Ventilator-associated pneumonia (VAP), defined as pneumonia occurring >48 - 72 hours after endotracheal intubation, is the most common and fatal nosocomial infection of intensive care. Risk factors include both impaired host immunity and the introduction of an endotracheal tube, which contributes to the development of VAP in the critically ill patient. VAP is associated with increased mortality and morbidity, increased duration of mechanical ventilation, prolonged intensive care unit and hospital stay, and increased cost of hospitalisation.

Both the Centers for Disease Control Guidelines and Pugin’s Clinical Pulmonary Infection Score (CPIS) criteria note that diagnosing VAP requires a combination of clinical signs, impaired gas exchange, radiological changes and positive microscopy to differentiate an episode of VAP from mere colonisation. In a resource-strapped environment, semi-quantitative analysis of specimens obtained utilising a non-invasive sampling technique is an acceptable option. Specific guidelines have been developed to both prevent VAP and treat it appropriately as soon as possible. The guidelines provide targeted strategies, while additional management of VAP includes the provision of essential care, psychosocial support, ventilatory support, enteral feeding and relevant medication including deep-vein thrombosis prophylaxis, and the prevention of complications. The Care Bundle approach offers an interventional tool to implement strategies specifically directed to the prevention of VAP and the facilitation of a team approach to improving its clinical management. The evidence available presents a strong argument to consider a team approach to reducing the incidence of VAP in our own critical care units.

Prevention and management of ventilator-associated pneumonia – the Care Bundle approach

Ventilator-associated pneumonia (VAP), defined as pneumonia occurring >48 - 72 hours after endotracheal intubation, remains the most common and fatal nosocomial intensive care unit (ICU) infection among mechanically ventilated patients. Each episode of VAP results in extended ICU and hospital stay and increased cost of treatment per patient. VAP is not particularly selective, and any patient mechanically ventilated for >48 hours is at risk of developing an episode. Patients (adults, children and neonates) who are critically ill and cannot maintain their own respiratory function adequately, or have a compromised airway, require an artificial airway to provide ventilatory support and for clearance of secretions. The indications for endotracheal intubation to facilitate mechanical ventilation to provide adequate oxygenation and respiratory support may be either pulmonary or non-pulmonary, and therefore include trauma, surgical (emergency or elective), and medical patients. The consequences of VAP warrant efforts to implement prevention strategies and manage each episode effectively.

Ventilator-associated pneumonia

Definition

Pneumonia is defined as inflammation of the lung parenchyma caused by infection. VAP is defined as pneumonia occurring >48 - 72 hours after endotracheal intubation. VAP is therefore also a nosocomial infection, i.e. an infection that develops >48 hours after a patient has been admitted to a hospital or health care facility. The current classification scheme for pneumonia as outlined by the American Thoracic Society Guidelines for the Management of Adults with Pneumonia refers to nosocomial pneumonia as hospital-acquired pneumonia (HAP), which includes both...
VAP and health care-associated pneumonia (HCAP). Both are clinically and microbiologically distinct from community-acquired pneumonia (CAP). VAP is further defined as early-onset VAP (occurring <5 days after intubation) and late-onset VAP (occurring ≥5 days after intubation).

Pathogenesis of VAP

Impaired host immunity and displacement of normal oropharyngeal flora by pathogens predispose the critically ill, mechanically ventilated patient to VAP. Normal nonspecific host responses, such as the epiglottis, vocal cords, cough reflex, and ciliated epithelium and mucus of the upper airways are bypassed or rendered ineffective during intubation. Bacteria gain access to the lower respiratory tract via aspiration through the endotracheal tube (where they may establish colonies impervious to the effects of antibiotics in the glycoalyx biofilm that coats the lumen of the artificial airway devices), migration around it (particularly if cuff inflation pressure is not maintained), or, in rare instances, hematogenous spread from blood stream infections. Displacement of normal flora by pathogens is also necessary for the development of VAP. The facial sinuses and stomach may serve as potential pathogen reservoirs, but measures to minimize passage of pathogens from these sources into the lower airways have provided mixed results. The specific effects of the endotracheal tube (ETT) include 'the direct impact of the cuff on the local mucosa, an enhanced capacity of tracheobronchial cells to bind Gram-negative organisms, the creation of additional binding sites for bacteria due to exposure of the basement membrane of the bronchial tree, the creation of a biofilm in the ETT serving as a reservoir for bacteria, and the presence of pooled sub-glottic secretions that accumulate between the cuff of the ETT and the tracheal wall leading to increased aspiration'.

