

# Current Concepts in Ventilator-associated Pneumonia

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## Abstract

*Ventilator-associated pneumonia (VAP) is a common problem in the intensive care unit (ICU). It is associated with a distinct spectrum of pathogens and its pathogenesis involves microaspiration of oropharyngeal organisms. Clinical and radiographic criteria have been shown to be unreliable in diagnosing VAP, and it remains a challenge for intensivists to utilise the array of diagnostic procedures at their disposal to optimise diagnostic accuracy (improve specificity) and guide in therapy. These procedures and guided antibiotic therapy may not always improve the outcome and therefore simple preventive measures should be employed to reduce the incidence.*

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**Key words:** *Bronchoalveolar lavage (BAL), Gastropulmonary, Microaspiration, Protected specimen brush (PSB), Selective digestive decontamination (SDD)*

## Definition

Ventilator-associated pneumonia (VAP) may be defined as lung parenchymal infection, usually bacterial, occurring after at least 48 hours of initiating mechanical ventilation. It excludes any infection that was either present or incubating at the time of endotracheal intubation.

## Epidemiology

Pneumonia is the commonest nosocomial infection in the intensive care unit (ICU) and this is not surprising as mechanical ventilation and endotracheal intubation can increase the risk of nosocomial pneumonia by up to 21-fold. Pneumonia is also the commonest cause of death among all nosocomial infections.<sup>1</sup> VAP cannot be reliably diagnosed from conventional clinical and radiographic criteria<sup>2,3</sup> as there may be a high rate of misclassification and inaccuracy. It may occur in up to 65% of ICU patients but this prevalence may be overestimated due to unreliable and inaccurate diagnoses using conventional criteria.

The crude mortality may approach 55%<sup>4,5</sup> but in a recent study assessing the *attributable mortality* linked to VAP (percentage of VAP deaths that would not have occurred in the absence of this infection), VAP did not remain a significant risk factor for death when confounding factors were controlled for.<sup>6</sup> VAP is also associated with substantial morbidity and increased

treatment costs.<sup>7,8</sup> Fagon et al<sup>9</sup> reported that when VAP was linked to *Pseudomonas aeruginosa*, there was increase in mortality, duration of mechanical ventilation, and hospitalisation.

## Pathogens

As cultures of tracheal aspirates cannot accurately identify pathogens in the distal lung causing pneumonia, four epidemiologic studies of mechanically ventilated patients have identified pathogens by more specific microbiologic criteria (e.g. quantitative cultures of protected specimen brush samples, transthoracic needle aspiration, pleural fluid and blood cultures).<sup>10-13</sup> In these studies, *Pseudomonas aeruginosa* (14% to 30% of identified pathogens), *Acinetobacter* species (10% to 39%) and *Staphylococcus aureus* (4% to 20%) were the most frequent pathogens. Up to 47% of cases of ventilator-associated pneumonia are polymicrobial.<sup>1</sup>

Underlying disease, duration of intubation, and prior antibiotic therapy are the most important factors related to the infective organisms in patients with VAP. Within the first week of intubation, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenza* are the predominant respiratory pathogens (with the exception of chronic obstructive pulmonary disease patients who may have been colonised with *Pseudomonas aeruginosa*). These organisms are soon replaced by the multi-resistant organisms listed above and this change

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of flora occurs as a result of previous antibiotic therapy, among other factors. Immunosuppression is a predisposing factor to fungal infections.<sup>14</sup> Prompt recognition of the aetiological agents and appropriate antibiotic therapy facilitates optimal management and outcome.

Pathophysiology

The risk factors for VAP are listed in Table I. They should be regarded as possible risk factors because most of the published studies on identifying risk factors failed to use both accurate diagnostic methods to identify VAP (leading again to high misclassification rates), as well as multivariable statistical techniques for data analysis.<sup>15</sup> The distinct spectrum of pathogens associated with VAP, namely the aerobic Gram-negative bacilli as well as *Staphylococcus aureus*, colonise the upper aerodigestive tract in large numbers prior to the development of VAP. The possible origins of these organisms are uncertain but the potential sites include dental plaque, periodontal disease, paranasal sinuses, trachea and the gastrointestinal tract.

Transcolonisation of the oropharynx from these contiguous structures leads to contamination of the endotracheal tube as well as ventilator circuits during and after intubation. The presence of an indwelling endotracheal tube impairs coughing and impedes pulmonary clearance mechanisms. During mechanical ventilation, contaminated secretions lining the tube are inoculated into the distal airways, a process known as microaspiration, where an inflammatory response is induced, leading to pneumonia<sup>16</sup> (usually involving the lower lobes preferentially”).

