Ventilator-associated pneumonia: A review of the clinically relevant challenges in diagnosis and prevention

Varun Goel, Savita Gupta and Tarun Goel

Abstract
Ventilator-associated pneumonia is one of the most commonly encountered nosocomial infections in the intensive care units and is associated with high morbidity and high costs of care. Despite extensive studies for decades, a clear diagnostic and prevention strategy is still eluding Ventilator-associated pneumonia. Clinical diagnosis has been criticized to have poor accuracy and reliability. Quantitative cultures obtained by different methods seem to be rather equivalent in its diagnosis. Blood cultures are relatively insensitive to diagnose Ventilator-associated pneumonia. Thus, the Centers for Disease Control and Prevention has introduced a new definition based upon objective and recordable data. New preventive strategies are focused on the improvement of secretions drainage and prevention of bacterial colonization. We performed a literature review to describe the evidence-based Ventilator-associated pneumonia-diagnosis and prevention strategies that have resulted in clinically relevant outcomes. An integrated approach should be followed in diagnosing and preventing Ventilator-associated pneumonia.

Keywords: Pneumonia, Nosocomial Infections, Ventilator Associated Pneumonia, ventilator bundle

INTRODUCTION
Ventilator-associated pneumonia (VAP) is a type of nosocomial pneumonia that occurs in patients who receive mechanical ventilation and is usually acquired in the hospital setting approximately 48–72 hours after mechanical ventilation.\(^1\) VAP is one of the most frequent hospital-acquired infections occurring in mechanically ventilated patients and is associated with increased mortality, morbidity, and health-related costs. Several risk factors have been reported to be associated with VAP, including the duration of mechanical ventilation, and the presence of chronic pulmonary disease, sepsis, acute respiratory distress syndrome (ARDS), neurological disease, trauma, prior use of antibiotics, and red cell transfusions.\(^2\) VAP occurrence is closely related to intubation and the presence of the endotracheal tube (ETT) itself.

Since there are inadequate objective tools that are utilized to make an assessment of bacterial-induced lung injury in a heterogeneous group of hosts, the diagnosis of VAP is challenging. Around 90% of ICU-acquired pneumonias occur during mechanical ventilation, and 50% of these ventilator-associated pneumonias begin in the first 4 days after intubation.\(^3\) VAP has a cumulative incidence of 10-25% and accounts for approximately 25% of all ICU infections and 50% of its antibiotic prescription, making it the primary focus for risk-reduction strategies.\(^4\) For all these reasons, early diagnosis and prevention of VAP has held a prominent position on the research agenda of intensive care medicine in the past 25 years, with an ultimate goal of improving patient outcome, preferably by reducing mortality.

The keywords, ‘ventilator-associated pneumonia,’ in PUBMED revealed a total of 3612 titles and 625 review articles within the search limit of 10 years, between 2005 and 2014. Only articles in English were chosen.

PATHOGENESIS
Understanding the pathogenesis of VAP is the first step in the formulation of its appropriate preventive and therapeutic strategies. The initial step in the pathogenesis of VAP is bacterial colonization of the oropharynx and gastric mucosa, followed by translocation of the pathogens to lower respiratory tract. The most common means of acquiring pneumonia is via aspiration which is promoted by supine position and upper airway and nasogastric tube placement.\(^5,6\) In a mechanically ventilated patients, aspiration occurs around the outside of the endotracheal tube rather than through the lumen. Secondly, aerobic Gram-negative bacteria presumably reach the lower airway via aspiration of gastric contents or of upper airway secretions. Other means by which VAP can be acquired include aspiration from the stomach or nose and paranasal sinuses. Figure 1 depicts the essential elements favoring colonization of lower respiratory tract with the bacterial pathogens with subsequent development of pneumonia.\(^5,6\)
Figure 1: Pathogenesis of Ventilator-associated pneumonia

*Gastric alkalinization; prior antimicrobials; ICU stay; intubation; supine position; circuit/airway manipulation and mishandling; device cross-contamination; sedation; diminished cough reflex; and malnutrition predispose to colonization and aspiration. As the duration of ICU stay increases, colonization with MDR Gram-negative pathogens like Pseudomonas and Acinetobacter increases.
†Via contaminated nebulizers/aerosols