Pathogens vary from unit to unit and between hospitals, but in the USA the most common pathogens isolated from patients with VAP are methicillin-resistant Staphylococcus aureus (MRSA), Pseudomonas, Enterobacter, Escherichia coli and Acinetobacter. These pathogens are also frequently isolated from patients admitted to South African critical care units. Multidrug-resistant (MDR) strains of pathogens are on the increase both locally and internationally.

Risk factors

Risk factors for the development of VAP include the following:

- Presence of invasive devices (e.g. ETT, central venous pressure, urinary catheters)
- Prior use of antibiotics (indiscriminate use of broad-spectrum antibiotics)
- Red cell transfusions (immunomodulatory effects)
- Supine position
- Surgery
- Medications (e.g. stress ulcer prophylaxis therapy).

Host factors:

- Advanced age
- Co-morbid disease:
  - Depressed level of consciousness
  - Pre-existing/chronic lung disease (e.g. tuberculosis, chronic obstructive pulmonary disease, bronchiectasis)
  - Colonisation of the oropharyngeal cavity with hospital-acquired pathogens
  - Sinus colonisation or sinusitis
  - Possibly gastric colonisation and aspiration
  - Large-volume gastric aspiration
  - Immune suppression from disease (e.g. HIV) or medication (e.g. steroids)
  - Malnutrition, with a decreased serum albumin level
  - Sepsis
  - Acute respiratory distress syndrome (prolonged ventilation, devastated local airway host defences)
  - Organ failure
  - Neurological/neuromuscular disease
  - Burns, trauma.

Incidence and consequences

VAP is described as the most common nosocomial infection of intensive care and is often fatal, although attributable mortality varies. The incidence differs between units (ICUs, HCUs (high-care units) and HDUs (high-density units)), hospitals (public and private sector) and countries (developed and developing). The range varies from 9% to 27% in Europe and America. Mortality rates in patients with VAP range from 20% to 50% and may be as high as 70% when the infection is caused by multi-resistant, invasive pathogens. VAP-attributable mortality is difficult to quantify because of confounding effects of associated conditions but has been estimated to increase mortality by 30% and even twofold in critically ill patients. Making ‘a timely and accurate diagnosis of VAP is critical as delayed administration of appropriate antibiotics increases mortality. And inappropriate use of antibiotics increases cost, incurs the risk of adverse drug reactions, and selects for resistant microbial flora that increase morbidity and mortality. VAP is associated with increased mortality and morbidity, increased duration of mechanical ventilation, prolonged ICU and
hospital stay, and increased cost of hospitalisation. In 2005 Safdar et al. calculated the cost of VAP at more than US$10 000 per patient at 2003 dollar value cost estimates at a university-affiliated US teaching hospital. In 2003 Warren et al. found the attributable cost of VAP to be $11 897 in their study, which was conducted in a non-teaching US hospital at a suburban community medical centre. In South Africa, a stay in an ICU costs a minimum of R5 000 per day in a public sector hospital.