The interaction between impaired host defences and exposure to large numbers of pathogens allow colonisa-

tion of the airways with these organisms to occur through the molecular mechanism of bacterial adherence. Bacterial adherence is a cell-cell interaction mediated by 3 variables: host receptors, bacterial adhesins, and the proper microenvironment on the respiratory mucosa. Once adherence is accomplished, colonisation and proliferation then occur, and in the presence of impaired host defences, colonisation progresses to overt lung parenchymal infection.”

Diagnosis

Conventional noninvasive clinical and radiographic criteria used to diagnose VAP such as fever, leukocytosis, new infiltrates on chest X-rays, and purulent endotracheal aspirates have been shown to be unreliable in diagnosing VAP.<sup>19,20</sup> These criteria are sensitive but not specific, and the high false positive rate of diagnosis may lead to excessive empiric use of broad-spectrum antibiotics in ventilated patients without pneumonia, resulting in colonisation, superinfection and subsequently VAP with virulent and multi-resistant organisms.

In Meduri et al’s prospective study<sup>21</sup> of patients suspected to have VAP based on the above clinical criteria, only 42% actually had nosocomial pneumonia. In this study, a systematic diagnostic protocol was used to identify the causes of fever and pulmonary densities in their patients, with all patients undergoing a bronchoscopy-assisted lower airway sampling technique. Pneumonia was diagnosed when there was significant growth in these specimens on quantitative cultures.

Pulmonary fibroproliferation, a frequent cause of fever in late adult respiratory distress syndrome (ARDS), was found in 11% of their patients. This diagnosis was made by tissue histology after pneumonia was excluded by bronchoscopy. Corticosteroid treatment has been

TABLE I: POSSIBLE RISK FACTORS FOR VAP<sup>15</sup>

|                                                                                 |
|---------------------------------------------------------------------------------|
| 1. Intracranial pressure monitoring                                             |
| 2. Prophylaxis with gastric acid inhibitors                                     |
| 3. 24-hour ventilator circuit changes (rather than 48-hour circuit changes)     |
| 4. Fall-winter season                                                           |
| 5. Chronic obstructive pulmonary disease                                        |
| 6. Depressed consciousness                                                      |
| 7. Nasotracheal or orotracheal intubation                                       |
| 8. Aspiration of gastric contents                                               |
| 9. Thoracoabdominal surgery                                                     |
| 10. Advanced age                                                                |
| 11. Duration of mechanical ventilation                                          |
| 12. Reintubation                                                                |
| 13. Use of positive end expiratory pressure                                     |
| 14. Nasogastric intubation                                                      |
| 15. Multiple organ system failure                                               |
| 16. Prior antibiotic administration                                             |
| 17. Supine head positioning during the first 24 hours of mechanical ventilation |

TABLEII: THE TWO SCHOOLS OF THOUGHT ON INVASIVE DIAGNOSTIC TESTING IN SUSPECTED VAP<sup>27,28</sup>

|                                                                                                                                                                                                                                 |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Invasive diagnostic testing should be routinely used in suspected VAP                                                                                                                                                           |
| 1. Allows a therapeutic strategy to be devised that is superior to the one based only on clinical evaluation.                                                                                                                   |
| 2. Enables identification of patients in need of immediate treatment as well as provides a guide on selection of optimal therapy (when performed before new antibiotics are administered).                                      |
| 3. Procedure is safe and well tolerated.                                                                                                                                                                                        |
| 4. Prevents liberal use of broad spectrum antibiotic cover in all patients who develop a clinical suspicion of infection.                                                                                                       |
| Invasive diagnostic testing is not required routinely in suspected VAP                                                                                                                                                          |
| 1. Clinical methods used in conjunction with quantitative endotracheal tube aspirates may be sufficient.                                                                                                                        |
| 2. No prospective, randomised trial to show whether invasive methods improve survival or other meaningful end points such as antimicrobial resistance, antibiotic complications, or cost when compared with clinical diagnosis. |

VAP: Ventilator-associated pneumonia

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advocated for the treatment of progressive fibroproliferation in late ARDS,<sup>22</sup> emphasising the value of bronchoscopy-assisted lower airway sampling techniques for excluding infection in these cases. Fagon et al<sup>3</sup> have also reported that clinical judgement is often flawed when compared with a bronchoscopy-assisted lower airway sampling technique.

A consensus conference<sup>23</sup> has concluded that only two criteria definitely confirm the presence of clinically suspected VAP, histologic confirmation by open lung biopsy or postmortem examination, and radiographic evidence of pulmonary abscess with a positive needle aspirate from the cavity. These criteria reflect the weak relationship between microbiology and histology and it is that lung histology is more reliable than bacteriology as a diagnostic test.

