Ventilator-associated pneumonia

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Key points

• Ventilator-associated pneumonia (VAP) is the most common healthcare-associated infection in adult critical care units.
• VAP is associated with increased intensive care unit stay, patient ventilator days, and mortality.
• There is no agreed definition of VAP.
• The main pathogenic factor in the development of VAP is biofilm formation within the tracheal tube (TT) and microaspiration of secretions.
• The incidence of VAP can be reduced by many means including the use of care bundles and modified TTs.

Ventilator-associated pneumonia (VAP) is the most common healthcare-associated infection (HAI) in adult critical care units.¹ It is associated with increased intensive care unit (ICU) stay, patient ventilator days, and mortality.² VAP is thought to increase the mortality of the underlying disease by ~30%.³ At present, there is no consensus definition for VAP, although many have been proposed. VAP is complicated by the lack of a consensus ‘gold standard’ definition to test the accuracy of potential diagnostic criteria. This article reviews the currently used diagnostic criteria, the role of care bundles and other novel techniques in VAP prevention, and recent advances in surveillance systems to overcome the diagnostic difficulties.

Diagnosis

Currently, the diagnosis of VAP is based on a combination of clinical, radiological, and microbiological criteria. There are a wide range of clinical conditions that mimic VAP in ventilated patients, including acute respiratory distress syndrome (ARDS), pulmonary contusion, tracheobronchitis, and thromboembolic disease. Some of the clinical features used to define a VAP (e.g. change in tracheal secretions) are subjective and are subject to inter- and intra-observer variation. The diagnostic value of these clinical criteria in isolation, and in combination, has been reviewed recently by Klompas.⁴ While individual clinical criteria appear to lack clinical sensitivity, combination of clinical criteria with laboratory criteria and radiological features improves the accuracy of a clinical diagnosis.⁵ Fabregas and colleagues⁶ found radiological infiltrates plus two from three of fever, leucocytosis, and purulent secretions, to have a sensitivity of 69% and specificity of 75% for diagnosing VAP.

There are no radiological criteria pathognomonic of VAP and the interpretation of chest radiographs in ventilated patients is very difficult. Single air bronchograms and fissure abutment are highly specific, but they lack sensitivity.⁴ Invasive and non-invasive sampling techniques are used to obtain microbiological specimens to diagnose VAP. Invasive techniques include bronchoscopy alveolar lavage (BAL) and protected specimen brushings (PSB), while less invasive techniques include mini BALs. Tracheal aspirates are the least invasive to obtain but the most likely to be contaminated with oro-pharyngeal colonizing bacteria. Quantitative cultures are often used to differentiate between colonization and infection. The diagnostic threshold for BALs is 10⁵ colony forming units per millilitre (CFU ml⁻¹) and this is often the gold standard against which other diagnostic
criteria are compared. However, as bronchoscopic sampling cannot guarantee sampling from the area of the lung most affected, the sensitivity of this test is low, although the specificity is quite high (significant false-negative rate). Several studies have compared the value of quantitative invasive vs non-quantitative, non-invasive cultures. Meta-analyses comparing these have come to the conclusion that neither method confers any advantage on survival, length of ICU stay, or duration of mechanical ventilation.

Current definitions

The Clinical Pulmonary Infection Score (CPIS) was developed by Pugin and colleagues to facilitate the diagnosis of VAP using clinical variables. It gives a score of 0–3 for temperature, leucocytosis, $P_{A}O_{2}/FiO_{2}$ ratio, chest radiography, tracheal secretions, and culture of tracheal aspirate. The maximum score that can be obtained is 12 and a score >6 is diagnostic of VAP. The assessment of the CPIS score is prone to considerable inter-observer variability, particularly with regard to interpretation of the tracheal secretions and the chest X-ray (CXR).

The United States Centre for Disease Control (CDC) definition was designed as a surveillance tool for HAIs but has been used in the diagnosis of VAP. It was not meant for the diagnosis of pneumonia, neither is it specific for VAP. However, it has been shown to have good sensitivity and positive predictive value, but its low specificity limits its value when compared with bronchoscopic cultures.

The Johansson criteria diagnosed a VAP based on the presence of new or progressive infiltrates on the CXR associated with at least two of three clinical features—leucocytosis, purulent secretions, temperature >38°C. Diagnosis by these criteria was compared with immediate post-mortem lung biopsies; the sensitivity was only 69%, while the maximum specificity was 75%.

