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REVIEW ARTICLE

Ventilator-associated pneumonia Diagnosis, pathogenesis and prevention

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Summary

Ventilator-associated pneumonia is common, difficult to diagnose, affects the most vulnerable of patients and carries a high mortality. During prolonged mechanical ventilation the oropharynx, sinuses, dentition and stomach of critically ill patients become colonised with pathogenic bacteria. Colonised secretions pool in the oropharynx and subglottic space. These secretions repeatedly gain access to the lower airways by leakage past the tracheal tube cuff. If host defence mechanisms are overwhelmed, multiplication occurs in the lower respiratory tract producing an inflammatory response in the bronchioles and alveoli. The inflammatory response is characterised by capillary congestion, leucocyte and macrophage infiltration and fibrinous exudation into the alveolar spaces. If this inflammatory response occurs more than 48 h after intubation, it is called ventilator-associated pneumonia. Prevention depends on reducing upper airway and gastrointestinal reservoirs of bacteria, reducing or abolishing aspiration of these bacteria past the tracheal tube cuff and enhancing bacterial clearance from the lower airways.

Keywords *Ventilation, mechanical*; ventilator-associated pneumonia. *Intubation*; tracheal.

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Despite an increased understanding of the pathogenesis and diagnosis of ventilator-associated pneumonia (VAP), prevention has remained problematic. There is now good evidence for continuous leakage of infected secretions past the tracheal tube cuff being responsible for VAP. As a result, VAP strikes critically ill patients and increases their morbidity and mortality. The aim of this review is to discuss the diagnosis and pathogenesis of VAP, including a brief review of natural defence mechanisms. The review also covers the prevention of VAP with special reference to new developments aimed at reducing aspiration past the cuff.

Definition

VAP is usually a bacterial nosocomial pneumonia that develops in patients with acute respiratory failure supported by mechanical ventilation. The pneumonia was neither present nor incubating at the time of intubation [1].

Incidence, morbidity and mortality

The European Prevalence of Infection in Intensive Care (EPIC) study identified intensive care unit (ICU)-acquired pneumonia as the most prevalent infection found in European ICUs [2]. The incidence of VAP in adult ICU patients ranges from 3 to 52% [3]. Such large variation in incidence is due to case-mix differences, differences in the diagnostic criteria used, and the variable sensitivity and specificity of the available diagnostic tests. The incremental risk of VAP in a medical adult ICU population is ~ 1% per day of ventilation (Fig. 1); for example, the cumulative risk at 10 days of mechanical ventilation was 6.5% and at 20 days this had risen to 19% [4]. Tracheal intubation and mechanical ventilation increase the risk of pneumonia in hospitalised patients by 7–21 times [5, 6]. As well as increasing length of stay by up to threefold [7, 8] and increasing cost [9], mortality rates are higher for patients with VAP (71%) than for those without (29%) [4]. However, it is likely that many patients die *with*, rather than *of*, VAP. Crude mortality rates for patients with VAP depend on the case mix and range from 13 to 71% [10], and the mortality directly attributable to the VAP is estimated at 27% although it is higher with *Pseudomonas aeruginosa* and *Acinetobacter* infections [8]. The bacteria responsible for VAP vary with case mix, institution and antibiotic usage.

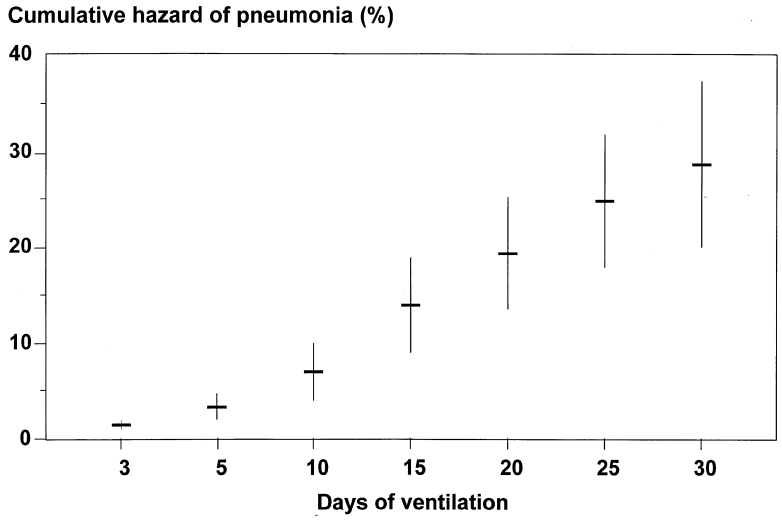

Figure 1 Cumulative hazard of VAP in 567 patients. Data points are mean values (1 SD) (adapted from Fagon *et al.* [4] with permission).

Table 1 shows the common organisms isolated, but 40% of cases of VAP are polymicrobial [4].

Diagnosis

Gold standard

The gold standard for the diagnosis of VAP is combined histopathological and microbiological examination of lung tissue showing both an inflammatory response and micro-organisms (Fig. 2). Clearly, this is rarely possible in critically ill patients when an ante-mortem diagnosis is required. However, even this gold standard has recently been called into question when the rate of histological recognition of VAP varied between pathologists [11], and the microbiologial infection of lung tissue and histological changes of pneumonia were found to be poorly related.

Table 1 Frequency of organisms recovered from protected specimen brush specimens ($> 10^3$ cfu.ml^{-1}) in 83 episodes of VAP. Adapted from Fagon *et al.* [4].