The low clinical utility of conventional criteria has led to extensive research into the optimal method of confirming the diagnosis of clinically suspected VAP. The two most widely studied diagnostic techniques are the protected specimen brush (PSB) and bronchoalveolar lavage (BAL), via fiberoptic bronchoscopy.<sup>24</sup> The PSB (Fig. 1) is a sterile brush housed within a hollow catheter that is capped with a gelatin plug. This is expelled when the sterile brush is extruded through the protective catheter after it is positioned by the fiberoptic bronchoscope through its working channel. Contamination of the brush by upper airway flora is thus minimised.

BAL is a procedure whereby the tip of the fiberoptic bronchoscope is wedged into a segmental bronchus. This segment is then flooded with aliquots of sterile saline with the effluent then aspirated and sent for analysis. Significant contamination from upper airway flora occurs and hence techniques for protected BAL have been developed.

Both these techniques require bronchoscopy, which is rather invasive, expensive and not readily available.

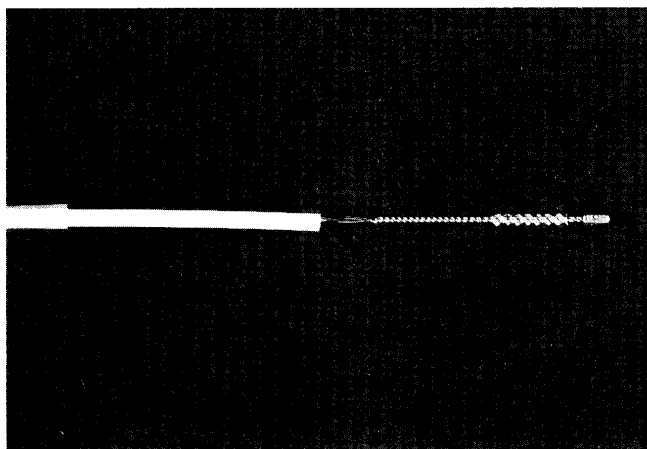


Fig. 1. Protected specimen brush.

Therefore, other ingenious techniques have been devised, including nonbronchoscopic BAL, non-bronchoscopic protected mini-BAL and blind PSB, and these may yet prove to be safe, cost-effective, widely available and technically simple procedures for diagnosing VAP. With the aforementioned techniques, there has been a boom of papers investigating their clinical utility.<sup>25</sup> These have been too voluminous to discuss in this article but one must note that prior antibiotic therapy definitely alters the sensitivity and specificity of any lower airway sampling technique.<sup>26</sup> Suffice to say, there are two schools of thought on whether these new techniques should be used routinely in clinical practice<sup>27,28</sup> (Table II).

There has been research not only on how best to obtain appropriate specimens for analysis, but also on the optimal method of evaluating the yield obtained. Quantitative or semiquantitative cultures are usually performed on the bronchoscopic specimens, with the diagnosis of VAP made when an appropriate threshold is exceeded.<sup>29</sup> These thresholds are necessary to improve diagnostic specificity due to the presence of tracheo-bronchial colonisation. A major problem is the effect of prior antibiotic therapy on these quantitative cultures. Cultures that do not reach quantitative significance may either represent colonisation, early pneumonia, or pathogens suppressed by the antibiotics. The discontinuation of antibiotics for 48 hours prior to bronchoscopic lower airway sampling may improve diagnostic accuracy but this is rarely feasible in practice.<sup>30</sup>

Another problem with quantitative cultures is that these may take up to 4 days to be of value, delaying crucial treatment decisions. Quantitative cultures have also been applied to endotracheal aspirates in an attempt to improve the diagnostic specificity. This, however, has been evaluated and shown to be of limited value in ventilated patients when bronchoscopy-assisted lower airway sampling techniques were available.<sup>31</sup>

Two other methods that have been applied to improve the diagnostic accuracy of endotracheal aspirates are:

- 1) potassium hydroxide staining for the presence of elastin fibres (an indication of parenchymal necrosis due to VAP),<sup>32</sup> and
- 2) antibody coating of bacteria (fluorescein-labelled antibody used to detect antibody coating of bacteria).<sup>33</sup>

Other diagnostic modalities include the examination of the BAL fluid for intracellular bacteria. The presence of  $\geq 5\%$  intracellular organisms infecting polymorphonuclear leukocytes and/or macrophages of BAL fluid has been shown to be a specific marker of VAP.<sup>34</sup> Significant concentrations of endotoxin have also been found in BAL fluid of patients with VAP due to Gram-negative pneumonia and the utility of elevated concentrations of endotoxin for rapid diagnoses of Gram-negative VAP