The HELICS criteria are used for VAP surveillance in Europe. These again rely on a combination of clinical, radiological, and microbiological criteria and classify the pneumonia from PN1 to PN5 based on the microbiological method used. PN1 refers to diagnosis by minimally contaminated lower respiratory tract (LRT) specimens (BAL, PBS, distal protected aspirates), while PN4 refers to positive sputum culture or to non-quantitative LRT aspirates such as tracheal aspirates. Therefore, a unit’s VAP rate can vary significantly depending on the microbiological method used.

VAP pathogenesis

The main pathogenic factor in the development of VAP is biofilm formation within the tracheal tube (TT) and microaspiration of secretions. The presence of a TT interferes with the normal protective upper airway reflexes and prevents effective coughing. The oropharynx becomes rapidly colonized by aerobic gram-negative bacteria after illness, antibiotic administration, and hospital admission. These contaminated secretions pool above the TT cuff and slowly gain access to the lower airway through a fold in the wall of the cuff. A bacterial biofilm, which is impervious to antibiotics, gradually forms on the inner surface of the tube and serves as a nidus for infection. This pathogen-rich biofilm is pushed into the distal airways by ventilator cycling and in the setting of immunosuppression associated with critical illness causes pneumonia. The longer the duration of ventilation, the greater the risk of developing VAP. Nursing patients in a supine position increases the risk of microaspiration and enteral feeding via a nasogastric tube increases the risk of aspiration of gastric contents. It follows that attempts to prevent VAP would focus on measures to reduce biofilm formation and microaspiration.

VAP prevention

The role of care bundles

A care bundle refers to a group of evidence-based interventions related to a particular condition which when applied together significantly improves patient outcome. In 2007, the Department of Health launched ‘Saving Lives: reducing infection, delivering clean and safe care’, a campaign to prevent and control hospital-acquired infection. This included ‘High Impact Intervention No 5—Care bundle for ventilated patients’, the aim of which was to reduce VAP. The original document consisted of daily sedation holds, bed head elevation, gastric ulcer prophylaxis, and oral care. It was updated in 2010 to include oral hygiene with adequate strength anti-septics, subglottic aspiration, and TT cuff pressure monitoring in addition to the initial four care interventions. A before and after study based in a large Scottish ICU studied the effectiveness of the original four high impact interventions (HI). They were able to demonstrate over 95% adherence with the bed end elevation and chlorhexidine elements and 70% compliance with the wake and wean elements (overall bundle compliance 70%). There was a significant reduction in their VAP rates (from 32 cases per 1000 ventilator days pre-intervention to 12 cases post-intervention), mexitilin-resistant Staphylococcus aureus rates, and antibiotic use. However, they were unable to demonstrate a reduction in the duration of mechanical ventilation and overall ICU admission duration. A similar study based in Spain used intra-cuff pressure control in addition to the other four methods. Although overall compliance was <30%, they were able to demonstrate reduction in VAP rates, ICU length of stay (LOS), and duration of mechanical ventilation. However, a systematic literature review of four studies concluded that the lack of methodological rigor precluded any conclusive statements regarding the bundles’ effectiveness or cost-effectiveness.

TT modification

As it is the TT that provides the continuous path between the oral cavity and the distal airways, VAP prevention strategies have focused on TT cuff design to prevent microaspiration.

Cuff pressure control

An inflating cuff pressure <20 cm H$_2$O favours increased passage of secretions between the cuff and the wall of the trachea, while >30 cm H$_2$O may cause tracheal mucosal damage. Despite routine cuff pressure controls, variations in TT cuff pressure frequently occur, exposing patients to increased risk of VAP. Several devices have been developed to constantly monitor and adjust the TT cuff inflation pressure. Randomized controlled trials have shown a reduced rate of VAP in the treatment arm of a study testing the Nosten device (Nosten; Leved, St Maur, France).

Subglottic secretion drainage

Subglottic secretion drainage systems usually consist of an accessory aspiration conduit opening above the TT cuff and a vacuum source. Secretions may be continuously or intermittently removed from the subglottic space. A meta-analysis of 13 randomized controlled trials showed that subglottic secretion drainage was effective at reducing VAP rates, also reducing the
time to onset of first VAP, reduced duration of mechanical ventilation, and reduced ICU LOS.13

**TT cuff design**
Most common TT cuffs have a high volume–low pressure cuff made of polyvinyl chloride. The surface of a traditional TT cuff folds when inflated in the trachea, creating potential channels through which secretions can drain. A tapered cuff shape made of ultra thin polyurethane seems to offer the most protection against secretion channelling leading to VAP.14

**TT coating**
Bacterial colonization and biofilm formation on the inner surface of the TT can be prevented by coating it with a thin layer of antimicrobial agents. Among many agents, silver appears to have been the most widely studied. NASCENT was a multicentre study that recruited more than 2000 patients to be randomized to either a silver-coated TT or a standard TT. They reported a significant reduction in VAP rates in the treatment arm and delayed time to onset of VAP. However, they were unable to show a reduction in ICU LOS or duration of ventilation.15 Other agents used for coating include chlorhexidine and titanium dioxide.