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Table 1: CDC Algorithm for VAP diagnosis

<table>
<thead>
<tr>
<th>1= Purulent respiratory secretions AND one of the following:</th>
<th>2= One of the following (without requirement for purulent respiratory secretions):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive culture of endotracheal aspirate, ≥ 10⁵ CFU/ml*</td>
<td>Positive pleural fluid culture</td>
</tr>
<tr>
<td>Positive culture of bronchoalveolar lavage, ≥ 10⁴ CFU/ml*</td>
<td>Positive lung histopathology</td>
</tr>
<tr>
<td>Positive culture of lung tissue, ≥ 10⁶ CFU/ml*</td>
<td>Positive diagnostic test for Legionella spp.</td>
</tr>
<tr>
<td>Positive culture of protected specimen brush, ≥ 10³ CFU/ml*</td>
<td>Positive diagnostic test on respiratory secretions for influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus</td>
</tr>
</tbody>
</table>

On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, criteria 1 or 2 is met (*or equivalent semi-quantitative result).

Table 2: Practices for which insufficient evidence or no consensus exists about Efficacy

<table>
<thead>
<tr>
<th>Practice</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotational or turning therapy</td>
<td>Routine use of turning or rotational therapy, either by ‘kinetic’ therapy or by continuous lateral rotational therapy</td>
</tr>
<tr>
<td>Systemic antimicrobial agent prophylaxis</td>
<td>Routine administration of systemic antimicrobial agent(s) to prevent pneumonia in those receiving mechanically-assisted ventilation. Changes in the antimicrobial agents class used for empiric therapy</td>
</tr>
<tr>
<td>Oral chlorhexidine rinse for oropharyngeal colonization</td>
<td>Routine use of an oral chlorhexidine rinse for the prevention of healthcare-associated pneumonia in all postoperative or critically ill patients and/or other patients at high risk for pneumonia.</td>
</tr>
<tr>
<td>Ventilator breathing circuits with HMEs</td>
<td>No recommendation can be made for the preferential use of HMEs to prevent pneumonia in patients receiving mechanically assisted ventilation. No recommendation can be made for placing a filter or trap at the distal end of the expiratory-phase tubing of the breathing circuit to collect condensate</td>
</tr>
<tr>
<td>Suctioning of respiratory tract secretions</td>
<td>No recommendation can be made for the preferential use of either the multiuse closed-system suction catheter or the single-use open-system suction catheter</td>
</tr>
<tr>
<td>Prevention of aspiration associated with enteral feeding</td>
<td>Small-bore tubes for enteral feeding</td>
</tr>
<tr>
<td>Patient care with tracheostomy</td>
<td>Daily application of topical antimicrobial agent at the tracheostoma</td>
</tr>
<tr>
<td>Gloving</td>
<td>Wearing sterile rather than clean gloves when performing endotracheal suctioning</td>
</tr>
</tbody>
</table>
COMMON CAUSES

The specific microbial causes of VAP vary widely depending in epidemiological and clinical factors. Common pathogens include aerobic gram negative bacteria such as *Pseudomonas aeruginosa* and members of family *Enterobacteriaceae*, staphylococci, streptococci, and *Haemophilus* species. Microorganisms like *Pseudomonas spp.*, *Acinetobacter spp.* and Methicillin-Resistant *Staphylococcus aureus* occur commonly after prior antibiotic treatment, prolonged hospitalization, mechanical ventilation or when other risk factors are present.6,7

Moreover, deliberated ill patients may have defect in phagocytosis and behave as functionally immunosuppressed even prior to emergence of nosocomial infection as seen by many recent studies.8,9