Organism	Frequency (%)
Gram-negative bacteria	
Pseudomonas aeruginosa	31
Acinetobacter spp.	15
Proteus spp.	15
Haemophilus spp.	10
Branhamella catarrhalis	10
Escherichia coli	8
Klebsiella spp.	4
Enterobacter cloacae	2
Gram-positive bacteria	
Staphylococcus aureus	33
Streptococcus pneumoniae	6
Other streptococci	15
Corynebacterium spp.	8
Anaerobes	2

Post-mortem studies demonstrated that following prolonged mechanical ventilation, there is widespread polymicrobial colonisation and infection of the lungs of critically ill patients [12, 13]. Importantly, the bacterial counts from lung biopsy cultures appeared to be poorly related to the presence, absence or histopathological grade of pneumonia. Lack of a definitive measure of VAP is one of the major confounding influences in studying strategies for reducing VAP.

Clinical diagnosis

The clinical diagnosis of VAP is difficult and depends upon a clinical suspicion and laboratory tests (see below). The laboratory tests are required because of the poor specificity (i.e. many false positives) when clinical suspicion alone is used.

Classification of probability of VAP

The following diagnostic criteria have been adapted from the recommendations of the first international consensus conference on the clinical investigation of VAP [14].

Clinical suspicion of VAP depends upon:

1 fever $> 38.3\,^{\circ}$C, leucocytosis and deterioration in gas exchange;

2 radiographic appearance of new and persistent infiltrates;

3 grossly purulent tracheobronchial secretions.

Unfortunately clinical criteria alone have poor specificity but with further investigation, patients can be categorised according to the likelihood of VAP (Table 2). Clearly most diagnoses of VAP fall into the probable VAP group, and in centres relying on endotracheal aspirate (ETA) sampling the diagnosis falls outside this classification.

The diagnostic value of the chest X-ray

The consensus diagnostic criteria [14] and the Centers of Disease Control (CDC) criteria [15] imply that the

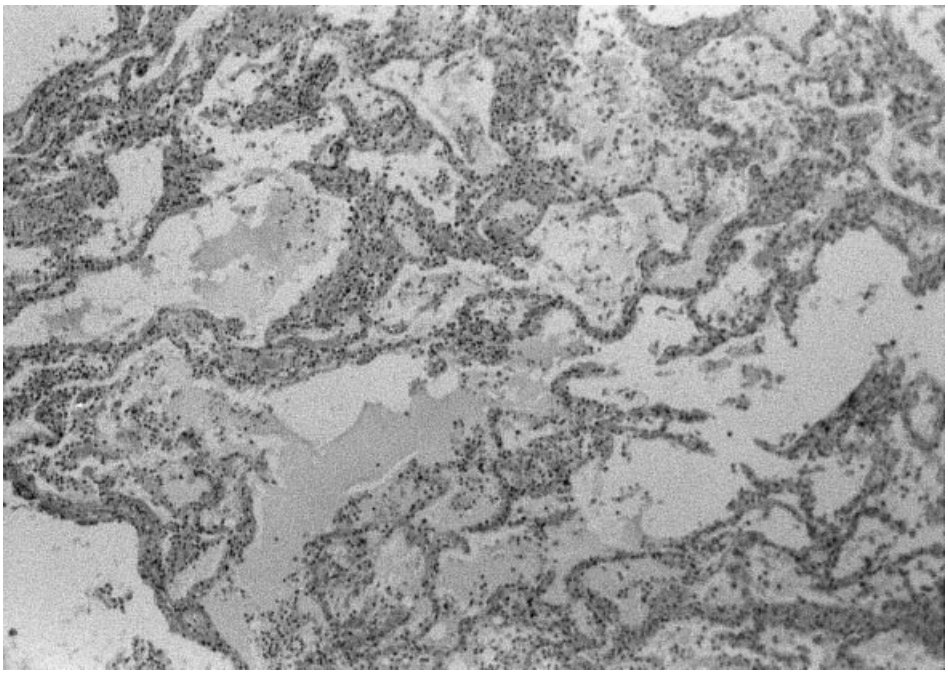

Figure 2 Histological sample of lung tissue in VAP.

radiographic appearance of new and persistent infiltrates must always be present in VAP (i.e. 100% sensitivity; Fig. 3). However, many patients without new and persistent infiltrates at post-mortem had histological or microbiological pneumonia [13]. Only 44% of pulmonary densities on ICU chest radiographs are in fact infectious [16]. Thus, while pulmonary infiltrates are essential for the diagnosis of VAP, the cause of such infiltrates is frequently non-infective and VAP may exist without infiltrates.

Protected specimen brushing (PSB)

In order to obtain a reliable lower respiratory tract specimen that is not contaminated by tracheal organisms, protected specimen brushings can be employed. With this technique, the brush is enclosed in a concentric dual catheter device with its distal end occluded by a dissolvable plug. When the catheter has been bronchoscopically placed in the desired distal airway the brush is advanced expelling the plug. A brushing is taken and the brush is

Table 2 First International Consensus Conference on the Clinical Investigation of Ventilator-Associated Pneumonia criteria for the definition of pneumonia. Adapted from Pingleton *et al.* [14].

Definite VAP
Clinical suspicion plus one of the following:
1. Positive needle aspirate culture from a pulmonary abscess.
2. Histopathological evidence of pneumonia on open lung biopsy or post-mortem examination, and a positive quantitative culture of lung parenchyma at $> 10^4$ micro-organisms per gram of tissue.

Probable VAP
Clinical suspicion plus one of the following:
1. The presence of positive quantitative culture by reliable lower respiratory specimen (BAL or protected specimen brush at $> 10^4$ and $> 10^3$ cfu.ml^{-1}, respectively).
2. The presence of a positive blood culture unrelated to another source of, and identical organism to, that recovered from the lower respiratory tract.
3. Positive pleural fluid culture of an identical micro-organism to that recovered from the lower respiratory tract.

Probable absence of VAP
Lack of significant growth in a reliable respiratory specimen with one of:
1. Resolution of clinical suspicion of VAP without antibiotics.
2. Alternative diagnosis established for fever and infiltrates.

