

## CLINICAL REVIEW

## Ventilator associated pneumonia

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Ventilator associated pneumonia is the most common nosocomial infection in patients receiving mechanical ventilation, and it accounts for about half of all antibiotics given in the intensive care unit (ICU).<sup>1</sup> Its reported incidence depends on case mix, duration of mechanical ventilation, and the diagnostic criteria used. It occurs in 9-27% of mechanically ventilated patients, with about five cases per 1000 ventilator days.<sup>2</sup> The condition is associated with increased ICU and hospital stay and has an estimated attributable mortality of 9%.<sup>3</sup>

A number of evidence based strategies have been described for the prevention of ventilator associated pneumonia, and its incidence can be reduced by combining several in a care bundle.<sup>4</sup>

The purpose of this review is to update readers on the diagnosis, management, and prevention of this serious infection.

Ventilator associated pneumonia is a hospital acquired pneumonia that occurs 48 hours or more after tracheal intubation.<sup>5</sup> It can usefully be classified as early onset or late onset pneumonia. Early onset pneumonia occurs within four days of intubation and mechanical ventilation, and it is generally caused by antibiotic sensitive bacteria. Late onset pneumonia develops after four days and is commonly caused by multidrug resistant pathogens. However, patients who have been in hospital for two or more days before intubation will probably harbour organisms more commonly associated with late onset pneumonia, regardless of the duration of ventilation.

### What causes ventilator associated pneumonia

The principal risk factor for the development of ventilator associated pneumonia is the presence of an endotracheal tube.<sup>6</sup> These tubes interfere with the normal protective upper airway reflexes, prevent effective coughing, and encourage microaspiration of contaminated pharyngeal contents. The importance of the endotracheal tube is emphasised by the incidence of pneumonia being significantly lower for non-invasive ventilation via a tight fitting facemask.<sup>7</sup> Reintubation after unsuccessful extubation also increases the risk of pneumonia.<sup>8</sup>

Most cases are caused by microaspiration of contaminated oropharyngeal secretions.<sup>9</sup> The oropharynx becomes rapidly colonised with aerobic Gram negative bacteria after illness, antibiotic treatment, or hospital admission as a result of

alterations in host defences and subsequent changes in bacterial adherence to mucosal surfaces. These contaminated secretions pool above the cuff of the trachea or tracheostomy tube and slowly gain access to the airway via folds in the wall of the cuff.<sup>6</sup> A bacterial biofilm, which is impervious to systemic antibiotics, gradually forms on the inner surface of the endotracheal tube and serves as a nidus for infection.<sup>10</sup> Ventilator cycling propels pathogen rich biofilm and secretions to the distal airways. The size of the biofilm and the virulence of the bacteria within it contribute to the risk of infection, but it is the host's immune response that determines whether parenchymal infection and ventilator associated pneumonia will develop.

Critical illness is associated with immunosuppression, and this increases susceptibility to nosocomial infection.<sup>11</sup> Neutrophils are central to the body's response to most bacterial infections, and mechanically ventilated patients have neutrophil dysfunction and impaired phagocytosis. Recent work by Morris and colleagues examined neutrophil function in patients with a high clinical suspicion of ventilator associated pneumonia. They found that patients had significantly reduced phagocytic activity secondary to the overexpression of the inflammatory anaphylotoxin C5a, excess levels of which cause neutrophil dysfunction.<sup>12</sup> Further work by the same group suggests that this C5a driven immunosuppression precedes the acquisition of nosocomial infection and is not merely a coincidental finding.<sup>13</sup>

### What are the risk factors for developing ventilator associated pneumonia?

Patients who are nursed in the supine position have an increased risk of pneumonia, presumably because of the increased likelihood of gastric aspiration.<sup>14</sup> Enteral feeding via a nasogastric tube may cause reflux of gastric contents and increase the risk of aspiration, but most intensive care physicians would agree that the benefits of providing adequate nutrition outweigh the increased risk of pneumonia.