DIAGNOSIS

Clinical Diagnosis

No gold standard of diagnosis for identifying VAP is there inspite of variety of proposed definitions. VAP has traditionally been diagnosed by clinical criteria of Johanson and colleagues (appearance of new or progressive pulmonary infiltrates, fever, leucocytosis and purulent tracheobronchial secretions), which are non-specific. When findings on histologic analysis and cultures of lung samples obtained immediately after death were used as references, a new and persistent (>48-h) infiltrate on chest radiograph plus two or more of the three criteria (i) fever of >38.3°C, (ii) leukocytosis of >12 × 10^9/ml, and/or (iii) purulent tracheobronchial secretions had a sensitivity of 69% and a specificity of 75% for establishing the diagnosis of VAP.10

Because of the poor specificity of the clinical diagnosis of VAP and of qualitative evaluation of ETAs, Pugin et al. developed a composite clinical score, called the clinical pulmonary infection score (CPIS), based on six variables: temperature, blood leucocyte count, volume and purulence of tracheal secretions, oxygenation, pulmonary radiography, and semi-quantitative culture of tracheal aspirate. The score varied from 0 to 12. A CPIS of >6 had a sensitivity of 93% and a specificity of 100%.11 Accuracy of CPIS in diagnosis of VAP is debated, despite of its clinical popularity. In one meta-analysis study evaluating the accuracy of CPIS in diagnosing VAP reported pooled estimates for sensitivity and specificity for CPIS as 65% (95 % CI 61-69 %) and 64 % (95 % CI 60-67 %), respectively.12 The poor accuracy of clinical criteria for diagnosing VAP is due to purulent tracheobronchial secretions in patients receiving prolonged mechanical ventilation which are rarely caused by pneumonia. Moreover, in pneumonia systemic signs such as fever, tachycardia, and leucocytosis are nonspecific; they can be caused by any state that releases the cytokines interleukin-1, interleukin-6, interleukin-8, tumor necrosis factor alpha (TNFα), and gamma interferon.13,14 The weak point of CPIS is probably the inter-individual variability (kappa= 0.16), since a subjective evaluation is required when we are judging the quality of tracheal secretion (purulent/not purulent) and the presence of infiltrate at chest ray.15

Radiologic Diagnosis

Radiographical evidence of pneumonia in ventilated patients is also notoriously inaccurate. In a study of autopsy proven VAP, of the total population, only air bronchograms correlated with pneumonia and no specific roentgenographic sign correlated with pneumonia in patients with adult respiratory distress syndrome. The differential diagnoses of VAP based on radiographical appearance, include adult respiratory distress syndrome, congestive heart failure, atelectasis, pulmonary embolism and neoplastic infiltration.16

Microbiologic Diagnosis

The type of specimen that should be obtained for microbiologic processing as soon as VAP is suspected is another area of importance. The use of quantitative cultures is one of the main issues for any diagnostic laboratory because there is oropharyngeal bacterial contamination of all respiratory secretion samples, despite this is not always undertaken in many hospitals today.16,17

Blood cultures

Blood cultures have limited value because organisms isolated from blood in suspected VAP cases are often from extrapulmonary sites of origin.18 Blood cultures in patients with VAP are clearly useful if there is suspicion of another probable infectious condition, but the isolation of a microorganism in the blood does not confirm that microorganism as the pathogen causing VAP.

Quantitative cultures of airway specimens

Simple qualitative culture of endotracheal aspirates has high percentage of false-positive results due to bacterial colonization of the proximal airways observed in most patients in the ICU.19 Quantitative culture techniques suggest that endotracheal aspirate cultures (QEA) may have an acceptable overall diagnostic accuracy, similar to that with several other, more invasive techniques including BAL, protected BAL (pBAL), protected specimen brush (PSB) or tracheobronchial aspirate(TBA).7,19,20 Threshold values often employed for diagnosing pneumonia by quantitative cultures are ≥10^3 to 10^5, ≥10^4, and ≥10^5 CFU/ml for QEA, bronchoscopy BAL, and PSB, respectively, with ≥10^3 CFU/ml being the most widely accepted value for QEA.21,22,23 Also, blind aspiration sampling can lead to errors but bronchoscope also carries risks, such as inducing cardiac arrhythmia, hypoxemia, bleeding, pneumothorax, along with greater costs both in terms of time and resources. It is accepted that before administering the first dose of antibiotic or before any change in treatment patient specimens for culture should be taken, so that the results interpreted are valid.24 Lalwani et al., in their study, observed
that culture results of a properly collected tracheal aspirate should be taken into consideration along with Centre for Disease Control and Prevention (CDC’s) diagnostic criteria to maximize the diagnosis of VAP.\textsuperscript{25}

