Ventilator-associated pneumonia; a concise review

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Ventilator-associated pneumonia (VAP) continues to be the most common nosocomial infection in critically ill patients requiring mechanical ventilation. In this review data was sourced from Medline, the National Institute for Clinical Effectiveness (NICE), study authors and review articles. Development of VAP prolongs length of stay in the intensive care unit and may increase mortality. Although diagnosis is difficult, with little consensus on ideal diagnostic criteria, there is general agreement that rapid and accurate diagnosis of VAP is essential as delayed administration of appropriate antibiotic therapy increases mortality. Implementation of evidence-based strategies for the prevention of VAP may reduce morbidity, mortality and length of stay.

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Introduction

Ventilator-associated pneumonia (VAP) can be defined as an inflammation of the lung parenchyma occurring 48-72 hours or more after intubation of the trachea, due to organisms not present or incubating at the time mechanical ventilation was commenced.[1] It is the most common nosocomial infection encountered in the ICU, with 9-28% of all intubated patients developing VAP.[2,3] Intubation independently increases the risk of developing nosocomial pneumonia at least seven-fold, with a peak in incidence occurring around day five of ventilation.[4]

It is useful to differentiate early-onset VAP, which occurs within the first four days of intubation, from late-onset VAP which develops five or more days after intubation. The former is usually due to antibiotic-sensitive bacteria, while late-onset VAP is commonly caused by opportunistic and multi-drug resistant pathogens and is consequently more severe.[5]

Although the development of VAP is recognised as an adverse prognostic factor, it is currently unclear whether VAP independently increases mortality in a heterogeneous group of critically ill patients. More severely ill patients and those with significant co-morbidity have a higher mortality and are especially prone to VAP, making it difficult to determine the contribution to mortality made by the development of nosocomial pneumonia. Interestingly, several observational studies using matched controls fail to demonstrate any attributable mortality from the development of VAP.[6,7] Other studies suggest the risk of death is 2-3 times higher in critically ill patients who develop VAP than those who do not.[8,9]

Pathogenesis

Most cases of VAP develop as a result of aspiration of infected oropharyngeal secretions. The oropharynx of critically ill individuals is rapidly colonised with aerobic gram-negative bacilli (AGNB) which adhere to mucosal surfaces through adhesion molecules.[10] The stomach may also act as a reservoir for infecting bacteria, although not all authors agree on the clinical significance of the gastropulmonary route.[11] Contaminated secretions pool above the high-volume, low-pressure cuffs of the endotracheal tubes commonly used to secure the airway in the critically ill, and slowly gain access to the trachea along folds in the cuff. The inner surface of the tracheal tube also rapidly develops a biofilm which can quickly become colonised with bacteria. Ventilator cycling ensures that these secretions are eventually propelled to the distal airways exposing the lung parenchyma to pathogenic organisms. Whether pneumonia develops or not is dependent on the complex interaction between the host's immune response and the size and pathogenicity of the inoculum.[12]

Risk factors

Risk factors for the development of VAP may be host-related (eg severity of illness, age) or intervention-related (eg use of antibiotics, nasogastric tubes).

Host-related factors

Multivariate analysis has identified severity of illness, age >60 years, pre-existing pulmonary disease and hypoalbuminaemia, as independent risk factors for development of VAP.[1]

Intervention-related factors

The presence of a tracheal tube increases the risk of developing VAP, with several studies suggesting that non-invasive mechanical ventilation is associated with a lower incidence of pneumonia.[13] Reintubation for unplanned or failed extubation independently increases the likelihood of developing VAP and should be avoided if possible.[14]

Adoption of the supine body position is associated with the development of VAP, especially when the patient is being enterally fed.[15] Although multivariate analysis has identified enteral feeding as a risk factor because of an increased incidence of aspiration of stomach contents, most clinicians recognise the importance of early enteral feeding.[16] The size of

Sign	Point(s)
Temperature, °C	
36.5-38.4	0
38.5-38.9	1
≤36 or ≥39	2
Blood leucocytes, cells/μL	
4000-11000	0
<4000 or >11000	1
Band forms ≥ 50%	2
Oxygenation, PaO_2/FiO_2 (mm Hg)	
>240 or ARDS	0
≤240 and no evidence of ARDS	2
Pulmonary radiography	
No infiltrate	0
Diffuse (or patchy) infiltrates	1
Localised infiltrate	2
Tracheal secretions	
Absence of tracheal secretions	0
Presence of non-purulent sputum	1
Purulent secretions	2
Culture of tracheal aspirate	
Pathogenic bacteria cultured, minimal or no growth	0
Pathogenic bacteria cultured, moderate or more growth	1
Moderate or greater growth of pathogenic bacteria consistent with that seen on original Gram stain	2

