedures (bronchoscopy and BAL) may improve outcome, current guidelines do not mandate their use and VAP is still predominantly diagnosed using clinical criteria.

Under the scope of evidence showing that initial appropriate antibiotic therapy is crucial for improving the prognosis of patients with VAP, some investigators have evaluated whether microbiological data, obtained by non-invasive or invasive bronchoscopic procedures can be used to modify antibiotic therapy. When the prognostic value of this strategy has been evaluated (i.e. changing from inadequate to adequate antibiotic therapy), most studies have found no improvement in mortality. Sanchez-Nieto et al. compared the impact of invasive diagnostic techniques (via fiberoptic bronchoscopy) and non-invasive diagnostic techniques (via quantitative endotracheal aspirates) on the outcome of patients with VAP. They found that bronchoscopy led to more frequent changes in antibiotic therapy than non-invasive techniques, but did not favorably influence mortality (35).

Even when combining either non-invasive or invasive sampling techniques with clinical criteria to improve diagnostic yield in patients with radiographic infiltrates, there is a percentage of patients in whom the diagnosis of pneumonia cannot be established. Thus, the potential of underdiagnosis might impair the outcome for these patients. Neverthless, in other settings, the overdiagnosis of pneumonia might enhance antibiotic consumption, increase the emergence of resistance, or increase the likelihood of fungal colonization or infection, and needlessly increase costs.

De-escalation therapy

Once the microbiological data have become available and the patient's response to therapy is evaluated, it is also necessary to de-escalate therapy in order to avoid unnecessary prolonged use of an antibiotic of a spectrum broader than justified by the available information. Although a de-escalating approach to antibiotic therapy (i.e. culture-guided treatment) may not help individual patients, it could benefit the ICU as a whole by reducing selection pressure for resistance. The use of microbiological data may also reveal information important for future patients. The cultures of respiratory specimens from clinical infection sites can serve as a form of database for defining local patterns of antibiotic resistance, which can then guide therapeutic recommendations.

Considering the importance of adequate initial antibiotic therapy in critically ill patients with VAP, a de-escalating strategy (i.e. starting with broad-spectrum antibiotic therapy followed by narrow-spectrum specific therapy, according to microbiological results) seems to be the preferred approach than starting narrow-spectrum therapy and then broadening the spectrum once culture data becomes available. Thus, initial broad-spectrum antibiotic therapy provides maximum benefit for the individual, severely infected patient, whereas switching to a specific antibiotic therapy according to microbiological data may help minimize the risk of emerging resistance (36).

Antibiotic cycling

Strategies such as scheduled changes of antibiotic regimens or routine microbiological surveillance-guided changes of antibiotic policy may also reduce the risk of emerging resistant strains. Kollef et al. (37) have shown that a planned proactive approach of change by routinely varying the antibiotic policy (e.g., from using ceftazidime to using ciprofloxacin) in an ICU setting may be useful in preventing the emergence of resistance by reducing the selection pressure on bacteria. Instead of using a certain standard antibiotic regimen for a period of time and then changing to another regimen for the next period, an alternative approach might be treating consecutive patients with different antibiotic regimens within the same time period to reduce selection pressure for highly resistant nosocomial pathogens within the ward.

The first trials on antibiotic cycling have yielded conflicting results. Dominguez et al. observed a reduced rate of Gram-negative resistance in their hematology-oncology unit when comparing four different time periods with different antibiotic regimens, but also observed an increase in Gram-positive resistance, which was mainly due to a marked increase in enterococcal infections (38).

Of major concern regarding the widespread use of broad-spectrum empiric therapy in the ICU is the fear of emergence of multidrug-resistant pathogens. Additional well-known factors predisposing patients to resistance are numerous, including prior antibiotic use especially at suboptimal levels, suboptimal treatment duration, or prolonged duration of stay in the hospital or ICU (39).

Conclusions

Besides vigorous efforts to improve the procedures for establishing the diagnosis of VAP, a strategy that might lower the unacceptably high fatality rate of this common ICU disease could be the initiation of an immediate broad-spectrum antibiotic treatment covering all potential high-risk pathogens in severely ill patients with suspected VAP.

At present, no antibiotic regimen or combination of antibiotics could be linked to a sustained better outcome in severely ill patients with VAP in terms of morbidity and mortality rates. For this reason, what appears to be currently needed are well-performed clinical studies aimed at determining the most effective, least toxic, and most cost-efficient approaches for the initial empiric treatment of suspected VAP.

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