Definite absence of VAP
1. Post-mortem shows no histological signs of lung infection.
2. Definite alternative aetiology, and negative reliable lower respiratory specimen.

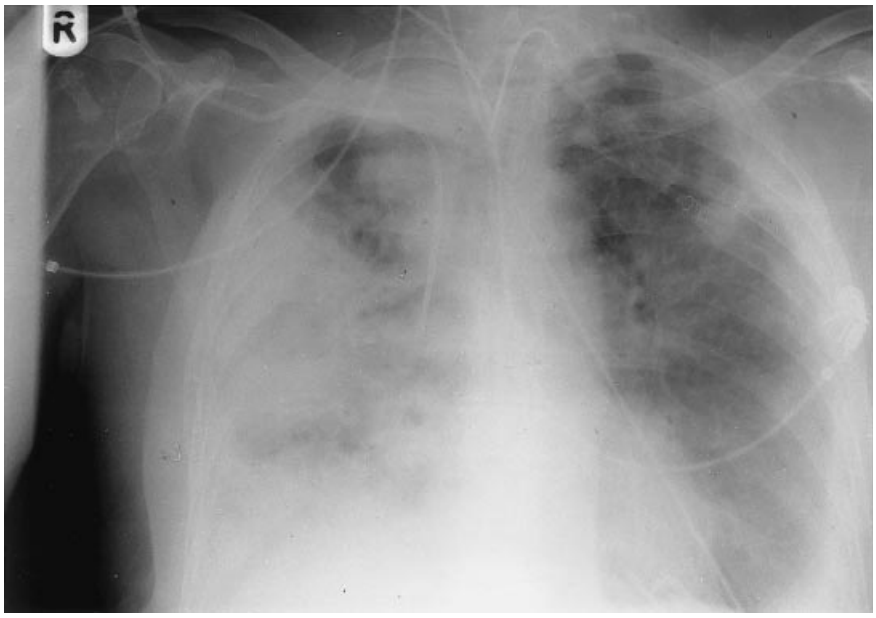

Figure 3 Chest X-ray of a patient with VAP.

then retracted and isolated within the catheter, before being withdrawn through the bronchoscope. The brush is placed in 1 ml of transport medium and a quantitative culture obtained. A growth of 10^3 colony forming units (cfu) per ml indicates a positive result. This equates to 10^5–10^6 cfu.ml^{-1} in the bronchial secretions. In 16 reported studies, PSB quantitative cultures had a mean sensitivity of 82% and a mean specificity of 92% [17].

Bronchioalveolar lavage (BAL)

Bronchioalveolar lavage is performed by wedging the bronchoscope in a distal airway and instilling 120 ml of normal saline [18]. When lavage volumes of 10–20 ml are used this is called mini-BAL and if a balloon-tipped catheter is used to isolate the bronchopulmonary segment, this is known a protected BAL. As much of the saline as possible is aspirated and quantitatively cultured. This method samples a larger portion of lung parenchyma than PSB. A growth of 10^4 cfu.ml^{-1} indicates a VAP. This also equates to 10^5–10^6 cfu.ml^{-1} in the bronchial secretions. Also BAL fluid enables earlier diagnosis as the microscopic identification of intracellular organisms in $>2\%$ of phagocytic cells is $>95\%$ specific for pneumonia.

In seven reported studies, BAL quantitative cultures had a mean sensitivity of 86% and a mean specificity of 87% [17].

Nonbronchoscopic PSB and BAL

Nonbronchoscopic PSB is performed by inserting the brush directly through the tracheal tube to ≈ 35 cm or until resistance is felt. A specimen is obtained by expressing and retracting the inner cannula and brush as with bronchoscopic PSB. Nonbronchoscopic BAL is performed by guiding a directional tip catheter to the main stem bronchus of the lung with suspected pneumonia. The inner cannula is then advanced until resistance is felt and the catheter is wedged. Up to 100 ml of saline is instilled and suctioned until at least 25 ml of specimen is obtained. This blind technique is quicker and cheaper to perform and has good concordance with bronchoscopic techniques [19]. The good agreement between bronchoscopic and nonbronchoscopic techniques emphasises the disseminated nature of lower respiratory tract colonisation and infection in intubated critically ill patients. In nine reported studies of nonbronchoscopic techniques (PSB and BAL), the mean sensitivity was 80% and a mean specificity was 82% [17].

Endotracheal aspirates

An ETA is collected in a sputum trap by passing a sterile suction catheter blindly down the tracheal or tracheostomy tube into the distal trachea or proximal bronchial tree and applying suction as the catheter is withdrawn. The bacterial origin may therefore be from bronchial or tracheal secretions, tube biofilm or contaminant. Specificity is therefore unfortunately low, particularly if nonquantitative cultures are used. In five reported studies of ETA nonquantitative cultures, the mean sensitivity was 78% with a mean specificity of 19%. In nine reported studies of ETA quantitative cultures, the mean sensitivity was 69% with a mean specificity of 80% [17]. The significant

growth level of 10^6 cfu.ml^{-1} is often, but not invariably, used. If lower values are used then the test becomes more sensitive and less specific.

Complications of BAL, PSB and ETA

The most common complication of these procedures is hypoxaemia, particularly associated with BAL. A median fall in arterial oxygen pressure of 1 kPa was seen in a study of 35 patients with unchanged inspiratory oxygen before and after BAL [20]. PSB can cause minor bleeding and three pneumothoraces occurred in 25 patients in one study [21]. However, ETAs are safe and, apart from minor haemorrhage, serious complications are uncommon.