Table 1 Clinical Pulmonary Infection Score (CPIS).

the feeding tube has no influence on the risk of aspiration, but post-pyloric placement significantly reduces the risk of VAP.[17]

Stress ulcer prophylaxis using agents which block gastric acid secretion (proton pump inhibitors, H_2 blockers) encourages gastric colonisation with AGNB. Although a meta-analysis of the efficacy of stress ulcer prophylaxis in critically ill patients concluded that there was a trend toward an increased risk of pneumonia associated with H_2 blockers, a large randomised controlled trial comparing ranitidine to sucralfate failed to confirm this.[19,20] While nasal intubation predisposes to the development of sinusitis, it is unclear whether it is associated with a higher incidence of VAP.[18]

Diagnosis of VAP

The accurate diagnosis of VAP remains difficult and challenging, with no universally accepted 'gold standard,' leading to both under and over diagnosis of the condition.[21] Clinical signs of infection such as pyrexia, leucocytosis or the presence of purulent secretions have a low specificity for its diagnosis, while the presence of infiltrates on chest X-ray (CXR) can be caused by a variety of non-infectious conditions commonly encountered in the critically ill, such as pulmonary haemorrhage, atelectasis and acute lung injury.[22] Establishment of a firm diagnosis therefore relies on three components:[23]

- clinical signs of severe infection
- radiological signs of new or worsening infiltrates on CXR
- microbiological evidence of infection.

Using these criteria, Pugin and colleagues have devised the Clinical Pulmonary Infection Score (CPIS) in order to increase the accuracy of diagnosis (**Table 1**).[24] A score greater than six suggests the presence of VAP, although both the sensitivity and specificity of the score is low (77% and 42% respectively).[25] Nevertheless, the appearance of new infiltrates on CXR plus two or more signs of pulmonary infection such as new purulent secretions, worsening gas exchange, leucocytosis or pyrexia, significantly increases the likelihood of VAP and should initiate microbiological analysis of pulmonary secretions.[21,23] However, the optimal methods of obtaining and processing the specimens remains contentious.

Appropriate specimens can be obtained using a variety of different techniques, and processed either quantitatively or non-quantitatively. The simplest, cheapest and most widespread method is sampling endotracheal aspirates (ETA).[26] However, non-quantitative analysis of ETAs lacks specificity and yields a high percentage of false positive results because of bacterial colonisation of the tracheal tube and proximal airways.[27] Specificity may be increased by quantitative culture of the specimens using 10^6 colony forming units (CFUs) as a cut-off point, although this may decrease sensitivity.[28] Due to this lack of specificity, many recommend that samples are obtained invasively from the distal airways and that they are analysed quantitatively.[21] This can be achieved using bronchoscopically-guided protected specimen brush (PSB) samples or bronchoalveolar lavage (BAL). As these techniques are time-consuming, require specialist equipment and some degree of technical expertise, blind sampling using mini-BAL is becoming increasingly popular.[26] Blind mini-BAL is a technically simple and safe technique and yields results comparable to those obtained by guided bronchoscopy, reflecting the diffuse nature of VAP.[29]

The thresholds usually applied to quantitative culture of secretions for the diagnosis of VAP are 10^4 CFU/mL for BAL, 10^3 CFU/mL for PSB and 10^5 CFU/mL for tracheal aspirates. The reported sensitivities of PSB and BAL are 33-100% and 42-93%, respectively, and the specificities 50-100% and 45-100%.[30] The reported sensitivity of quantitatively cultured ETAs varies from 38-100% with a specificity of 14-100%.[31] There is therefore a high likelihood of false positives and false negatives with all of these techniques, and none is totally reliable for the diagnosis of VAP.

A study by Fagon and colleagues comparing a non-invasive strategy using qualitative cultures of ETAs with an invasive management strategy employing quantitative BAL in 413 patients suspected of having VAP, demonstrated fewer deaths at 14 days and less antibiotic use in patients managed using the invasive strategy.[32] Other studies have failed to demonstrate any reduction in mortality associated with an invasive approach to VAP diagnosis and management.[33,34] However, employing an invasive approach leads to an increased likelihood of adjustment of antibiotic therapy.[35]