Diagnosis

The objective of making a correct diagnosis of VAP is to be able to determine whether the patient has pneumonia, identify the causative pathogen, and target therapy accordingly to achieve a better outcome for the patient. The process is problematic, given the poor specificity and sensitivity of clinical criteria alone and microscopy alone. The guidelines of both the Infectious Diseases Society of America and the American Thoracic Society recommend the combination of clinical signs, radiological changes, impaired gas exchange and quantitative microbiological data to diagnose and manage VAP. These criteria are captured by both the Centers for Disease Control and Prevention (CDC) and Pugin’s Clinical Pulmonary Infection Score (CPIS) definitions of VAP as set out in Tables I and II. The method of specimen collection and specimen analysis differs between the two, however, with the former favouring the invasive sampling techniques of broncho-alveolar lavage (BAL) and protected specimen brush (PSB) and quantitative specimen analysis. The CPIS accepts the non-invasive sampling techniques of endotracheal aspirates (EAs or TAs), blinded PSB and mini-BAL and semi-quantitative specimen analysis. Subsequent research has demonstrated no clear outcome benefit in using invasive sampling, which is particularly useful in a resource-strapped setting. The important issue that quantitative versus semi-quantitative analysis of respiratory tract specimens must distinguish is between colonisation versus infection. These results can provide useful data in guiding decisions regarding antibiotic therapy adjustment. In addition, the evaluation of biomarkers such as measuring C-reactive protein (CRP) (less reliable), procalcitonin (PCT) and soluble triggering receptor expressed on myeloid cells (sTREM) appear to be promising in improving the process of diagnosing VAP.

Table I. CDC National Healthcare Safety Network definition for ventilator-associated pneumonia

<table>
<thead>
<tr>
<th>Radiological signs</th>
<th>Clinical signs</th>
<th>Microbiological criteria (optional)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two or more serial chest radiographs with at least one of the following:</td>
<td>At least one of the following:</td>
<td>At least one of the following:</td>
</tr>
<tr>
<td>• New or progressive and persistent infiltrate</td>
<td>• Fever (temperature &gt;38°C with no other recognised cause)</td>
<td>• Positive growth in blood culture not related to another source of infection</td>
</tr>
<tr>
<td>• Consolidation</td>
<td>• Leucopenia (&lt;4 000 WBCs/µl)</td>
<td>• Positive growth in culture of pleural fluid</td>
</tr>
<tr>
<td>• Cavitation</td>
<td>• Adults 70 years or older – altered mental status with no other recognised cause</td>
<td>• Positive quantitative culture from broncho-alveolar lavage ≥10⁴ colony-forming units/ml or protected brush specimen ≥10³ colony-forming units/ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Five per cent or more of cells with intracellular bacteria on direct microscopic examination of Gram-stained broncho-alveolar lavage fluid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Histopathological evidence of pneumonia</td>
</tr>
</tbody>
</table>

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Management and treatment

Given the risk, incidence, increased costs and attributable mortality, measures should be employed to prevent VAP where possible. This is particularly relevant in developing countries, where VAP poses the greatest risk to patients, with the incidence measured at 41% and the crude mortality rate at 44.9%. Antibiotic therapy remains the mainstay of treating VAP and should be initiated as soon as possible once the patient has been admitted, the clinical diagnosis suspected and the required specimens collected. The choice of antibiotic/s is determined by individual patient risk factors, the institutional pathogens and specific antibiograms. The process should be according to protocol and usually involves initiating empiric broad-spectrum cover in the critically ill patient, which is adjusted and preferably de-escalated once the causative pathogen has been adequately identified and the appropriate sensitivity tests performed. Inadequate or delayed initial antimicrobial therapy has been associated with increased mortality, and should therefore be specifically targeted in the institutional protocol. Critically ill patients require intravenous antibiotics. Eight days of antibiotic therapy has been proven to be effective in treating most cases of VAP, with cases caused by a non-fermenting Gram-negative bacillus such as Pseudomonas or Acinetobacter being exceptions and requiring longer duration of therapy.

A number of evidence-based guidelines have been developed in recent years to direct clinical practice in an attempt to improve patient care, and in particular care of the critically ill. Specific guidelines have been developed to both prevent VAP and treat it appropriately as soon as possible. The guidelines provide targeted strategies, while additional management of VAP includes the provision of essential care, psychosocial support, ventilatory support, enteral feeding, relevant medication including deep-vein thrombosis prophylaxis, and the prevention of