Choice between PSB, BAL or ETA

The choice of diagnostic test depends upon the following:
1 The sensitivity and specificity of the three techniques (Table 3). The choice of technique depends upon how important the clinician feels the diagnosis is. If no cases should be missed then the test with the highest sensitivity should be chosen (e.g. bronchoscopic BAL) or lower thresholds used for the quantitative culture (reduced from 10^4 to 10^3 cfu.ml^{-1}).
2 Prior antibiotic therapy. If given prior to the test, antibiotics alter the investigation's receiver–operator characteristic curve and so alter the combination of sensitivity and specificity [22]. Ideally specimens need to be taken prior to the introduction of new antibiotics, but in clinical practice this may be difficult.
3 Complication rate, ease of sampling and speed of result also influence choice.

BAL and ETA allow earlier identification of organisms than PSB as the fluid can be examined microscopically. PSB and BAL are more invasive, expensive, labour-intensive and associated with more complications than ETA. The need for specialised equipment and staff to obtain a BAL or PSB specimen could delay antibiotic introduction compared with collecting an ETA. The introduction of early appropriate antibiotic treatment should be a priority as this improves the outcome of VAP [23, 24]. The poor relationship between bacterial counts from lung biopsy and the presence of pneumonia brings into question the validity of bronchoscopically guided BAL and PSB analyses for the diagnosis of pneumonia. Kirtland *et al.* [13] found that qualitative ETAs had a sensitivity of 87% in recognising bacteria simultaneously present in lung parenchyma, and suggested that empirical antibiotic therapy can be accurately guided by ETAs. Quantitative ETAs may be as useful as BAL and PSB for the diagnosis of VAP and as a guide to appropriate antibiotic treatment [25, 26]; in fact, bronchoscopic techniques may lead to greater antibiotic use with no reduction in mortality [27]. Advantages of ETA compared with bronchoscopic techniques include simplicity (as it can be performed by nonmedical staff), fewer delays in sampling and therefore more expedient antibiotic treatment, fewer complications and reduced costs.

Overall, while bronchoscopic techniques are probably the most scientifically robust at present, the ease of use and comparable performance of quantitative ETAs makes this the technique of choice in most ICUs.

Pathogenesis

Colonisation implies the presence of bacteria on the mucosa without a host response. In health the oropharynx is colonised by nonpathogenic bacteria and the lower respiratory tract is sterile. In the ventilated patient, the colonisation of the contiguous structures of the subgingival plaque, peridontal areas, oropharynx, sinuses, stomach and trachea with pathogenic bacteria have been termed transcolonisation [28]. This transcolonisation normally occurs prior to the development of VAP [29]. Colonisation patterns vary and although the enteric Gram-negative bacteria (GNB) usually colonise the oropharynx before the trachea, the opposite may be true of *Pseudomonas* spp. [30, 31]. This is caused by the increased binding affinity of *Pseudomonas* spp. to ciliated tracheal epithelial cells compared with buccal cells. Therefore concomitant exposure of the oral and tracheal surfaces to an inoculum of *Pseudomonas* may only lead to tracheal colonisation [28].

Table 3 Sensitivity and specificity data from clinical trials for quantitative cultures of protected specimen brushes, BAL, nonbronchoscopic PSB or BAL and endotracheal aspirates; and nonquantitative endotracheal aspirates. Mean values adapted from Griffin & Meduri [17].

Technique	Bronchoscopic PSB (Quantitative)	Bronchoscopic BAL BAL (Quantitative)	Nonbronchoscopic BAL or PSB (Quantitative)	Endotracheal aspirate (Quantitative)	Endotracheal aspirate (Nonquantitative)
Number of studies	16	7	9	9	5
Mean sensitivity [range]; %	82 [62–100]	86 [72–100]	80 [60–100]	69 [38–91]	78 [57–88
Mean specificity [range]; %	92 [60–100]	87 [69–100]	82 [66–100]	80 [59–92]	19 [0–33]

Normal adults aspirate oropharyngeal flora during sleep [32] yet rarely develop pneumonia. There is a balance between the size and nature of the inoculum and the host's defence capabilities as to the susceptibility to VAP. For example, healthy hamsters withstand infection with an intratracheal inoculation of 6×10^3 organisms of *Ps. aeruginosa*; however, when increased to 5×10^6 organisms, foci of bronchopneumonia are observed which resolve without treatment [33]. Bolus inoculation or aspiration of a nidus of contaminated material, as opposed to aerosolisation, are both more efficient in producing pneumonia in animal models [28].

Host susceptibility is also an important determinant of whether tissue invasion and VAP will develop. Pre-existing lung injury in the hamster model increased the bacterial concentrations in lung tissue and the severity of pneumonia at a given inoculum [33]. In humans, VAP occurs more often in patients with acute respiratory distress syndrome (ARDS) [34, 35]. There is also a change in bacterial flora with illness. At post-mortem the pulmonary parenchyma of previously healthy individuals invariably contained oropharyngeal flora with infrequent aerobic GNB. However, hospitalised patients' lungs have a 62% incidence of aerobic GNB [36]. Aerobic GNB colonisation increases with increasing severity of illness, as indicated by the presence of coma, respiratory tract disease, hypotension, tracheal intubation, acidosis, uraemia and either leucocytosis or leucopenia [37]. Comorbidities such as diabetes mellitus, malnutrition, renal failure, neoplastic and liver disease all increase the rate of GNB colonisation and impair leucocyte function. Pulmonary oedema may impair respiratory bacterial clearance; resultant surfactant loss is associated with impaired alveolar macrophage function and alveolar fluid can serve as a bacterial growth medium [38]. The combination of comorbidities, and especially lung pathology, weakens the host defences against bacterial colonisation and hence VAP in critically ill patients (Fig. 4).