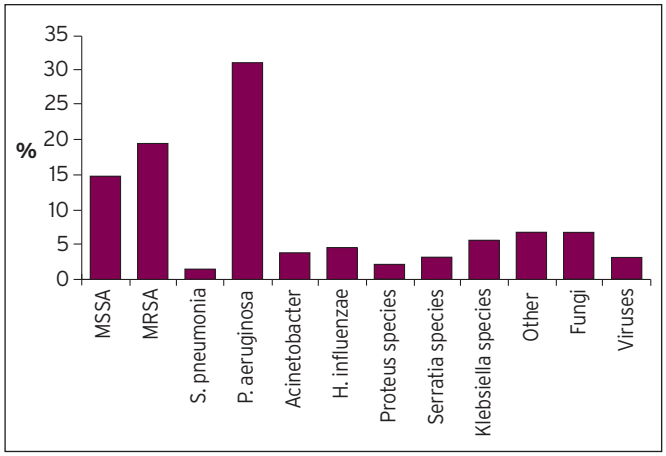

Figure 1 Summary of pathogens responsible for VAP in a study of 420 patients. Adapted from Bercault and Boulain[6].
Key MSSA, meticillin sensitive *Staphylococcus aureus*; MRSA, meticillin-resistant *Staphylococcus aureus*.

Most recently, in a large, multi-centre trial of 740 patients with suspected VAP, quantitative culture of BAL fluid was compared with non-quantitative culture of ETAs, and failed to demonstrate any significant difference between the two groups in either mortality or the use of antibiotics.[36]

As recent antimicrobial therapy decreases the accuracy of culture, there is widespread agreement that samples should be obtained prior to initiation of antibiotic therapy regardless of the method employed to obtain the samples.[21]

Treatment

Prompt initiation of adequate antibiotic therapy is associated with a reduced mortality in patients suspected of VAP.[37] As such, a high clinical suspicion of pneumonia should lead to the empirical administration of appropriate antibiotics, preferably after suitable microbiological specimens have been obtained.

A variety of factors should influence the choice of initial antibiotic therapy including knowledge of the likely organisms (**Figure 1**), local microbial epidemiology and their sensitivities, and the results of surveillance cultures from the patient.[5] Multi-drug resistant (MDR) pathogens are more likely in patients who have had a prolonged period of hospitalisation, those receiving mechanical ventilation for more than seven days and those who have received prior antibiotic therapy.[38] Patients suspected of VAP who have recently received antibiotic therapy should receive an antimicrobial agent from a different class than used previously to discourage resistance.[39]

Guidelines for the empirical treatment of VAP have recently been produced by the British Society for Antimicrobial Chemotherapy.[40] The use of cefuroxime or co-amoxiclav is recommended for patients with early-onset VAP who have not received prior antibiotic therapy and have no other risk factors. For those recently treated with antibiotics and with other risk factors, a third-generation cephalosporin (cefotaxime or ceftriaxone), a fluoroquinolone or piperacillin/tazobactam is suggested. Patients with late onset VAP or other risk factors for MDR pathogens should receive antibiotics with activity against *Pseudomonas aeruginosa*. No one agent has proven to be superior, and options include ceftazidime, ciprofloxacin, meropenem and piperacillin /tazobactam.[40]

Those with late-onset VAP who have previously received antibiotics are especially prone to developing meticillin-resistant *Staphylococcus aureus* (MRSA) pneumonia, and this must be considered when initiating antimicrobial therapy. While the glycopeptides vancomycin and teicoplanin remain the mainstay of treatment of MRSA VAP, there is evidence linezolid treatment results in better clinical cure and survival rates.[41]

Although empirical combination therapy is commonly employed, as it is believed to increase the likelihood of success through antimicrobial synergy and an extended spectrum of activity, there is little evidence to support its use over monotherapy.[40]

The optimal duration of empirical antimicrobial therapy for VAP is unknown. In a prospective, randomised, multi-centre clinical trial, a total of 401 patients with confirmed VAP were randomised to receive either eight days or 15 days of antibiotic treatment. Those treated for eight days had neither excess mortality nor more recurrent infections. The emergence of MDR pathogens was also lower in those receiving the shorter course of antibiotics.[42] On this basis, empirical antibiotic therapy should not be administered for longer than eight days in those responding to treatment.[40]

Prevention

Prevention of any nosocomial infection in the ICU requires a multi-disciplinary approach, with staff education, infection control programmes, adequate staffing and antibiotic control strategies. However, a number of specific interventions have been shown to reduce the incidence of VAP. These interventions broadly fall into three groups: reducing upper aero-digestive tract colonisation, reducing aspiration of infected secretions and minimising the duration of intubation.