Because the risk of developing pneumonia increases with duration of mechanical ventilation, modifiable factors associated with prolonged intubation such as oversedation or lack of protocol driven weaning increase the likelihood of pneumonia.<sup>15</sup>

### Summary points

- Ventilator associated pneumonia is the most common healthcare associated infection in intensive care
- The condition is associated with increased morbidity, mortality, length of stay, and costs
- Lack of a "gold standard" definition leads to both underdiagnosis and overdiagnosis
- A high clinical suspicion of pneumonia in a ventilated patient should prompt the immediate administration of an appropriate broad spectrum antibiotic(s)
- Implement evidence based interventions that reduce the incidence of pneumonia in all patients receiving mechanical ventilation

### Sources and selection criteria

I searched various sources to identify relevant evidence on the definition, epidemiology, and management of patients with ventilator associated pneumonia. These included PubMed, the Cochrane Library, and conference proceedings. I searched [www.clinicaltrials.gov](http://www.clinicaltrials.gov) for current research.

## How is ventilator associated pneumonia diagnosed?

Accurate diagnosis remains a challenge, with no consensus on a reference "gold standard" definition. Clinical diagnosis lacks sensitivity and specificity, leading to both overdiagnosis and underdiagnosis of the condition.<sup>5</sup> Despite the difficulties of establishing an accurate diagnosis, a high clinical suspicion of pneumonia should lead to the immediate administration of appropriate antibiotics. Delays in antimicrobial treatment increase mortality.<sup>16 17</sup>

Despite the lack of a universally agreed definition, ICU physicians generally agree that pneumonia should be suspected when there are new or persistent infiltrates on chest radiography plus two or more of the following<sup>18</sup>:

- Purulent tracheal secretions
- Blood leucocytosis ( $>12 \times 10^9$  white blood cells/L) or leucopenia ( $<4 \times 10^9$  white blood cells/L)
- Temperature greater than  $38.3^\circ\text{C}$ .

The Hospitals in Europe Link for Infection Control through Surveillance (HELICS) criteria are widely used for surveillance of ventilator associated pneumonia rates in Europe (fig 1⇓). Ventilator associated pneumonia is categorised as pneumonia (PN) 1-5 depending on the microbiological method used to make the diagnosis.

Making the diagnosis can be a challenge because many conditions commonly encountered in critically ill patients—such as pulmonary oedema, pulmonary haemorrhage, and acute respiratory distress syndrome—can mimic the signs and symptoms of pneumonia. Many ventilated patients have infiltrates on chest radiography that are not attributable to infectious pathology (fig 2⇓), and the presence of a new infiltrate only marginally increases the likelihood of ventilator associated pneumonia (summary likelihood ratio 1.7; 95% confidence interval 1.1 to 2.5).<sup>5</sup> Purulent tracheal secretions are often secondary to tracheobronchitis rather than parenchymal infection, and alterations in white cell count and fever symptoms can be caused by sepsis outside of the respiratory system.

Postmortem studies of patients suspected of having ventilator associated pneumonia suggest that using clinical criteria alone for diagnosis produces 30-35% false negative results and 20-25% false positive results.<sup>5</sup> Because of this lack of sensitivity and specificity, it is good practice to obtain microbiological samples of lower respiratory tract secretions before antibiotics are started. Samples can be obtained invasively or non-invasively. Invasive sampling methods include bronchoalveolar lavage (BAL), protected specimen brushing, and increasingly blind "mini-BAL." Mini-BAL, which is also

referred to as non-bronchoscopic BAL or blind BAL, is performed using specially designed catheters that allow sampling of the distal airways via the tracheal tube. Because a bronchoscope is not needed it is quick and technically simple, with culture results that are comparable to other lavage methods.<sup>19</sup> Invasively obtained samples are analysed quantitatively to differentiate oropharyngeal contaminants (which are present at low concentrations) from higher concentrations of infecting organisms. The diagnostic threshold is  $10^3$  colony forming units/mL for protected specimen brushing and  $10^4$  colony forming units/mL for BAL. However, bronchoscopically directed sampling may miss the portion of lung worst affected by disease, so its sensitivity and specificity vary greatly (11-77% and 42-94%).<sup>20 21</sup> Sampling can also be performed non-invasively, and the tracheal aspirates analysed quantitatively or qualitatively. This technique also misses many cases of pneumonia, with a reported sensitivity of 56-69% and a specificity of 75-95%.<sup>21</sup>