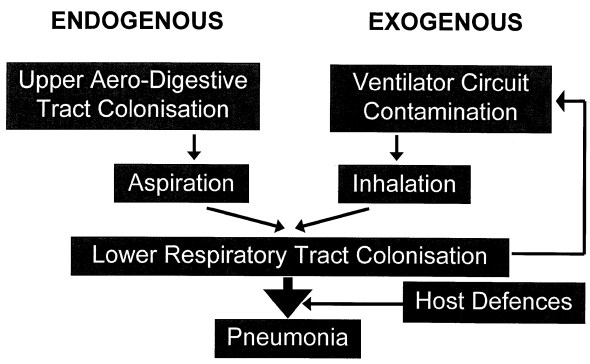

Figure 4 The pathogenesis of VAP.

Sources of colonising bacteria – upper airway and gastrointestinal bacterial reservoirs

Dentition

During critical illness effective oral hygiene, despite best nursing care, will decline and there is a rapid shift of dental plaque colonisation from nonrespiratory pathogens to aerobic GNB and *Staphylococcus aureus* [39]. Dental plaque increases with ICU stay, and the bacterial flora frequently mirrors that of tracheal aspirates [40].

Oropharynx

In health, the oropharynx is colonised predominantly by nonpathogenic bacteria, but in hospitalised patients, this flora is replaced with pathogenic bacteria, predominantly aerobic GNB and staphylococci, and this increases the risk of VAP [41]. Prolonged exposure of the epithelial surface to the bacterial adhesin molecules and the changes in host epithelial cell receptors in critical illness promote this abnormal colonisation. Fibronectin is normally secreted into the oropharynx with the saliva and coats the buccal epithelium. The fibronectin creates an adhesive surface favouring the binding of commensal oral strepococci. Decreases in serum fibronectin associated with sepsis may cause decreases in salivary fibronectin. Also oropharyngeal inflammation and the release of polymorphonuclear elastase increase proteolytic breakdown of buccal fibronectin and many respiratory pathogens also release proteases capable of degrading fibronectin. Fibronectin depletion reduces streptococcal binding sites and favours aerobic GNB colonisation [28]. Aerobic GNB colonisation rates increase with severity of illness and systemic antibiotic therapy [37] by reducing the normal inhibitory flora. In the critically ill, supine, ventilated patient oropharyngeal secretions pool in the oropharynx and subglottic space above the tracheal tube cuff [42], so forming a reservoir of infected secretions.

Sinuses

The risk of nosocomial sinusitis is increased with nasotracheal and nasogastric intubation [43]. The incidence (1.4–100%) of sinus infection is often underestimated because of a lack of clinical signs. The predominant organisms involved are aerobic GNB, there is a clear association between sinusitis and VAP, and sinusitis increases the risk of VAP by 3.8 [44].

Stomach

The stomach is a potential large reservoir for aerobic GNB. Reductions in gastric acidity increase the rate of gastric colonisation. H_2 antagonists and antacids increase pH and gastric colonisation more than the cytoprotective

agent sucralfate [45, 46]. Risk factors for gastric colonisation include duodenal [47] and gastric [48] enteral feeding. The importance of the gastropulmonary route for VAP pathogenesis remains controversial because studies of colonisation sequences prior to the development of VAP have failed to show consistently the stomach as an initial or preceding site of colonisation [48–50]. However, many of the organisms causing VAP do arise from the gastrointestinal tract and this is the basis for selective decontamination of the digestive tract (SDDT).

Faeco-oral or faeco-tracheal route

Cross-colonisation or transfer of rectal bacteria by nursing and medical staff may play a role in colonisation [50], and good infection control measures are essential, but this route should only play a minor role in the pathogenesis of VAP in hospitalised patients.

Microbial entry mechanisms

Aspiration past the tracheal tube cuff

The high-volume low-pressure (HVLP) cuff of a tracheal tube does not prevent the leakage of potentially infected fluid from the subglottis to the trachea. Dye placed in the subglottic space will pass along folds within the cuff wall to the trachea in 87–100% of cases [51–53]. In a ventilatory model [54] and in the cadaveric trachea [55], the rate of leakage along the cuff folds was found to be of the order of magnitude of millilitres per minute and leakage occurred despite increasing the cuff pressure above normal (Fig. 5).

Figure 5 An HVLP cuff inflated to an intracuff pressure of 30 cmH_2O in a 2-cm-diameter cylinder demonstrating the mechanism of leakage along folds within the cuff wall.

Contamination through the respiratory apparatus

The usual sequence of contamination of the tracheal tube and ventilator circuit has been demonstrated recently [56]. Normally the bacteria are acquired endogenously from the oropharynx or stomach, seed the trachea past the tube cuff and subsequently contaminate the tracheal tube and ventilator tubing. However, *Ps. aeruginosa* may colonise the trachea without first colonising the oropharynx as discussed previously [30, 31]. Rarely direct inoculation through the respiratory apparatus may be responsible, in some cases due to cross-contamination or inadequate cleaning and sterilisation procedures.

Biofilms

The inner lumen of a tracheal tube rapidly develops viscous adhesive layers of accretions containing bacteria, including aerobic GNB and *Staph. aureus,* at concentrations of up to 10^6 $cfu.cm^{-1}$ of tube. Particles of this biofilm can be propelled into the trachea and distal lung by shear forces of gas flow and passing tracheal suction catheters [57].

Ventilator circuit

A recent systematic review of randomised trials of airway management in the ICU [58] showed that the frequency of ventilator circuit changes had little influence on the rate of VAP, although infrequent changes were associated with a modest decrease in VAP rate. The increased rate of VAP with circuit changes might be due to more manipulations of the patient, the tracheal tube and the ventilator tubing. This can result in the inadvertent flushing of contaminated tubing condensate into the patient's trachea or increased leakage of secretions past the cuff of the tracheal tube. A recent study of 637 patients showed that 7- and 30-day circuit change intervals have lower risks for VAP than 2-day change intervals [59].