**Nebulized gentamicin**
This has been investigated as a means of prevention of biofilm formation. Compared with systemic cephalosporins, nebulized gentamicin attained a higher concentration within the TT and there was a lower incidence of biofilm formation. Interestingly, none of these biofilms was from organisms that commonly cause VAP. However, more work needs to be done before this method can be recommended.16

**Kinetic therapy**
Mucociliary clearance is inhibited by immobility. Mechanical rotation of patients with 40° turns achieves more significant clearance of secretions than current standard therapy of 2 hourly turns. It has been shown to lower the incidence of VAP, but have no effect on duration of ventilation, LOS, or mortality. However, kinetic therapy requires specialist equipment and has been associated with significant complications such as intolerance to rotation, unplanned extubations, loss of vascular access, and arrhythmias.17

**Care of airway equipment**
Studies have shown that TT colonization and biofilm formation begins within 24 h of intubation. Strict attention to hand hygiene when handling the TT, closed-circuit suction systems, use of heat and moisture exchangers, and limiting ventilator tube changes to whenever they are soiled, all contribute towards reducing biofilm formation.

**Feeding**
Although the early establishment of enteral feeding is of benefit to critical care patients, reflux and aspiration of gastric contents is the main cause of VAP. It has been suggested that post-pyloric feeding may reduce the incidence of VAP. Several studies so far have shown a non-significant trend towards a reduction in VAP, but more conclusive evidence is needed before a definite recommendation is made.

**Probiotics**
Probiotics compete with VAP-producing organisms in the oropharynx and stomach. The improved microbial balance has been shown to reduce the incidence of VAP but does not improve ICU or hospital mortality or duration of ventilation.18 This meta-analysis was based on several small studies of varying heterogeneity and its methodology has been questioned.

**Intubation-related events**
Reducing the duration of intubation with the use of sedation holds and weaning protocols and reducing unplanned extubations and minimizing re-intubation have also been shown to reduce VAP incidence.14

**The 2013 CDC VAE/VAC definitions**
Most preventive strategies have shown a reduction in the incidence of VAP, but this has not translated to a definite outcome benefit such as a reduction in duration of ventilation, LOS, or mortality. As ICU patients are a heterogeneous group of patients with multiple factors affecting their individual outcome, it is often difficult to show an outcome benefit from a single intervention. Another complicating factor is that the criteria used for diagnosis of VAP vary from study to study. Often, they are based on clinical criteria only. This cannot solely be blamed on study design as critical care societies and other governing bodies have so far not been able to agree upon common diagnostic criteria. As VAP rates are related to surveillance and carry monetary fines, it has become imperative that a common overarching definition is agreed upon. It was with this intention that a new official multisociety definition was created last year (Table 1).

The new surveillance definition has broadened the focus beyond pneumonia to encompass other common complications of ventilation and making surveillance as objective as possible. The new definition identifies a hierarchy of surveillance targets. The first tier of ventilator-associated condition (VAC) identifies patients whose respiratory status has deteriorated after a period of stability or improvement. This is designed to capture all pulmonary and non-pulmonary complications serious enough to lead to persistently higher FiO2, PEEP, or both settings. Subsequent tiers are designed to identify the subset of VACs that are infection-related. An infection-related ventilator-associated complication (IVAC) occurs in a patient who has concurrent systemic features requiring antibiotic treatment and a possible pneumonia occurs in a patient with an IVAC and positive qualitative cultures, while a probable VAP occurs in a patient with positive quantitative cultures. The probable VAP criteria can also be met by positive pleural fluid culture, lung tissue with histological evidence of infection, positive diagnostic tests for Legionella, or selected respiratory viruses. Of note, compared with previous definitions of VAP, radiographic evidence of pneumonia is not included in any part of the new algorithm.