Reducing aero-digestive tract colonisation

Oral decontamination of mechanically ventilated patients using a variety of topical antiseptics including chlorhexidine 0.12-2% and povidone iodine 10% significantly reduces the rate of pneumonia (relative risk 0.56, 0.39-0.81; p=0.002).[43] Despite this reduction, no impact on mortality or length of stay in the ICU has been demonstrated. However, NICE in collaboration with the National Patient Safety Agency (NPSA) recently recommended that all mechanically ventilated patients with an artificial airway should receive oral antiseptics.[44]

The role of selective decontamination of the digestive tract (SDD) in the prevention of VAP remains contentious. Regimens vary but normally two or three non-absorbable antimicrobials (eg usually tobramycin, polymyxin E and amphotericin B) are applied as a paste to the mouth and administered enterally to eradicate AGNB and fungi from the oropharynx and GI tract. Some regimens also include a parenterally administered antibiotic, most commonly a cephalosporin. A recent systematic review of SDD that included a meta-analysis of data from 27 randomised controlled trials (RCTs) concluded that SDD reduces the incidence of VAP and length of stay in mechanically ventilated ICU patients.[45] The addition of a parenteral antibiotic to the

- Mechanically ventilated patients who are intubated should be positioned with their upper body elevated (in a semi-recumbent or seated position) for as much of the time as possible. For some patients this will not be appropriate (for example, those with spinal injuries).
- Oral antiseptics (for example, chlorhexidine) should be included as part of the oral hygiene regimen for all patients who are intubated and receiving mechanical ventilation.

Table 2 Summary of NICE guidance on VAP.

regimen was associated with a reduction in mortality.

Although studies suggest that SDD is effective in reducing the incidence of VAP, this intervention is not commonly used in the UK because of fears of encouraging *Clostridium difficile*, antimicrobial resistance and the emergence of MDR pathogens. As most SDD trials were conducted overseas, an opportunity exists to conduct an RCT of SDD within the UK examining its influence not only on the prevention of VAP but also microbiological outcomes including *Clostridium difficile*.

Although ventilator circuits are a potential source of contaminated secretions frequent changes do not reduce the risk of VAP, and circuits should not be changed more frequently than weekly, provided they do not become soiled.[46] The use of heat and moisture exchangers instead of heat humidifiers in suitable patients is also associated with a decrease in the risk of developing VAP.[47]

Reducing aspiration

As the presence of a tracheal tube greatly increases the incidence of nosocomial pneumonia, intubation and mechanical ventilation should be avoided if possible. Non-invasive ventilation is associated with decreased VAP rates and is increasingly being successfully used as an alternative ventilation mode in those with acute respiratory failure.[48]

Unless specifically contra-indicated all mechanically ventilated patients should be nursed in the semi-recumbent position (45° head up). Drakulovic *et al* demonstrated that adoption of this position significantly reduces the incidence of clinically-suspected and microbiologically-confirmed pneumonia, especially in patients receiving enteral nutrition.[15] This intervention has also been recommended by NICE/NPSA (**Table 2**).[44]

Subglottic suctioning using tracheal tubes with a large bore distal channel to allow aspiration of subglottic secretions has been shown to reduce the incidence of VAP but has no influence on mortality, length of stay or duration of mechanical ventilation.[49]

Maintenance of tracheal cuff pressure above 20 cm H_2O appears to reduce the incidence of VAP by decreasing micro-aspiration. The recently introduced LoTrach™ system uses a cuff pressure controller to maintain the specially designed tracheal tube cuff at a constant 30 cm H_2O.

Minimising duration of ventilation

There is increasing evidence to suggest that performance of an early tracheostomy in patients expected to require prolonged mechanical ventilation is beneficial. In a recent study of 120 patients expected to require mechanical ventilation for longer than 14 days, those who were randomised to receive percutaneous dilatational tracheostomy within 48 hours of admission had a significantly lower incidence of VAP than those who received a tracheostomy after 14-16 days (5% *vs* 25%, p<0.005).[50] Duration of ventilation may also be reduced by daily interruption of the sedative regime.

Conclusions

VAP is a common and serious nosocomial infection. Although the accurate diagnosis of VAP remains challenging, the combination of new infiltrates on CXR with at least two of the following – fever, leucocytosis or purulent sputum – substantially increases the likelihood of VAP. A clinical suspicion of VAP should prompt collection of lower respiratory tract secretions for microbiological analysis and the rapid administration of appropriate empirical antibiotics, the choice being based on individual patient risk factors and the nature and susceptibility patterns of the organisms prevalent on the unit. Antibiotic therapy should be routinely evaluated according to clinical response and microbiological results.

A number of evidence-based interventions have been demonstrated to reduce the incidence of VAP. In particular, all patients should be nursed in the semi-recumbent position and receive oral decontamination with antiseptic.

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