Closed suction systems have been developed for multiple use to remove the requirement to break the closed circuit in order to pass a suction catheter. This device reduces the incidence of arterial desaturation during suctioning due to the maintenance of ventilation and positive end-expiratory pressure (PEEP) [60]. However, there is no difference in VAP rates with closed, as opposed to open, tracheal

suction systems (increased tracheal colonisation occurred with the closed system in one study [61]), despite their 11-fold cost [62]. Further evidence of the beneficial effect of closed suction systems is awaited.

Humidifier

Heat and moisture exchange (HME) humidification, as opposed to heated humidifiers, may have a protective effect through minimising tubing condensate and colonisation. HME humidifiers have a relative risk of VAP occurrence of 0.34–0.86 [58]. Ventilator tube condensate frequently has high bacterial counts with a median level of colonisation at 24 h of 7×10^4 organisms.ml^{-1}; condensate can collect in circuits at a mean rate of 30 ml.h^{-1} [63]. This infected condensate may wash back from the ventilator tubing into the trachea.

Nebulisers

As many as 68% of in-circuit nebulisers, if used repeatedly in the same patient, become contaminated with high levels of organisms ($> 10^3$.ml^{-1}). These bacteria are aerosolised to small particles capable of reaching the peripheral lung [64]. Thorough cleaning of the nebulisers between treatments reduced this contamination to 20%, and the use of modern disposable systems may reduce this further.

Host defence mechanisms – microbial clearance

Microbial clearance falls into two broad categories, mechanical mechanisms and immunological mechanisms.

Cough

A tracheal tube bypasses the epiglottis thereby reducing an effective cough. Sedation, opioid analgesia, neuromuscular also all depress the cough reflex.

Mucociliary clearance

Cilial beating on viscous mucus propels debris towards the larynx for expectoration. As well as providing a physical barrier to mucus clearance, tracheal intubation can reduce tracheal mucus velocity [65]. Increasing oxygen concentrations are associated with tracheobronchial inflammation and epithelial sloughing and a progressive reduction in tracheal mucus velocity [66].

Inadequate humidification causes dehydration of the periciliary mucus layer and damage to cilia thereby impairing the function of the mucociliary elevator; the degree of damage is proportional to the duration of ventilation with dry gases [67]. Thus, intubation itself predisposed to VAP through the breakdown of host defences.

Tracheobronchial tree

Immunologically active cells, such as neutrophils and macrophages, and substances within the mucus layers, such as antimicrobial lysozyme, secretory immunoglobulin (Ig) A and antiproteases, are usually responsible for bacterial degradation and clearance. In health a cuffed tracheal tube causes mucosal injury at the vocal cords, at the level of the cuff and at the tube tip [68]. Bile and gastric aspiration may exacerbate these injuries and delay healing [69]. Tracheal toilet with suction catheters causes tracheal and brochial mucosal injury [70]. Mucosal injury and exposure of basement membrane predispose to bacterial adhesion [28].

Alveoli

Bacteria entering the alveolus are exposed to opsonins (e.g. IgA, IgG, complement 3b, surfactant phospholipids) in the fluid lining the epithelium. Coating of the bacteria with opsonins enhances alveolar macrophage phagocytosis. Phagocytosed bacteria are exposed to a highly bacteriocidal mixture of proteases, lysozyme, acid and free radicals. Alveolar macrophages release neutrophil chemotactic factors and early inflammatory cytokines such as tumour necrosis factor (TNF)-α and interleukin (IL)-1β. TNF-α and IL-1β stimulate lung endothelial cells to express surface adhesion molecules, intercellullar adhesion molecule-1 and extracellular leucocyte adhesion molecule-1. These bind to circulating neutrophils facilitating their migration into the interstitium and ultimately to the alveolus. The *in vitro* clearance of bacteria by neutrophil phagocytosis is dose dependent, the maximum bacteriocidal capacity being a ratio of 10 bacteria to one neutrophil [71]. Even the defences of healthy lung tissue will be overwhelmed when exposed to an excessive bacterial load.

Prevention

Reduction in pathogenic bacterial reservoirs

Reductions in pathogenic bacterial reservoirs can be achieved by the methods described below.

Nursing care

Strict infection-control procedures should be in place, for example, hand washing and the sterilisation of equipment. Routine oral hygiene and the removal of secretions in the mouth and subglottis are important [42, 72]. The use of oral chlorhexidine rinse in cardiac surgical patients reduced postoperative respiratory infections by 69%, and subsequently reduced antibiotic usage. Antibiotic resistance was unaffected [73].

Oral vs. nasal intubation

The use of oral rather than nasal tracheal intubation has been associated with lower rates of VAP, and is due to the

reduced incidence of sinusitis with oral as opposed to nasal tracheal and gastric tubes (95.5% vs. 22.5%) [43, 44].

Selective decontamination of the digestive tract
SDDT involves infection control by general hygiene, topical nonabsorbable bacteriocidal antimicrobials administered to the oropharynx and gut often with parenteral antibiotics. SDDT reduces colonisation rates and lower respiratory tract infection without demonstrable change in mortality [74], although subgroup analysis has shown some benefit in trauma patients [75]. Its use remains controversial because of concerns regarding increases in colonisation and infection rates with multiresistant pathogens [76]. SDDT reinforces the point that patients may die *with* rather than *of* VAP. Respiratory failure is an important organ failure in the critically ill and possible mechanisms for reducing VAP are to be encouraged.