The recent guidelines of Society for Healthcare Epidemiology of America/Infectious Diseases Society of America (SHEA/IDSA) recommend Gram staining of endotracheal aspirates. However, the sensitivity (57-95%) and specificity (48-87%) of this technique are highly variable. The role of procalcitonin and other biomarkers for the diagnosis of VAP is yet unsubstantiated.\textsuperscript{5,26}

Since VAP diagnosis founded on radiographic findings of pneumonia, which have intrinsic variability in technique, interpretation, and reporting, and on clinical signs and symptoms— that are subjective— in 2011 a Working Group of the CDC proposed a new approach to surveillance for Ventilator-Associated Events (VAE). Table 1 According to the new CDC definition algorithm, VAP is an Infection-related Ventilator-Associated Complication (IVAC) occurring after 3 days of mechanical ventilation and 2 days before or after the onset of worsening oxygenation, if purulent respiratory secretions with positive cultures or objective signs of respiratory infection have been found.\textsuperscript{27}

\section*{STRATEGIES FOR VAP PREVENTION}

There are multiple recommended measures for prevention of VAP. Practices for which insufficient evidence or no consensus exists about efficacy are summarized in Table 2. Preventive VAP strategies can be grouped into two classes: non-pharmacologic strategies, which are focused on preventing aspiration, and pharmacologic strategies, which are aimed at preventing colonization.

\subsection*{Non-Pharmacologic Strategies}

\textit{Staff Education in the Intensive Care Unit}

Various barriers to adhering to VAP prevention recommendations include disagreement with the reported results of source studies, resource paucity, elevated costs, inconvenience for nurses, fear of potential adverse effects and patient discomfort. There is considerable variability in practice between countries regarding humidification systems, intubation route, endotracheal suction system, kinetic therapy beds, subglottic secretion drainage and body position. For efficient patient care staffing must be sufficient while ensuring that staff is able to comply with essential infection control practices and other prevention strategies.\textsuperscript{17,26}

\textit{Hand Hygiene}

Microorganisms can be spread easily from patient to patient on the hands of healthcare workers. Moreover, wrist watches, rings, bangles and other jewelry commonly act as reservoirs for organisms, and impede effective hand cleaning. Moreover, healthcare workers compliance to hand hygiene is low, and high workload decreases their compliance.\textsuperscript{29}

\subsection*{Impact of patient position}

Patients positioned semi-recumbently 45 degrees have significantly lower incidence of clinically diagnosed VAP compared to patients positioned supinely.\textsuperscript{30} Moreover, the incidence of clinically diagnosed VAP among patients positioned prone, does not differ significantly from the incidence of clinically diagnosed VAP among patients positioned supine.\textsuperscript{31,32}

\textit{Kinetic Beds}

Critical patients often for a long time remain immobile in the supine position so the functional residual capacity is decreased because of alveolar closure in dependent lung zones and impaired mucociliary clearance. This leads to the accumulation of mucus, atelectasis onset and ensuing infection.\textsuperscript{33} Rotational therapy uses a special bed designed to turn continuously, or nearly continuously, the patient from side to side; specific designs include kinetic therapy and continuous lateral rotation therapy (CLRT).\textsuperscript{34,35}

\subsection*{Artificial Airway Management}

\textit{Oral vs Nasal Intubation:} Both nasogastric and nasotracheal tubes can cause oropharyngeal colonization and nosocomial sinusitis. Thus, use of the oral route for both endotracheal and gastric intubation should be considered to decrease the risk of VAP.\textsuperscript{36}

\textit{Endotracheal tube cuff pressure:} The secretions that pool above inflated endotracheal tube cuffs may be a source of aspirated material and ensuing VAP. The pressure of the endotracheal tube cuff should be optimized in order to prevent the leakage of colonized subglottic secretions into the lower airways. Persistent pressures into the tube cuff below 20 cm H\textsubscript{2}O have been associated with the development of VAP.\textsuperscript{37}