TABLE III: STRATEGIES TO PREVENT VAP<sup>37,38</sup>

| Nonpharmacologic                                                                                                                                                                                                    | Rationale                                                                                                                                                                                                                                                                                                                                                           |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Hand washing, aseptic techniques                                                                                                                                                                                    | Prevention of nosocomial spread of organisms                                                                                                                                                                                                                                                                                                                        |
| Elevation of head of bed to 30% to 45%                                                                                                                                                                              | Supine position is a risk factor for aspiration of gastric contents in mechanically-ventilated patients with an indwelling nasogastric tube                                                                                                                                                                                                                         |
| Use of <ul style="list-style-type: none"> <li>. Smaller size nasogastric tube</li> <li>. Nasojejunal tube, or</li> <li>. Orogastric route</li> <li>. Orotracheal rather than nasoendotracheal intubation</li> </ul> | <ul style="list-style-type: none"> <li>. Smaller nasogastric tube reduces the incidence of gastroesophageal reflux</li> <li>. More distally placed feeding tubes may reduce the risk of aspiration</li> <li>. Orogastric route reduces predisposition to sinusitis</li> <li>. Nasoendotracheal route associated with increased risk of sinusitis and VAP</li> </ul> |
| Intermittent rather than continuous enteral feeding (major cause of gastric alkalinisation)                                                                                                                         | Intermittent enteral feeding restores gastric acidity thereby reducing bacterial colonisation                                                                                                                                                                                                                                                                       |
| Proper disinfection and decreased manipulation of respiratory equipment (ventilator circuits to be changed not more often than every 48 hours)                                                                      | More frequent changing of ventilator circuits to reduce induction of VAP may actually increase the risk of VAP                                                                                                                                                                                                                                                      |
| Continuous suction of subglottic secretions                                                                                                                                                                         | Reduce aspiration of subglottic secretions above the tracheal cuff                                                                                                                                                                                                                                                                                                  |
| Rotational bed therapy                                                                                                                                                                                              | Prevent accumulation of bronchopulmonary secretions and reduce the incidence of atelectasis and nosocomial pneumonias                                                                                                                                                                                                                                               |
| Pharmacologic                                                                                                                                                                                                       | Rationale                                                                                                                                                                                                                                                                                                                                                           |
| Selective digestive tract decontamination                                                                                                                                                                           | Eradication of pathogenic organisms from the gastrointestinal tract (presumed to play a major causal role in the development of VAP)                                                                                                                                                                                                                                |
| Prophylactic endotracheal antibiotics                                                                                                                                                                               | Reducing airway colonisation with Gram-negative bacilli especially <i>Pseudomonas aeruginosa</i> <sup>38</sup>                                                                                                                                                                                                                                                      |
| Use of sucralfate instead of antacids or H2 blockers for stress ulcer prophylaxis                                                                                                                                   | Reduction in gastric acidity following treatment with H2 blockers promotes bacterial growth                                                                                                                                                                                                                                                                         |
| Immunomodulation: <sup>39</sup> <ul style="list-style-type: none"> <li>. Prophylaxis</li> <li>. Treatment</li> </ul>                                                                                                | <ul style="list-style-type: none"> <li>. Vaccination of patients with multiple risk factors against <i>Pseudomonas aeruginosa</i></li> <li>. Monoclonal antibody and anticytokine therapy</li> </ul>                                                                                                                                                                |

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has been investigated by Pugin et al.<sup>35</sup> These novel methods are still largely experimental and not widely available at present.

## Prevention

Table III summarises the strategies available for prevention of VAP<sup>36,37</sup> and several of these strategies deserve special mention. Retrograde oropharyngeal colonisation by organisms from the stomach (especially when gastric pH is high) has been assumed to play a major role in the pathogenesis of VAP, the so-called gastropulmonary route of infection.<sup>40-43</sup> The first prospective, controlled, randomised study to show that antacid or H2-receptor antagonists increased the risk of VAP was done by Nitin et al,<sup>44</sup> and they cautioned that drugs that increase gastric pH should be avoided, particularly in patients receiving enteral feedings. Following this, stress ulcer prophylaxis with sucralfate was shown to reduce the risk for late-onset pneumonia in ventilated patients compared with antacids or ranitidine.

However Marc et al<sup>45</sup> subsequently found that antacids and sucralfate had a similar effect on intragastric acidity, colonisation rates, and incidence of VAP. In their randomised double-blind study, they found that intragastric acidity influenced gastric colonisation but not colonisation of the upper respiratory tract or the incidence of VAP and they concluded that it is unlikely that the gastropulmonary route is important in the development of VAP.