The relative benefits of non-invasive and invasive techniques for obtaining samples and differentiating between airway colonisation and true infection are still unclear. Although one French randomised uncontrolled study showed a reduction in mortality when an invasive diagnostic strategy was used,<sup>22</sup> five other trials found no differences in hospital mortality, length of stay, or duration of mechanical ventilation when compared with non-quantitative culture of endotracheal aspirates.<sup>23</sup> A randomised trial by the Canadian Critical Care Trials Group randomised 740 patients with suspected ventilator associated pneumonia to undergo either BAL and quantitative culture or tracheal aspiration with non-quantitative culture of the specimens. No significant difference was seen between groups in the primary outcome (28 day mortality; 18.9% and 18.4%;  $P=0.94$ ), days alive without antibiotics, or length of stay.<sup>24</sup> A recent systematic review of qualitative versus quantitative analysis concluded that quantitative analysis was not associated with reduced mortality, reduced length of stay in intensive care, or higher rates of antibiotic change.<sup>25</sup>

Several biomarkers have been investigated for diagnosing ventilator associated pneumonia, including procalcitonin, C reactive protein, and a glycoprotein known as soluble triggering receptor expressed on myeloid cells type 1 (sTREM-1).<sup>26</sup> The expression of sTREM-1 on phagocytes is strongly upregulated by exposure to bacteria. Although sTREM-1 concentrations are raised in BAL fluid from patients with ventilator associated pneumonia, the discriminatory value of this test is poor.<sup>27</sup> Procalcitonin, a calcitonin precursor hormone, is secreted in response to bacterial infection. Although it lacks sensitivity and specificity for the accurate diagnosis of pneumonia, its serial measurement may help reduce antibiotic exposure.<sup>28</sup> C reactive

protein also lacks sufficient sensitivity and specificity for the diagnosis of pneumonia, but it can be useful for assessing the appropriateness of antibiotic treatment.<sup>29</sup>

## Which organisms are associated with ventilator associated pneumonia?

To select the optimal antibiotic treatment it is essential to be aware of the organisms commonly associated with ventilator associated pneumonia. Most cases are bacterial in origin (table 1) and several organisms are often involved.<sup>30</sup> The clinical relevance of fungal and viral pneumonia is still poorly understood.

The duration of mechanical ventilation before the onset of pneumonia is an important determinant of the likely pathogen. Pneumonia that occurs within four days of intubation is typically caused by antibiotic sensitive community bacteria such as *Haemophilus* spp, streptococci including *Streptococcus pneumoniae*, and methicillin sensitive *Staphylococcus aureus*. Later infection is more commonly caused by multidrug resistant pathogens, including *Pseudomonas aeruginosa*, *Acinetobacter* spp, and methicillin resistant *S aureus*. However, it is increasingly recognised that patients who have been in recent close contact with the healthcare system are more likely to develop infection with multidrug resistant organisms. Hospital admission for two or more days during the 90 days before the development of ventilator associated pneumonia, chronic haemodialysis, residence in a nursing home, and intravenous antibiotics or chemotherapy within the past 30 days all increase the likelihood of extremely drug resistant bacterial infection.<sup>31</sup>

The pathogens associated with ventilator associated pneumonia also depend on case mix, underlying comorbidity, hospital, and type of ICU.<sup>32</sup> Each individual unit must collect continuous microbiological surveillance data to ensure optimal empirical antibiotic treatment of suspected pneumonia.