\textit{Silver-Coated Endotracheal Tubes:} Silver-coated endotracheal tubes appear to be safe, reduces bacterial biofilm formation, has bactericidal activity, reduces bacterial burden and can delay airway colonization. However, further studies are needed to for determining its efficacy.\textsuperscript{38,39}

\textit{Mechanical Ventilation Management}

\textit{Ventilator Circuit Change:} The CDCs recommendation was ‘do not change routinely, on basis of duration of use, the breathing circuit that is in use on an individual patient. Change the circuit when it is visibly soiled or mechanically malfunctioning.’\textsuperscript{40}

\textit{Humidification With Heat and Moisture Exchangers:} The effect of HME in preventing VAP is still controversial and recent
studies have failed to show a significant difference in rates of infection.\textsuperscript{51}

*Subglottic secretion drainage:* Intermittent subglottic secretions drainage using inspiratory pause during mechanical ventilation results in a significant reduction in VAP.\textsuperscript{44} SSD reduces VAP in patients ventilated for >72 hours and should be considered with other recommended strategies such as semi-recumbent positioning.\textsuperscript{55}

**Pharmacologic Strategies**

*Modulation of Oropharyngeal Colonization*

Policies encouraging routine topical oral decontamination with chlorhexidine for patients merit reevaluation. It is a cheap measure, but whether is it a safe one – it does not select resistant microorganisms – remains to be investigated.\textsuperscript{44,46}

*Selective Decontamination of the Digestive Tract*

Selective decontamination of the digestive tract (SDD) is the decontamination of potentially pathogenic microorganisms living in the mouth and stomach, whilst preserving the indigenous anaerobic flora. SDD is an effective and safe preventive measure in ICUs where incidence rates of MRSA and VRE are low, but in ICUs with high rates of multi-resistant microorganisms it is a measure that is effective but not safe.\textsuperscript{45,46}

*Stress Ulcer Prophylaxis*

Patients at risk from important gastrointestinal bleeding (shock, respiratory failure requiring mechanical ventilation or coagulopathy) should receive H\textsubscript{2} antagonists such as ranitidine rather than sucralfate.\textsuperscript{57}

*Ventilator sedation protocol*

In patients receiving mechanical ventilation and requiring sedative infusions with midazolam or propofol, the use of a nurse-implemented sedation protocol decreases the rate of VAP and the duration of mechanical ventilation.\textsuperscript{48} An objective assessment-based Analgesia-Delirium-Sedation (ADS) protocol without daily interruption of medication infusion decreases ventilator days and hospital length of stay in critically ill trauma patients.\textsuperscript{49}

*Antibiotic Policy and Infection Control*

Rational antibiotic policy is a key issue for better patient care and preventing antimicrobial resistance.\textsuperscript{50-51} Infection control programs like using a scheduled switch of antibiotic class have demonstrated efficacy in reducing nosocomial infection rates and restraining multidrug resistant (MDR) microorganism emergence.\textsuperscript{52}

VAP prevention in low resource/developing countries

Though the incidence of VAP has declined in the developed countries, it continues to be unacceptably high in the developing world. Its incidence in these countries is 20 times that in the developed nations with significant morbidity, mortality, and increase in ICU length of stay, which may represent an additional burden on the scarce resources in developing countries.\textsuperscript{53} Insufficient preventive strategies and probably inappropriate antibiotics administration may have lead to this scenario. Since microbiology and resistance pattern in India is different from other countries, there is need for data from our country to choose appropriate antimicrobials for management.\textsuperscript{54} Simple and effective preventive measures can be instituted easily and at minimal costs. Such measures might include hand hygiene, diligent respiratory care, elevation of head, oral and not nasal cannulation, minimization of sedation, institution of weaning protocols, judicious antibiotics use, de-escalation, and leveraging PK/PD characteristics for antibiotics administered. More costly interventions should be reserved for appropriate situations. Strategies to prevent VAP, probably by emphasis on practical, low-cost, low technology, easily implemented measures is need of the hour.