Currently, it is unknown how well an IVAC will correlate with a prior definition of VAP. Preliminary data suggest that ∼40% of VACs meet the criteria for IVAC. In a retrospective analysis of a prospective multicentre study that measured the implementation of VAP prevention guidelines over 24 months, there was poor agreement between VAC, IVAC, and VAP (based on Johannson criteria) definitions.19 In theory, all VAP patients should form a subset of the VAC patients, but only a minority of the VAP patients meet the diagnosis for VAC. This may have been because some of the VAP cases may not have caused sufficient
New respiratory deterioration: ventilator-associated condition (VAC)

New respiratory deterioration associated with infection: infection-related ventilator-associated condition (IVAC)

New respiratory deterioration with possible evidence of pulmonary infection: possible pneumonia

New respiratory deterioration with probable evidence of pulmonary infection: probable pneumonia

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<tr>
<th>Definition</th>
<th>Criteria</th>
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<td>New respiratory deterioration: ventilator-associated condition (VAC)</td>
<td>≥2 days of stable respiratory function [stable or reducing PEEP or daily minimum fraction of inspired oxygen (FiO₂) followed by an increase in daily minimum PEEP ≥3 cm H₂O or a daily increase in FiO₂ by &gt;20 points sustained for ≥2 days.</td>
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| New respiratory deterioration associated with infection: infection-related ventilator-associated condition (IVAC) | On or after third day of mechanical ventilation patient has VAC+  
  - Temperature >38°C or <36°C or  
  - White cell count >12 000 mm⁻³ or ≤4000 mm⁻³  
  - One or more antibiotics started within 2 days before or after onset of VAC and continued for at least 4 days  
  - Positive culture of a potentially pathogenic organisms (tracheal aspirates ≥10⁵ CFU mm⁻³ or semi-quantitative equivalent)  
  - Purulent respiratory secretions from lungs, bronchi, or trachea that contain ≥neutrophils and ≥epithelial cells per low power field  
  - Positive cultures of a potentially pathogenic organisms (qualitative, semi-quantitative or quantitative)  
| New respiratory deterioration with possible evidence of pulmonary infection: possible pneumonia | IVAC+  
  - Positive culture of potentially pathogenic organisms (tracheal aspirates ≥10⁵ CFU mm⁻³, or bronchoalveolar lavage culture ≥10⁴ CFU mm⁻³ or semi-quantitative equivalent)  
  - Purulent respiratory secretions  
  - Positive cultures of a potentially pathogenic organisms (tracheal aspirates ≥10⁵ CFU mm⁻³, or bronchoalveolar lavage culture ≥10⁴ CFU mm⁻³ or semi-quantitative equivalent)  
  - Positive diagnostic test for Legionella species or  
  - Positive pleural fluid culture (specimen from thoracocentesis and not from indwelling chest drain) or  
  - Positive diagnostic test for respiratory viruses or  
  - Positive lung histopathology |
| New respiratory deterioration with probable evidence of pulmonary infection: probable pneumonia | |

deterioration in ventilation parameters or may not fit the stringent time criteria to fit the VAC definition. Both VAPs and IVACs may be caused by a non-infectious pulmonary process and an infectious non-pneumonic process, for example, ventilator-associated tracheobronchitis and a urinary tract infection.

Although VAC and IVAC may be non-specific, their higher correlation with worse outcomes, ease of data collection, and objective definitions make them promising options to replace VAP as a quality indicator. Over the last decade, a large body of knowledge has been collected regarding reduction in VAP incidence and its associated costs. It is possible that these interventions may have little impact on reducing VAC and IVAC as they have been designed solely for prevention of pulmonary infection.

Other problems with the new definition that will require modification include adjustments in the level of PEEP due to non-respiratory conditions, use of antibiotics for non-respiratory conditions, excluding manoeuvres used to provide comfort care in terminally ill patients from constituting a VAC.

While the new definitions have been designed to introduce clarity and objective criteria to the diagnosis of ventilator-related problems, further studies are required to authenticate the definition of IVAC and reimbursement should not be tied to the prevention of VAC until we know if it is a preventable and what steps need to be taken to prevent it.

It has long been recognized that respiratory tract infection is a complication of mechanical ventilation and we have developed successful strategies to minimize the risk. However, without agreement upon what defines a VAP, we will never be able to quantify the success of these strategies. Perhaps our focus should shift towards preventing all ventilator-associated events as defined by the new surveillance criteria. While VAP prevention methods would possibly work in the proportion of ventilator-associated events caused by IVACs, we would have to develop further strategies such as strict fluid balance and adherence to low tidal volume ventilation to mitigate non-infection-related ventilator-associated events.

### Declaration of interest

None declared.

### MCQs

The associated MCQs (to support CME/CPD activity) can be accessed at [https://access.oxfordjournals.org](https://access.oxfordjournals.org) by subscribers to BJA Education.

### References