## Which antibiotics are used to treat ventilator associated pneumonia?

A high clinical suspicion of pneumonia should lead to the immediate administration of appropriate empirical antibiotics. Ideally, airway samples for microbiological analysis should be taken before administration of antibiotics as long as this does not seriously delay treatment because delayed or inappropriate initial antimicrobial treatment is associated with excess mortality.<sup>16 33</sup>

Choose initial antibiotics on the basis of the results of local surveillance data and patient specific factors such as severity of illness, duration of hospital stay, and previous antibiotic exposure. Involvement of the local microbiologist is mandatory.

Although no optimal regimen has been identified, the chosen drug(s) should have a high degree of activity against aerobic Gram negative bacilli. Guidelines issued by the British Society for Antimicrobial Chemotherapy recommend co-amoxiclav or cefuroxime for patients with early onset infections who have not previously received antibiotics and have no other risk factors for multidrug resistant pathogens.<sup>34</sup> In those who have previously received antibiotics or who have other risk factors, a third generation cephalosporin (cefotaxime or ceftriaxone), a fluoroquinolone, or piperacillin-tazobactam would be appropriate. Late onset pneumonia is more commonly associated with drug resistant bacteria, particularly *P aeruginosa*. To date, no specific antibiotic or regimen has been proved to be superior in the management of patients with ventilator associated

pneumonia secondary to *P aeruginosa*, and acceptable treatment options include ceftazidime, ciprofloxacin, meropenem, and piperacillin-tazobactam. When methicillin resistant *S aureus* is a possibility, vancomycin or linezolid should be included in the antibiotic regimen. Although linezolid penetrates lung tissue better than vancomycin, a recent meta-analysis of randomised controlled trials suggest that it is no better than vancomycin.<sup>35</sup>

Combination antibiotic treatment does not seem to be better than empirical broad spectrum monotherapy, which is cheaper and exposes patients to fewer antibiotics.<sup>34</sup> A de-escalation strategy should be used once the results of antimicrobial susceptibility tests are available. Antibiotics can be safely discontinued after eight days if an adequate clinical response is suggested by a resolution in the signs and symptoms of active infection (such as a reduction in C reactive protein, white cell count, and temperature, plus an improvement in oxygenation).<sup>36</sup>

## Can ventilator associated pneumonia be prevented?

Although prevention of pneumonia is a vital part of the management of patients undergoing invasive mechanical ventilation, many studies of strategies and interventions that significantly reduce ventilator associated pneumonia rates fail to show a significant benefit in clinical outcomes, such as length of stay, duration of mechanical ventilation, or mortality.<sup>37</sup> This is probably because it is difficult to accurately diagnose ventilator associated pneumonia and many preventive measures simply reduce airway colonisation and not invasive infection.

The three main ways of preventing pneumonia are to reduce colonisation of the aerodigestive tract with pathogenic bacteria, prevent aspiration, and limit the duration of mechanical ventilation. Best results are seen by using various combinations (bundles) of interventions in all mechanically ventilated patients.<sup>4</sup> Recent guidance from the National Institute for Health and Clinical Excellence recommends that all bundles include oral antisepsis and nursing in the semirecumbent position.<sup>38</sup>

## Reducing airway colonisation

Selective decontamination of the digestive tract and oral decontamination both aim to decrease the bacterial load of the digestive tract. Oral decontamination using antiseptics such as chlorhexidine seems to lower the risk of ventilator associated pneumonia (relative risk 0.61, 0.45 to 0.82),<sup>39</sup> especially when combined with thorough mechanical cleaning of the oral cavity. Selective decontamination involves the oral and gastric administration of non-absorbable oral antibiotics (usually polymyxin, tobramycin, and amphotericin B) plus the intravenous administration of a broad spectrum antibiotic. Despite large meta-analyses showing a reduction in the incidence of pneumonia,<sup>40</sup> selective decontamination is not widely used in the United Kingdom because of worries about the emergence of antibiotic resistance and increased incidence of *Clostridium difficile* infection. However, there is no evidence to support these concerns.