Ventilator-associated events (VAE) surveillance: an objective patient safety opportunity

Surveillance for ventilator-associated pneumonia is challenging and contains many subjective elements, including the use of chest x-ray evidence of pneumonia. In January 2013, CDC convened a VAP Surveillance Definition Working Group which transitioned VAP surveillance to ventilator-associated event (VAE) surveillance in adult inpatient settings.\textsuperscript{55} The VAE algorithm—which is a surveillance algorithm and not intended for use in the clinical management of patients—consists of 3 tiers of definitions: Tier 1, Ventilator-Associated Conditions (VAC); Tier 2, Infection -related Ventilator-Associated Complications (IVAC); and Tier 3, Possible and Probable VAP.\textsuperscript{27} The tier 1, VAC attempts to identify sustained respiratory deterioration episodes, and capture both infectious and noninfectious conditions and complications occurring in patients receiving mechanical ventilation. The tier 2, IVAC, is intended to identify the subset of VACs that are potentially related to pulmonary and extra pulmonary infections of sufficient severity to trigger respiratory deterioration. The tier 3, possible and probable VAP, attempts to identify IVAC patient subsets with respiratory infections as manifested by objective evidence of purulent respiratory secretions (where purulence is defined by using quantitative or semi-quantitative criteria for the number of neutrophils on Gram stain) and/or positive results of microbiological tests done on respiratory specimens. Because of the wide range of the lower respiratory tract specimens, their collection procedure as well as in laboratory processing and reporting of results, the Working Group of CDC determined that it was not appropriate to include these data elements in the VAC and IVAC definitions.\textsuperscript{56}
This 3 tier approach is ineffective to accurately identify VAP for surveillance purposes and focuses on more mechanical ventilation complications. This approach may also reduce the likelihood of manipulation that could artificially lower event rates. Most VAEs are caused by pneumonia, pulmonary edema, atelectasis, or acute respiratory distress syndrome. In few recent studies concordance between the VAE algorithm and VAP was found to be poor.\textsuperscript{57} Thus, more studies are needed to further validate VAE surveillance compared with conventional VAP by using strong microbiobiocritia criteria, particularly bronchoalveolar lavage with a protected specimen brush for diagnosing VAP and to better characterize the clinical entities underlying VAE.

**Bundle approach to prevention of VAP**

One of the five goals of the ‘Saving 100,000 Lives’ campaign, launched by the Institute for Healthcare Improvement is to prevent VAP and deaths associated with it by implementing a set of interventions for better patient care known as the ‘ventilator bundle’. The interventions should have scientific support of effectiveness, based on randomized controlled trials. All the elements of the bundles must be executed at the same time. The bundles for VAP includes four components: (a) elevation of the head end of the bed to 30-45\(^\circ\), (b) daily interruption of sedation, (c) daily assessment of readiness to extubate and (d) prophylaxis for deep venous thrombosis and peptic ulcer disease. The bundle approach to prevention of VAP has been found to be highly effective in reducing the incidence, mortality and ICU stay.\textsuperscript{5,6,8,19,55} The ventilator bundle should be modified and expanded to include specific processes of care that have been definitively demonstrated to be effective in VAP reduction. A multidimensional framework with a long-lasting support of effectiveness, based on randomized controlled trials. \textsuperscript{42}

**CONCLUSION**

Ventilator Associated Pneumonia is one of the most common nosocomial infections in ICU presenting with nonspecific symptoms and clinical signs. Quantitative culture obtained by different methods, including EA, BAL, pBAL, PSB or TBA seem to be rather equivalent in diagnosing VAP. Clinical criteria used in combination, may be useful in VAP diagnosis; however, inter-observer variability and the moderate performance are to be considered.

Preventive strategies should focus on better secretion management and on reduction in bacterial colonization. Further research on targeted interventions is needed to effectively reduce VAP incidence. For VAP an approach based on multidisciplinary group is required including setting preventive benchmarks, establishing goals and time lines and providing appropriate education and training, audits and feedback to the staff, while continually updating themselves based on relevant clinical and preventive strategies.

**Acknowledgements**

NIL

**Competing Interests**

None declared

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