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### Table II. Pugin’s CPIS

<table>
<thead>
<tr>
<th>Sign</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (°C)</td>
<td></td>
</tr>
<tr>
<td>• 36.5 - 38.4</td>
<td>0</td>
</tr>
<tr>
<td>• 38.5 - 38.9</td>
<td>1</td>
</tr>
<tr>
<td>• ≤ 36 or ≥39</td>
<td>2</td>
</tr>
<tr>
<td>Blood leucocytes (cells/µl)</td>
<td></td>
</tr>
<tr>
<td>• 4 000 - 11 000</td>
<td>0</td>
</tr>
<tr>
<td>• &lt;4 000 or &gt;11 000</td>
<td>1</td>
</tr>
<tr>
<td>• &gt;500 band forms</td>
<td>2</td>
</tr>
<tr>
<td>Oxygenation, PaO2/FiO2</td>
<td></td>
</tr>
<tr>
<td>• &gt;240 or ARDS</td>
<td>0</td>
</tr>
<tr>
<td>• ≤240 and no evidence of ARDS</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary radiograph</td>
<td></td>
</tr>
<tr>
<td>• No infiltrate</td>
<td>0</td>
</tr>
<tr>
<td>• Diffuse or patchy infiltrates</td>
<td>1</td>
</tr>
<tr>
<td>• Localised infiltrate</td>
<td>2</td>
</tr>
<tr>
<td>Tracheal secretions</td>
<td></td>
</tr>
<tr>
<td>Score*</td>
<td></td>
</tr>
<tr>
<td>• &lt;14</td>
<td>0</td>
</tr>
<tr>
<td>• ≥14</td>
<td>1</td>
</tr>
<tr>
<td>• Purulent sputum</td>
<td>2</td>
</tr>
<tr>
<td>Culture of tracheal aspirate (semi-quantitative: 0 - 1 - 2 or 3+)</td>
<td></td>
</tr>
<tr>
<td>• Pathogenic bacteria cultured, minimal or no growth</td>
<td>0</td>
</tr>
<tr>
<td>• Pathogenic bacteria cultured, moderate or more growth</td>
<td>1</td>
</tr>
<tr>
<td>• Moderate or greater growth of pathogenic bacteria consistent with that seen on original Gram stain</td>
<td>2</td>
</tr>
<tr>
<td>Total score of &gt; 6 points suggests VAP</td>
<td></td>
</tr>
</tbody>
</table>

*Score calculated by quantifying amount of tracheal secretions on a subjective 0 - 4 scale multiple times per day, then summing all the patient’s scores for the day.
Complications. A website titled VAPAWAY is dedicated to research and the prevention of VAP, and provides access to relevant information at www.vapaway.com.22 The Institute for Healthcare Improvement (IHI) in the USA has developed the Ventilator Care Bundle to address VAP as part of their Preventing Harm to 5 Million Lives Campaign.23

**Care of the ventilated patient**

**Strategies to prevent VAP: Recommendations**17

VAP is preventable, and certain practices have been demonstrated to reduce its incidence and its associated burden of illness.17 Prevention of VAP is possible through the use of evidence-based strategies intended to minimise endotracheal intubation, the duration of mechanical ventilation, and the risk of aspiration of oropharyngeal pathogens.2

Modifiable risk factors require understanding and practical implementation. The vast amount of research findings are often overwhelming and conflicting. Having the data synthesised into evidence-based clinical practice guidelines (CPGs) by a credible group of multidisciplinary critical care clinicians (such as the Canadian Critical Care Society and Canadian Critical Care Trials Group) improves the accessibility of reliable evidence for application in clinical practice. Guidelines can improve the processes, outcomes and costs of critical care.17 Successful implementation requires a team approach that embraces an active strategy to improve patient care, participation by all team members, periodic review of guidelines and a continuous process to effect change in behaviour where required.

The following recommendations (Tables III and IV) are a summary of the recommendations of some of the more recent literature, including the updated (2008) CPGs of the Canadian Group17 and the recommendations of Pieracci and Barie.7

Note: The use of nebulised endotracheal tobramycin and the intratracheal instillation of tobramycin are not recommended for the prevention of VAP,18 but may be useful in treating tracheobronchitis.