Bonten et al<sup>46</sup> had the same sentiments about the gastropulmonary route of colonisation when they analysed the available contradictory evidence in a recently published review. Bonten's group found that none of the regimens supposed to prevent gastric colonisation such as the use of sucralfate for stress ulcer prophylaxis and modulation of enteral feeding (intermittent rather than continuous to restore gastric acidity), have been demonstrated to be unequivocally beneficial. In addition, analyses of the sequences of colonisation in patients who develop VAP suggest

that gastric colonisation may be less important than previously assumed. They concluded that the impact of other possible routes of colonisation may have been underestimated.

Selective digestive tract decontamination (SDD) is the use of topical nonabsorbable and systemic antibiotics to eradicate pathogenic aerobic Gram-negative bacilli and fungi in the stomach, thereby theoretically reducing the risk of pneumonia resulting from the controversial gastropulmonary route of infection. A key element in the strategy of SDD is the eradication of enteric aerobic Gram-negative bacilli and fungi without disrupting the anaerobic bacterial commensals that are instrumental in the population control of the gut.<sup>47</sup>

A recent meta-analysis of numerous results of studies on SDD revealed a trend towards reduced numbers of respiratory infections but no significant effect on mortality.<sup>48</sup> Due to the controversy, Ferrer et al<sup>49</sup> undertook a prospective, randomised, placebo-controlled, double-blind study with the end points of nosocomial pneumonia and mortality to shed light on the issue. This study reports that SDD did not significantly impact either nosocomial pneumonia or mortality.

The lack of efficacy of SDD is multifactorial and may be related to:

- 1) the different regimens used (e.g. failure to use systemic antibiotics and ineffectiveness of gentamicin compared with tobramycin), and
- 2) failure for SDD to prevent other important routes of colonisation (e.g. bacterial translocation leading to systemic endotoxaemia, an alternative haematogenous route of pulmonary infection).

Besides cost, another major concern with SDD is the potential risk of long-term induction of antimicrobial resistance. SDD is currently not recommended as a routine measure for the prevention of VAP. Ferrer et al had also pointed out that other methods such as appropriate positioning and the simple procedure of hand-washing may be more cost-effective in reducing the rate of nosocomial pneumonia.

*Pseudomonas* is known to directly colonise the tracheobronchial tree without prior oropharyngeal or gastric colonisation, proliferating in the biofilm along the inner surface of the endotracheal tube. The main route of colonisation seems to be direct introduction from external sources such as contaminated hands of personnel, contaminated respiratory equipment, or secondary to colonisation of other body sites.

Besides the aerobic Gram-negative bacilli, *Staphylococcus aureus* (often methicillin-resistant) is an important and commonly seen organism in the aetiology of VAP. Rumbak et al<sup>50</sup> showed a significant reduction in methicillin-resistant *Staphylococcus aureus* VAP (the infection rate was reduced from 0.2% to 0.026%) with the

institution of a prevention protocol. Their long-term, acute care ventilated patients with pneumonia had Bactroban, a 2% mupirocin ointment, applied to their anterior nares, and their bodies washed with chlorhexidine. This procedure was performed twice weekly, in addition to universal precautions and strict hand washing by the staff.

Finally, newer immunologic approaches have been explored both in the prevention as well as the treatment of VAP. Although there are no proven modalities for immunoprophylaxis of nosocomial pneumonia so far, it has been suggested that early administration of a single agent or combination of immune modulators may prove to be effective in reducing mortality.<sup>51</sup>

## Treatment

It is important to consider the potential pathogens (taking into account duration of intubation and resident flora in the hospital or ICU) and the severity of illness (including co-morbidity) when selecting appropriate antimicrobials for the treatment of VAP. However, it is also crucial to determine whether the patient does indeed have VAP, considering the fact that it has been shown that antimicrobial therapy before the advent of VAP may increase the risk of mortality. Rello et al<sup>52</sup> recommended avoidance of unnecessary antibiotics (a restrictive antibiotic policy) which they felt should be an important component of the management of mechanically-ventilated patients. This is easier said than done in critically ill patients on mechanical ventilation in the ICU.

Administering antibiotics to mechanically-ventilated patients without pneumonia increases the likelihood that the patients will develop a drug-resistant pneumonia. In a decision analysis by Sterling et al,<sup>53</sup> the survival of patients with VAP was closely linked to the accuracy of the method used to diagnose it. Although the use of invasive diagnostic techniques remains controversial, their analysis suggested that these procedures should be used to guide therapy, even in patients who had received prior antibiotics. The resulting judicious use of antibiotics would reduce the likelihood of resistant organisms and reduce mortality. The use of these diagnostic techniques would also be cost effective.