Gastric alkalinisation
The use of antacids to increase gastric pH is associated with the appearance of more new pathogens in the gastric contents than if a surface-active agent such as sucralfate is used (an incidence of 35% in the antacid group vs. 17% in the sucralfate group on the third postoperative day) [46]. Although there are conflicting data, the gastric colonisation associated with H_2 antagonists compared with sucralfate shows a trend towards an increase in VAP rates [77]. A meta-analysis of trials comparing ulcer prophylaxis in the ICU showed lower rates of lower respiratory tract infections with sucralfate (a 45% risk reduction compared with pH-altering drugs) [78]. However, in a recent multicentre, randomised study of 1200 patients, no significant difference in VAP rates, ICU stay or mortality could be demonstrated, although there was a trend towards lower VAP rates with sucralfate. The ranitidine group had lower rates of clinically significant gastrointestinal bleeding than the sucralfate group (1.7% vs. 3.8%) [79]. These conflicting data make recommendations difficult. However, ulcer prophylaxis with sucralfate alone maybe inadequate for patients at highest risk of peptic ulceration.

Gastro-oesophageal reflux
There is a fourfold reduction in pulmonary aspiration of radioactive-labelled gastric contents with the semirecombent (45° angle) rather than supine position. Furthermore, the isolation of the same organisms from the stomach, pharynx and endobronchial samples occurred in 32% of semirecombent patients compared with 68% of supine patients [80]. Gastro-oesophageal reflux, however, occurs irrespective of body position in mechanically ventilated patients with nasogastric tubes [81]. The use of fine bore (8 F) as opposed to large bore (14 F) feeding tubes does not appear to reduce gastro-oesophageal reflux in normal subjects [82].

Enteral feeding
Both continuous and intermittent (with a 6-h break) enteral feeding increase gastric pH, and are associated with Gram-negative colonisation of the stomach (80% gastric colonisation in both groups) [83]. Adequate nutritional status prevents VAP [30] and feeding enterally is undoubtedly the route of choice, so the clinician must decide upon the balance of risks. Avoiding stomach overdistension by monitoring residual gastric volume during feeding protocols, and the placing of jejunal feeding tubes may be appropriate.

Ventilator circuit
The ventilator circuit should be actively managed so that condensate fluid does not wash back into the patient but can be removed from water traps. HME filters should be considered. Tubing should be changed only if heavy soiling occurs.

Reduction in aspiration past the cuff

Subglottic secretion drainage
Subglottic secretion drainage is performed using a tracheal tube incorporating a separate dorsal lumen ending in the subglottic space just above a HVLP cuff (HI-LO EVAC tube, Mallinckrodt). Fluid can be drained along the channel with suction. This can reduce, but not eliminate, the volume of fluid aspirated into the lungs. Such a tube reduced the incidence of VAP from 29.1% to 13% with intermittent drainage [42], and from 32.5% to 18.4% with continuous drainage [84] of the subglottic space.

Cuff type
HVLP tracheal tube cuffs do not provide the barrier to fluid entering the tracheobronchial tree afforded by low-volume high-pressure (LVHP) cuffs [53]. Unfortunately LVHP cuffs are associated with tracheal wall injury and are unsuitable for use in long-term ventilation. Two new tracheal tubes have been described that appear to prevent aspiration with acceptable tracheal wall pressures. The pressure-limited cuff (PLC) is a LVHP cuff with inflation characteristics that enable tracheal wall pressure control at 30 cmH_2O while simultaneously providing complete protection against aspiration to the lungs [55] (Fig. 6). The cuff is used in combination with a constant-pressure inflation device and has been shown to reduce the aspiration of dye placed in the subglottis from 87% with a conventional HVLP cuff to 0% with the PLC [52]. The 'no pressure' laryngeal seal design by Kolobow and co-workers has been evaluated in sheep. This tube has

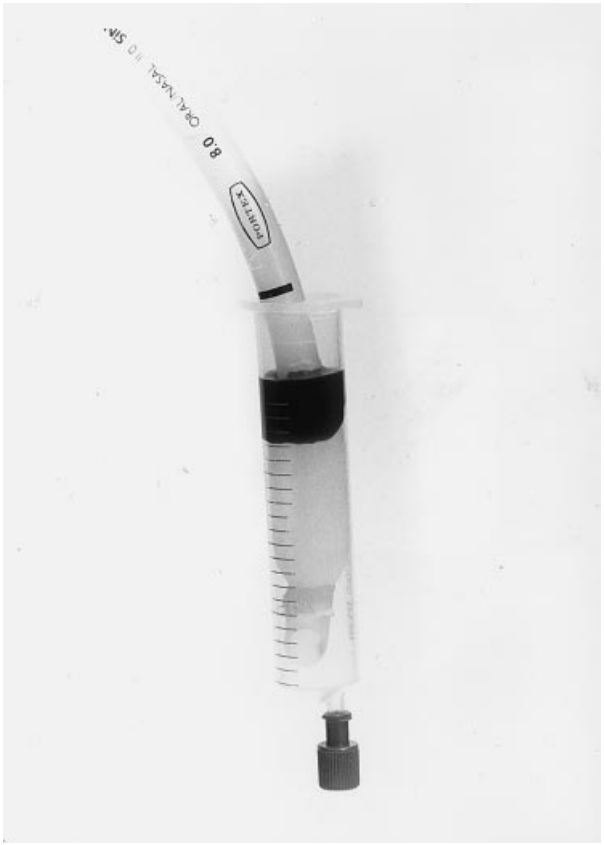

Figure 6 The PLC inflated to a tracheal wall pressure of 30 cmH_2O prevents leakage in a 2-cm-diameter cylinder.

Figure 7 An HVLP cuff lubricated with KY jelly and inflated to an intracuff pressure of 30 cmH_2O in a 2-cm-diameter cylinder. KY jelly prevents leakage.

12–20 thin polyurethane film gills that are positioned at the glottis thereby preventing air leaks and fluid aspiration [85, 86]. *In vitro* studies suggest that PEEP and lubrication (Fig. 7) of HVLP cuffs may, at least temporarily, prevent leakage of fluid past the cuff [54].