The application of a clinical guideline for the treatment of VAP was found to increase the initial administration of adequate antimicrobial treatment and decrease the overall duration of antibiotic treatment.19 In addition, routine ventilator-associated pneumonia prevention measures were applied, including semi-recumbent body position, discontinuation of mechanical ventilation using a medical intensive care unit specific weaning protocol, avoidance of gastric distension by monitoring residual volumes following feedings, and routine inspection of ventilator circuits to remove condensate.18

**Implementing clinical practice guidelines**

The IHI in the US recognised a need to reduce preventable errors after the release of the Institute of Medicine’s 1999 report on health care-related errors.29 The 100,000 Lives Campaign launched by the IHI in 2004 generated an unprecedented commitment to change and collaboration across the US health care industry, led to the launch of a similar programme in the UK, viz. the Saving Lives Campaign,30 and led to the expansion of the IHI programme to become the Protecting 5 Million Lives from Harm Campaign in 2006.23 The campaign is a national effort targeted at reducing preventable deaths in US hospitals, and protecting patients from harmful events that often have lasting effects. Medical harm is defined as ‘unintended physical injury resulting from or contributed to by medical care (including the absence of indicated medical treatment), that requires additional monitoring, treatment or hospitalization, or that results in death. Such injury is considered harm whether or not it is considered preventable, resulted from a medical error, or occurred within a hospital’.44 The initiative has led to new standards of care being developed and the implementation of relevant research findings at the bedside.

**The Ventilator Care Bundle**

The Ventilator Care Bundle is one of the six key programmes of the original campaign and consists of a series of (evidence-based) interventions related to ventilator care, that when implemented together, will achieve significantly better outcomes than when implemented individually.31 The key components of the Ventilator Care Bundle are:

- Elevation of the head of the bed (30 - 45°)32
- Daily ‘sedation vacations’ and assessment of readiness to extubate33
- Peptic ulcer disease prophylaxis34 (for high-risk patients only)
- Deep-vein thrombosis prophylaxis.35

Additional protocols could include:

- A structured oral care protocol38
- A patient mobility component
- Weaning protocols.

Resources are available to facilitate the implementation process.31 These include:

- Daily goal worksheets
- Checklists
- Audit tools.

**Impact of a protocol to prevent VAP**

The Canadian Critical Care Trials Group suggests that ‘Although scientific advances have the potential to improve the outcomes of critically ill patients
### Strategies to prevent VAP

**Physical strategies**
- Strict infection control, including hand hygiene with alcohol-based hand disinfectants, gowning and gloving to minimise person-to-person transmission of pathogens.
- Adequate ICU staffing.
- Minimise endotracheal intubation where possible.
  - Orotracheal route preferred to nasotracheal route.
  - Maintenance of orotracheal cuff pressure >20 cm H₂O (but <30).
- Sub-glottic secretion drainage via ETT with a dorsal lumen (in patients ventilated for >72 hours).
- Use of a closed endotracheal suctioning system for safety considerations (decrease transmission of infection-resistant organisms) does not prevent VAP.
- Closed endotracheal suctioning system changed between patients, or as clinically indicated.
- Minimise the duration of mechanical ventilation.
  - Daily interruption of sedation.
  - Standardised weaning protocols.
- Circuit changes only if the circuit becomes soiled or damaged, and between patients.
- Changing of heat-moisture exchangers (HMEs) every 5-7 days or as clinically indicated (clogged with secretions) if in use.
- Use of water bath humidification or a heated humidifier is acceptable.
- Bacterial filters are only indicated for use in patients with infectious diseases such as TB.
- Consider non-invasive ventilation if possible.
- Consider rotating beds, if available (kinetic bed therapy).
- Semi-recumbent positioning (30° - 45° head up) is protective, especially during enteral feeding (prevent gastro-oesophageal reflux and aspiration).
- Begin enteral feeding slowly, especially during the 48 hours after initiating mechanical ventilation, to minimise gastric reflux and potential aspiration risk.
- The gastric route for feeding is recommended (post-pyloric route not superior).
- Oral care.

**Pharmacological strategies**
- Oropharyngeal decontamination with a topical antiseptic such as chlorhexidine has been proven to be beneficial.
- Oral decontamination with povidone-iodine oral antiseptic only in patients with severe head injuries.
- Limit stress ulcer prophylaxis to high-risk patients (avoid antacids and histamine type 2 antagonists, sulcralfate and proton pump inhibitors (PPIs) preferable).
- Limit red blood cell transfusions in trauma and the critically ill.
- Targeted antibiotic administration strategies such as de-escalation and antibiotic rotation or ‘cycling’.