Microbial biofilms rapidly form on the luminal surface of endotracheal tubes and act as a reservoir for infection. Because silver has broad spectrum antimicrobial activity, coating the endotracheal tube with silver reduces bacterial colonisation and biofilm formation. A recent prospective randomised controlled study comparing traditional endotracheal tubes with silver coated ones showed a significant relative risk reduction of 35.9% (3.6% to 69%) in the occurrence of ventilator associated pneumonia



with silver tubes.<sup>41</sup> However, **no benefit** was seen on the duration of intubation, duration of stay in intensive care, or mortality.

## Preventing aspiration

All patients without specific contraindications should be nursed in the semirecumbent position, with the head raised at **45°**.<sup>42</sup>

Secretions that have pooled above the cuff of the tracheal tube can be removed by **subglottic secretion drainage** using specially designed tubes with a separate dorsal lumen that opens directly above the cuff. A meta-analysis of five prospective studies found this technique to be effective in preventing ventilator associated pneumonia (relative risk **0.51**, 0.37 to 0.71) in patients expected to need more than 72 hours of mechanical ventilation.<sup>43</sup>

Recently introduced endotracheal tubes feature an **ultrathin polyurethane** cuff membrane that has **narrower longitudinal folds** when inflated, which **limits microaspiration**.<sup>44</sup> A retrospective study reported a reduction in ventilator associated pneumonia rates from **5.3 per 1000** ventilator days to **2.8** per 1000 ventilator days after introduction of these tubes (P=0.0138),<sup>45</sup> although more robust studies are lacking.

## Limiting duration of mechanical ventilation

The duration of mechanical ventilation is strongly associated with the development of pneumonia. Therefore, strategies aimed at reducing the duration of tracheal intubation may reduce the incidence of pneumonia. **Oversedation prolongs** mechanical ventilation and should be avoided by careful assessment of sedation status and daily interruption of sedation if appropriate.<sup>15</sup> Weaning protocols have also been shown to hasten discontinuation of mechanical ventilation.<sup>46</sup> Although **tracheotomy** is often advocated to aid earlier weaning from respiratory support, **little evidence** exists to suggest that early tracheotomy **reduces** the incidence of **pneumonia**.<sup>47</sup>

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**Additional educational resources for healthcare professionals**

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**Unanswered questions and ongoing research**

Is the incidence of ventilator associated pneumonia a useful quality indicator in intensive care? There is an increasing demand to use this parameter as such, but the lack of a gold standard definition and the paucity of studies showing a clinically meaningful improvement with apparent reduction in pneumonia suggest that this should be resisted

Do aerosolised antibiotics have a role in the management of patients with ventilator associated pneumonia?

Do probiotics prevent ventilator associated pneumonia?

Do immunomodulatory agents have a role in the management of patients with ventilator associated pneumonia?

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## Table

**Table 1 | Distribution of organisms isolated from cases of ventilator associated pneumonia by bronchoscopic techniques in 24 studies (1989-2000) including 1689 episodes and 2490 pathogens<sup>30</sup>**

Pathogen	Frequency (%)
<i>Pseudomonas aeruginosa</i>	24.4
<i>Acinetobacter</i> spp	7.9
<i>Stenotrophomonas maltophilia</i>	1.7
Enterobacteriaceae*	14.1
<i>Haemophilus</i> spp	9.8
<i>Staphylococcus aureus</i> †	20.4
<i>Streptococcus</i> spp	8.0
<i>Streptococcus pneumoniae</i>	4.1
Coagulase negative staphylococci	1.4
<i>Neisseria</i> spp	2.6
Anaerobes	0.9
Fungi	0.9
Other (<1% each)‡	3.8

\*Distribution when specified: *Klebsiella* spp 15.6%; *Escherichia coli* 24.1%; *Proteus* spp 22.3%; *Enterobacter* spp 18.8%; *Serratia* spp 12.1%; *Citrobacter* spp 5.0%; *Hafnia alvei* 2.1%.