Noninvasive ventilation

A recent study showed that extubation and weaning with noninvasive (by facemask), as opposed to invasive (by tracheal tube), ventilation can reduce VAP (28% vs. 0%) and mortality in suitable patients with respiratory failure secondary to chronic obstructive airways disease [87]. Survival rates at 60 days were significantly higher in the noninvasive group (92% vs. 72%); the excess deaths related to the complications of conventional mechanical ventilation, in particular pneumonia.

Unplanned extubations

Appropriate securing of tracheal tubes and the prevention of the need for reintubations may reduce the risk of VAP [88].

Enhancement of bacterial clearance from airways and lung tissue

As well as tracheal suctioning, three mechanisms may help bacterial clearance.

Kinetic beds

In five studies (only one study showing a significant difference), kinetic beds have been associated with a reduction in VAP, although no difference in ICU stay or mortality was reported [58]. Possible advantages of rotational bed therapy include intrathoracic postural drainage, the limitation of pooled secretions in the upper airway with rotation and improvements in pulmonary gas exchange. These beds are expensive; there are inconsistent data demonstrating their effectiveness, and routine use cannot be recommended at present.

Physiotherapy

Chest physiotherapy, postural drainage, percussion and vibration in association with tracheal suctioning, are used to promote secretion drainage and improve lung expansion

[89]. Post-operative chest physiotherapy has cost implications and carries the risk of arterial desaturation [90]. Although routinely carried out and possibly advantageous from first principles, no data exist to conclusively support its use.

Immune enhancement
The use of intravenous immunoglobulin in high-risk surgical patients has been associated with a 50% reduction in the incidence of pneumonia [91]. This is expensive and at present remains experimental. The prophylactic use of cytokines such as granulocyte colony stimulating factor may reduce nosocomial infections in neutropenic oncology patients but there are no data of its use in VAP in critically ill patients.

Antimicrobial treatment

Early appropriate vs. late or inappropriate antibiotic treatment

Inappropriate antibiotic therapy independently worsens prognosis [5]. Early appropriate antibiotic therapy, however, reduces mortality [23]. Lower respiratory tract sampling should be immediate when there is a clinical diagnosis of VAP and therapy should not be delayed pending sampling or culture results [23].

Prophylactic antibiotics

Routine prophylactic antibiotics are inadvisable except in selected groups such as neutropenic oncology patients. Two prophylactic doses of cefuroxime following tracheal intubation in patients with coma secondary to head injury or stroke may reduce VAP [92]. In general, however, broad-spectrum antibiotic therapy prior to the development of VAP increases the rate of pneumonia caused by *Ps. aeruginosa* or *Acinetobacter* spp. and it is these organisms that are associated with a high mortality [93].

Choice of antibiotic

When a VAP is suspected, a respiratory specimen and blood culture should be taken without delay, and it is vital to begin early appropriate antibiotics. While culture results are pending, the choice of immediate antibiotic depends on whether the VAP is early- or late onset, the local prevalence of pathogenic bacteria and antibiotic resistance patterns, and patient-specific factors.

Epidemiological factors
The predominant organisms reported in 89 patients by the European Cooperative Group on Nosocomial Pneumonia were *Staphylococcus* spp. (26%) and aerobic GNB (53%) of which half were *Ps. aeruginosa* [94]. Early-onset pneumonia (< 5 days after hospital admission) is most likely to be caused by *Staph. aureus*, *Haemophilus influenzae*, *Streptococcus* spp. and *Enterobacteriaceae* spp., whereas late onset pneumonias are most likely to be caused by *Ps. aeruginosa, Acinetobacter* spp. and methicillin-resistant *Staph. aureus* [95].

Local pathogens and antibiotic resistance
Reducing the usage of unnecessary antibiotics in hospitals is critical in preventing the emergence of nosocomial pathogens [96]. Knowledge of local bacterial prevalence and antibiotic resistance patterns is vital when selecting treatment.

Patient factors
Recent respiratory specimen Gram stains and cultures, the severity of symptoms, recent antibiotic treatment, underlying chronic lung disease and specific risk factors, such as neutropenia or steroid therapy, influence antibiotic choice.

Monotherapy or combination therapy

Broad-spectrum empirical therapy may be mono- or combination therapy. The American Thoracic Society consensus recommendations, based on epidemiologic data, suggest that severe early-onset VAP can usually be covered adequately by monotherapy with a β-lactam/β-lactamase inhibitor combination, or a second or third generation cephalosporin. Severe late-onset VAP requires combination therapy with an aminoglycoside or ciprofloxacillin and adequate cover for *Ps. aeruginosa* with an antipseudomonal β-lactam, such as ceftazidime. Following laboratory identification of the pathogen and determination of its antibiotic susceptibility a change to a less broad-spectrum antibiotic can often be made. Patients with specific risk factors may need additional antibiotics.

Conclusions

VAP is a common and major complication during mechanical ventilation, increasing morbidity, mortality and cost. Accurate clinical diagnosis remains problematic. The development of preventative strategies depends upon an understanding of the pathogenesis of VAP. The pathogenesis begins with upper airway and gastrointestinal colonisation, laryngopharyngeal pooling of secretions, then aspiration past the tracheal tube cuff leading to the overwhelming of compromised lung defences. The recent development of tracheal tube cuff prototypes that prevent aspiration are promising and need further evaluation. Useful preventative strategies include: strict infection control procedures; improvements in upper airway hygiene; the avoidance of nasal intubation; the use of sucralfate, rather than gastric alkalinisation; infrequent ventilator circuit changes; and possibly the use of HME filters and kinetic beds. Appropriate antimicrobial treatment of an established

VAP requires early empirical therapy based on a knowledge of the epidemiology of early- and late-onset pneumonia, local pathogen patterns, recent antibiotic treatment, underlying lung disease and recent microbiological cultures, followed by the use of narrow-spectrum antibiotics after organism identification.

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