**Note:** Selective decontamination of the digestive tract (SDD) with topical or systemic antibiotics or antiseptics has not been shown to provide benefit outside of the Netherlands, may increase the incidence of MDR infections, and is therefore not recommended for general use.

**Strategies that have not proved beneficial include:**
- A systematic search for prevention of sinusitis (unless patient is intubated via the nasotracheal route).
- Prone positioning.
- Prophylactic antibiotics (aerolised, nasal or intravenous).
- Aerolised antibiotics.
- Intranasal mupirocin.
- Topical antibiotics.
- Post-pyloric feeding.

**Educational strategies**
- Staff education programmes.
who are at risk or who have VAP, the translation of research knowledge on effective strategies to prevent, diagnose, and treat VAP is not uniformly applied in practice in the intensive care unit. Knowledge about VAP may be used more effectively at the bedside by a systematic process of knowledge translation through implementation of clinical practice guidelines.

Clinical practice guidelines aim to improve the quality of care, to decrease costs, and to reduce inappropriate variation in decision making in the critical care setting. While there is some agreement regarding the evidence and the recommended strategies, implementation of guidelines remains a challenge in practice. In a study conducted in 2002 to establish why physicians do not follow guidelines, Rello et al. found that non-adherence to guidelines for preventing VAP was common, and largely uninfluenced by the degree of evidence. The most common reasons identified were disagreement with interpretation of clinical trials, unavailability of resources and costs.

Implementation

A team approach is essential for the successful implementation of a quality improvement initiative. The support of medical directors, nursing managers, administrators and ancillary services such as the laboratory, together with staff involvement, are key factors to success. The initiative requires a champion that will drive the process, written guidelines, user-friendly tools and regular feedback regarding the process, as well as ongoing review of the programme. Key elements are functional communication systems, accountability and continuous education of all staff. The Canadian Critical Care Trials Group promotes the concept of ‘a systematic process of knowledge translation that incorporates knowledge about clinical preferences and behaviour change theory’ – this process is defined as one that uses evidence-based clinical practice guidelines (CPGs) and includes a guideline implementation strategy that addresses understood barriers to clinician’s adherence to guidelines, and capitalizes on the facilitators.

Guideline implementation strategies

A combination of the following is required:

- Educational material, meetings and outreach visits
- Reminders
- Opinion leaders
- Computerised decision support systems
- Audit and feedback

The strategies need to be specifically suited to the complex and dynamic ICU environment, the multidisciplinary team, the organisational climate and culture of the ICU. Sinuff et al. found that ‘a coherent ICU team with common patient care goals and agreement with the purpose and goals of a guideline may facilitate guideline adherence’. Behaviour change theory can provide a framework within which to initiate the change process. Critical components include effective leadership, a collaborative team, continued education programme, an effective communication system and an audit-feedback system.

Conclusion

Significant improvements in quality indicators and patient outcomes have been reported by hospitals that have embraced the bundle approach and implemented the ventilator care bundle in particular. Cruden et al. found that the systematic and methodical implementation of the ventilator care bundle interventions over a 1-year period in a UK hospital
reduced the patient’s ICU length of stay and ventilator days, and increased the unit patient throughput. They found that the approach achieves these results by ensuring consistent delivery of evidence-based protocols and improving multidisciplinary communication. In a US-based study, Resar et al reported on a collaborative initiative to improve care in the ICU using a bundle approach, and found that VAP rates reported by 35 units decreased by an average of 44.5% during the 2-year study period. They suggest that the goal-oriented nature of the bundle appears to demand development of the teamwork necessary to improve reliability, and go on to state that ‘The observations seem sufficiently robust to support implementing the ventilator bundles to provide a focus for additional changes in ICUs.’ The evidence available presents a strong argument to consider a team approach to reducing the incidence of VAP in our own critical care units; even one less episode is worth the effort.