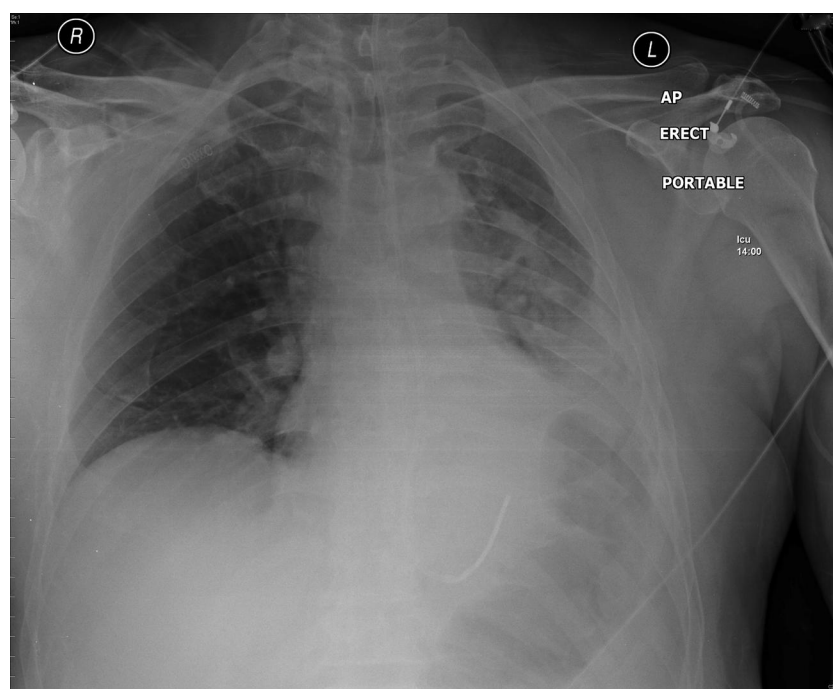
†Distribution when specified: methicillin resistant *S aureus* 55.7%; methicillin sensitive *S aureus* 44.3%.

‡Including *Corynebacterium* spp, *Moraxella* spp, and *Enterococcus* spp.

## Figures

<b>Radiography</b>	Two or more serial chest radiographs or computed tomograms suggestive of pneumonia for patients with underlying cardiac or pulmonary disease. In patients without underlying cardiac or pulmonary disease one definitive chest radiograph or computed tomogram is sufficient
<b>And at least one of the following</b>	
<b>Symptoms</b>	Fever $>38^{\circ}\text{C}$ with no other cause Leucopenia ( $<4 \times 10^9$ white blood cells/L) or leucocytosis ( $>12 \times 10^9$ white blood cells/L)
<b>And at least one of the following (or at least two if clinical pneumonia only = PN4 and PN5)</b>	
	New onset of purulent sputum or change in character of sputum (colour, odour, quantity, consistency) Cough, dyspnoea, or tachypnoea Suggestive auscultation (rales or bronchial breath sounds), rhonchi, wheezing Worsening gas exchange (for example, oxygen desaturation, increased oxygen requirements, or increased ventilation demand)
<b>And according to the used diagnostic method</b>	
<b>Microbiology</b>	PN1: Positive quantitative culture from minimally contaminated lower respiratory tract specimen – bronchoalveolar lavage specimen $\geq 10^4$ colony forming units/mL PN2: Positive quantitative culture of lower respiratory tract (tracheal aspirate) with a threshold of $10^5$ colony forming units/mL PN3: Positive culture related to no other source of infection – positive pleural fluid culture, pulmonary abscess with positive needle aspiration, positive histology, or positive exams for pneumonia with virus or particular organism (such as <i>Aspergillus</i> ) PN4: Positive sputum culture or non-quantitative lower respiratory tract culture PN5: No positive microbiology

**Fig 1** Hospitals in Europe Link for Infection Control through Surveillance (HELICS) criteria for ventilator associated pneumonia (PN)



**Fig 2** A typical chest radiograph from a critically ill patient with a tracheostomy showing patchy infiltration of the lower zone of the left lung, which may or may not be infective in origin