If antimicrobial therapy is indicated, the choice of antibiotics should be guided based on the knowledge of the local nosocomial pathogens, resistance patterns, duration of intubation, and recent antibiotic therapy. Broad-spectrum combination chemotherapy regimens that are effective against the commonest pathogens in VAP (mainly the aerobic Gram-negative bacilli, and *Staphylococcus aureus*) are required upon diagnosis until the results of the preliminary cultures return, and based on the causative organism and its sensitivity, the antibi-

TABLE IV: EMPIRIC COMBINATION CHEMOTHERAPY REGIMENS<sup>64</sup>

| Antibiotic regimen                           | Special circumstances                                        |
|----------------------------------------------|--------------------------------------------------------------|
| Piperacillin or Ticarcillin + aminoglycoside | Neutropenia, <i>Pseudomonas/Enterobacter/Serratia</i> likely |
| Cefoperazone or Ceftazidime + aminoglycoside | Neutropenia, <i>Pseudomonas/Enterobacter/Serratia</i> likely |
| Clindamycin + aminoglycoside                 | Gastric aspiration                                           |

otic coverage should be narrowed. Table IV shows empiric combination chemotherapy regimens that have been used with efficacy in the severely ill patient with VAP.

With the advent of newer broad spectrum antibiotics, monotherapy has been used successfully as well (e.g. ceftazidime, cefoperazone, imipenem/cilastatin and ticarcillin/clavulanate). However, caution is advised here as monotherapy has been associated with emergence of resistant strains in particular of *Pseudomonas aeruginosa*. Combination chemotherapy regimens that are effective against *Pseudomonas aeruginosa* (through a synergistic effect) are preferable in patients with neutropenia as well as in cases where this organism is a likely pathogen. It is advisable to tailor the antibiotic regimen to each individual patient's clinical circumstances (e.g. use of clindamycin for broad anaerobic coverage in a patient with suspected large volume aspiration and bad dentition, vancomycin for methicillin-resistant *Staphylococcus aureus* coverage in an institution where this organism is frequent, and erythromycin where legionella is suspected).

## Conclusion

VAP is a frequent and severe complication in mechanically-ventilated patients and the accurate diagnosis of both the presence and aetiology of this pneumonia is difficult. Antibiotic therapy may not always improve the outcome even when invasive diagnostic techniques are employed, hence as the old adage goes "prevention is better than cure".

## REFERENCES

- George DL. Epidemiology of nosocomial ventilator-associated pneumonia. *Infect Control Hosp Epidemiol* 1993;14:73-80.
- Bryant LR, Mobin-Uddin K, Dillon ML, Griffin W 0 Jr. Misdiagnosis of pneumonia in patients needing mechanical respiration. *Arch Surg* 1973; 106:286-8.
- Fagon JY, Chastre J, Hance A J, Guiguet M, Trouillet J L, Domart Y, et al. Detection of nosocomial lung infection in ventilated patients: use of a protected specimen brush and quantitative culture techniques in 147 patients. *Am Rev Respir Dis* 1988; 138:110-6.
- Gross P A, Neu H C, Aswapokee I, Van Antwerpen C, Aswapokee N. Deaths from nosocomial infection: Experience in a university hospital and a community hospital. *Am J Med* 1980; 68:219-23.
- Leu HS, Kaiser DL, Mori M, Woolson RF, Wenzel RI. Hospital-acquired pneumonia: attributable mortality and morbidity. *Am J Epidemiol* 1989; 129:1258-67.
- Papazian L, Bregeon F, Thirion X, Gregoire R, Saux P, Denis J P. Effect of ventilator-associated pneumonia on mortality and morbidity. *Am J Respir Crit Care Med* 1996; 154:91-7.
- Haley RW, Schaberg DR, Crossley KB, Von Allmen SD, McGowan JE Jr. Extra charges and prolongation of stay attributable to nosocomial infections: a prospective interhospital comparison. *Am J Med* 1981; 70:51-8.
- Dixon R E. Costs of nosocomial infections and benefits of infection control programs. In: Wenzel RP, editor. *Prevention and Control of Nosocomial Infections*. Baltimore, Md: Williams and Wilkins, 1987:19-25.
- Fagon J Y, Chastre J, Hance A J, Montravers P, Novara A, Gibert C. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. *Am J Med* 1993; 94:281-8.
- Fagon J Y, Chastre J, Domart Y, Trouillet J L, Pierre J, Darne C, et al. Nosocomial pneumonia in patients receiving continuous mechanical ventilation: prospective analysis of 52 episodes with the use of a protected specimen brush and quantitative culture techniques. *Am Rev Respir Dis* 1989; 139:877-84.
- Jimenez I, Torres A, Rodriguez-Roisin R, de la Bellacasa J P, Azna R, Gate11 J M, et al. Incidence and etiology of pneumonia acquired during mechanical ventilation. *Crit Care Med* 1989; 17:882-5.
- Torres A, Aznar R, Gate11 J M, Jimenez P, Gonzalez J, Ferrer A. Incidence, risk and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. *Am Rev Respir Dis* 1990; 142:523-8.
- Dreyfuss D, Djedaini K, Weber P, Brun P, Lanore J J, Rahmani J, et al. Prospective study of nosocomial pneumonia and of patient and circuit colonisation during mechanical ventilation with circuit changes every 48 hours versus no change. *Am Rev Respir Dis* 1991; 143:738-43.
- Rello J, Torres A. Microbial causes of ventilator-associated pneumonia. *Semin Respir Infect* 1996; 11:24-31.
- Mayhall C G. Nosocomial pneumonia. Diagnosis and prevention. *Infect Dis Clin North Am* 1997; 11:427-57.
- Estes RJ, Meduri G U. The pathogenesis of ventilator-associated pneumonia: I. Mechanisms of bacterial transcolonization and airway inoculation. *Intensive Care Med* 1995; 21:365-8.
- Flabregas N, Torres A. Histopathologic and microbiologic aspects of ventilator-associated pneumonia. *Anesthesiology* 1996; 84:760-71.
- Cassiere HA, Niederman MS. New etiopathologic concepts of ventilator-associated pneumonia. *Semin Respir Infect* 1996; 11:13-23.
- Andrews C J, Coalson J, Johanson W. Bacteriologic diagnosis of nosocomial pneumonia in acute, diffuse lung injury. *Chest* 1982; 80:254-8.
- Fagon J, Chastre J, Hance A, Domart Y, Trouillet J, Gibert C. Evaluation of clinical judgement in the identification and treatment of nosocomial pneumonia in ventilated patients. *Chest* 1993; 103:547-53.
- Meduri G U, Wunderink RG, Leeper K V, Trolley E, Mayhall G. Causes of fever and pulmonary densities in patients with clinical manifestations of ventilator-associated pneumonia. *Chest* 1994; 106:221-35.
- Meduri G U, Chinn A J, Leeper K V, Wunderink R G, Trolley E, Winer-Muram H T, et al. Corticosteroid rescue treatment of progressive fibroproliferation in late ARDS. *Chest* 1994; 105:1516-27.
- Pingleton S K, Fagon J Y, Leeper K V for the Diagnosis Group: International Consensus Conference on the Clinical Investigation of Ventilator-Associated Pneumonia. Patient selection for clinical investigation of ventilator-associated pneumonia. *Chest* 1992; 102(Suppl):553-65.
- Allen R M, Dunn W F, Limper A H. Diagnosing ventilator-associated pneumonia: The role of bronchoscopy. *Mayo Clin Proc* 1994; 69:962-8.
- Papazian L, Thomas P, Garbe L, Guignon I, Thirion X, Charrel J, et al.

- Bronchoscopic or blind sampling techniques for the diagnosis of ventilator associated pneumonia. *Am J Respir Crit Care Med* 1995; 152:1982-91.
26. Torres A, Mustafa EE, Padro L, Gonzalez J, de la Bellacasa JP, Ramirez J, et al. Validation of different techniques for the diagnosis of ventilator-associated pneumonia. *Am J Respir Crit Care Med* 1994; 149:324-31.
  27. Chastre J, Fagon J Y. Invasive diagnostic testing should be routinely used to manage ventilated patients with suspected pneumonia. *Am J Respir Crit Care Med* 1994; 150:570-4.
  28. Niederman MS, Torres A, Summer W. Invasive diagnostic testing is not needed routinely to manage suspected ventilator-associated pneumonia. *Am J Respir Crit Care Med* 1994; 150:565-9.
  29. Fagon J Y, Chastre J, Hance A J, Montravers I, Novara A, Gibert C. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. *Am J Med* 1993; 94:281-8.
  30. Hayner C E, Baughman R P. Nosocomial pneumonia. A review of diagnostic approaches. *Infect Med* 1995; 12:322-30.
  31. Jourdain B, Novara A, Joly-Guillou ML, Dombret M C, Calvat S, Troillet J L, et al. Role of quantitative cultures of endotracheal aspirates in the diagnosis of nosocomial pneumonia. *Am J Respir Crit Care Med* 1995; 152:241-6.
  32. Salata RA, Lederman MM, Shlaes DM, Jacobs MR, Eckstein E, Tweardy D, et al. Diagnosis of nosocomial pneumonia in intubated, intensive care unit patients. *Am Rev Respir Dis* 1987; 135:126-32.
  33. Wunderink R G, Russel G B, Mezger E, Adams D, Popovich J Jr. The diagnostic utility of the antibody-coated bacteria test in intubated patients. *Chest* 1991; 99:84-8.
  34. Torres A, El-Ebiary M, Fabregas N, Gonzalez J, de la Bellacasa J P, Hernandez C, et al. Value of intracellular bacteria detection in the diagnosis of ventilator-associated pneumonia. *Thorax* 1996; 51:378-84.
  35. Pugin J, Auchenthaler R, Delaspre O, Van Gessel E, Suter P M. Rapid diagnosis of Gram-negative pneumonia by assay of endotoxin in BAL fluid. *Thorax* 1992; 47:547-9.
  36. Valles J, Rello J. Nonpharmacologic strategies for preventing nosocomial pneumonia. *Clin Pulm Med* 1997; 4:141-7.
  37. Ip M. Practical strategies in the prevention of ventilator-associated pneumonia. *Clin Pulm Med* 1997; 4:135-40.
  38. Rosenfeld M, Cohen M, Ramsey B. Aerosolized antibiotics for bacterial lower airway infections: principles, efficacy, and pitfalls. *Clin Pulm Med* 1997; 4:101-12.
  39. Pennington J E. Immunological perspectives in prevention and treatment of nosocomial pneumonia. *Intensive Care Med* 1992; 18(Suppl):S35-8.
  40. Heyland D, Mandell LA. Gastric colonisation by Gram-negative bacilli and nosocomial pneumonia in the intensive care patient: evidence for causation. *Chest* 1992; 101:187-93.
  41. Du Moulin G C, Hedley-White J, Paterson D J, Lisbon A. Aspiration of gastric bacteria in antacid-treated patients: a frequent cause of postoperative colonisation of the airway. *Lancet* 1982; 1:242-5.
  42. Torres A, El-Ebiary M, Gonzalez J, Ferrer M, de la Bellacasa JP, Gene A, et al. Gastric and pharyngeal flora in nosocomial pneumonia acquired during mechanical ventilation. *Am Rev Respir Dis* 1993; 133:792-6.
  43. Tryba M. The gastropulmonary route of infection-fact or fiction? *Am J Med* 1991; 91(Suppl 2A):135-46S.
  44. Nitin M A, Dilip R K, Tushar P M, Gundu H T, Swati M, Geeta G B. Gastric colonisation and pneumonia in intubated critically ill patients receiving stress ulcer prophylaxis: A randomized, controlled trial. *Crit Care Med* 1992; 20:590-3.
  45. Marc J M B, Carlo A G, Siebe V D G, Frank H V T, Anton J B, Hans G W S, et al. The role of intragastric acidity and stress ulcer prophylaxis on colonisation and infection in mechanically ventilated ICU patients. *Am J Respir Crit Care Med* 1995; 152:1825-34.
  46. Bonten M J, Gaillard C A, de Leeuw P W, Stobberingh E E. Role of colonisation of the upper intestinal tract in the pathogenesis of ventilator-associated pneumonia. *Clin Infect Dis* 1997; 24:309-19.
  47. Bartlett J G. Selective decontamination of the digestive tract and its effect on antimicrobial resistance. *Crit Care Med* 1995; 23:613-5.
  48. Kollef M H. The role of selective digestive tract decontamination on mortality and respiratory tract infections: A meta-analysis. *Chest* 1994; 105:1101-8.
  49. Ferrer M, Torres A, Gonzalez J, de la Bellacasa JP, El-Ebiary M, Roca M, et al. Utility of selective digestive decontamination in mechanically ventilated patients. *Ann Intern Med* 1994; 120:389-95.
  50. Rumbak M J, Cancio M R. Significant reduction in methicillin-resistant *Staphylococcus aureus* ventilator-associated pneumonia associated with the institution of a prevention protocol. *Crit Care Med* 1995; 23:1200-3.
  51. Bassin A S, Niederman M S. Prevention of ventilator-associated pneumonia. An attainable goal? *Clin Chest Med* 1995; 16:195-208.
  52. Rello J, Ausina V, Ricart M, Castella J, Prats G. Impact of previous antimicrobial therapy on the etiology and outcome of ventilator-associated pneumonia. *Chest* 1993; 104:1230-5.
  53. Sterling T R, Edward J H, Walter T B, Kirkpatrick M B. Diagnosis and treatment of ventilator-associated pneumonia-Impact on survival. *Chest* 1996; 110:1025-34.
  54. Metersky M L. Ventilator-associated pneumonia: current concepts. *Infect Med* 1995; 12:727-33.