Ventilator associated events, conditions and prevention of VAP

Dr. Pratap Upadhyya
- Introduction
- Pathogenesis of VAP
- Diagnosis of VAP
- Ventilator-Associated Events: New Terminology and Its Relationship to VAP
- Prevention of VAP
Mechanical ventilation is an essential, life-saving therapy for patients with critical illness and respiratory failure. These patients are at high risk for complications and poor outcomes, including death.

Ventilator-associated pneumonia (VAP), sepsis, Acute Respiratory Distress Syndrome (ARDS), pulmonary embolism, barotrauma, and pulmonary edema are among the complications that can occur in patients receiving mechanical ventilation.

Surveillance for ventilator-associated events in the National Healthcare Safety Network (NHSN) prior to 2013 was limited to VAP. For the year 2012, VAP incidence for various types of hospital units ranged from 0.0-4.4 per 1,000 ventilator days

There is currently no valid, reliable definition for VAP, and even the most widely-used VAP criteria and definitions are neither sensitive nor specific.

JAMA 2007;297:1583-93
Am J Infect Control 2010;38:237-9
Clin Infect Dis 2008;46:1443-6
Pathogenesis of vap

Ventilator-associated pneumonia (VAP) is an infection of the lower respiratory tract associated with endotracheal intubation and which causes significant morbidity and mortality in the intensive care unit (ICU).

Approximately 10% of ventilated patients will develop the disease, with the risk of VAP rising as the duration of mechanical ventilation increases reaching a maximum on day 5 post-intubation.

VAP is associated with significant morbidity as it significantly increases the length of stay in the ICU, the duration of mechanical ventilation and hospital stay

VAP has longitudinal deleterious effects at the level of the individual patient, leading to the increased utilization of the health care system after ICU, further increasing the economic burden of this disease.
Common Sources of VAP Pathogens:
- Aspiration
- Intubation Procedure
- Biofilm Formation
- Contaminated Secretions
- Contaminated respiratory equipment

Microorganisms in the oropharyngeal cavity
Epiglottis

Contaminated respiratory equipment
Contaminated secretions
Biofilm formation on inner and outer surface of endotracheal (ET)
Dislodged biofilm
Carinal contaminated secretions
ET tube upon extubation
The pathophysiology of VAP is mediated largely by the **introduction of a foreign body**, the endotracheal tube (ETT), into the upper airway. This subverts the patient’s natural mechanisms for preventing access of microorganisms to the lower respiratory tract.

Critically ill patients have impaired innate and adaptive immunity

Diagnosis of VAP
The clinical diagnosis of VAP has included a combination of the following:

- clinical symptoms/signs,
- chest radiography, and
- microbiological data

JAMA. 2007;297(14):1583–93
Respir Care. 2013;58(6):990–1007
Table 1. Centers for Disease Control Diagnosis of Pneumonia

<table>
<thead>
<tr>
<th>Radiology</th>
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<tbody>
<tr>
<td>Two or more serial chest radiographs with at least one of the following:</td>
</tr>
<tr>
<td>New or progressive infiltrate</td>
</tr>
<tr>
<td>Consolidation</td>
</tr>
<tr>
<td>Cavitation</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Signs/symptoms</th>
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<tbody>
<tr>
<td>At least one of the following:</td>
</tr>
<tr>
<td>Fever (&gt; 38°C)</td>
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<tr>
<td>Leukopenia (&lt; 4,000 white blood cells/mL) or leukocytosis</td>
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<tr>
<td>(≥ 12,000 white blood cells/mL)</td>
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<tr>
<td>Altered mental status, if age ≥ 70 y</td>
</tr>
<tr>
<td>At least two of the following:</td>
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<tr>
<td>New purulent sputum (≥ 25 neutrophils and ≤ 10 squamous epithelial cells per low power field [× 100]) or change in sputum characteristics or amount</td>
</tr>
<tr>
<td>New or worsening cough, dyspnea, tachypnea</td>
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<tr>
<td>Rales</td>
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<tr>
<td>Worsening gas exchange</td>
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</table>

<table>
<thead>
<tr>
<th>Microbiology</th>
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<tbody>
<tr>
<td>At least one of the following:</td>
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<tr>
<td>Positive quantitative culture from minimally contaminated lower respiratory tract specimen. Specimen obtained via endotracheal suctioning is not a minimally contaminated specimen and therefore does not meet the laboratory criteria.</td>
</tr>
<tr>
<td>Positive culture of pleural fluid</td>
</tr>
<tr>
<td>Positive culture on lung tissue histological exam</td>
</tr>
<tr>
<td>Positive growth in blood culture not related to another source of infection</td>
</tr>
</tbody>
</table>
Clinical criteria plus microbiological sampling techniques lack specificity and sensitivity when compared to the demonstration of pneumonia on histological samples obtained by either biopsy or necropsy.
Accuracy of clinical definitions of ventilator-associated pneumonia: Comparison with autopsy findings

Eva Tejerina MD, PhD\textsuperscript{a,\,*}, Andrés Esteban MD, PhD\textsuperscript{a,c}, Pilar Fernández-Segoviano MD, PhD\textsuperscript{b}, Fernando Frutos-Vivar MD\textsuperscript{a,c}, José Aramburu MD\textsuperscript{b}, Daniel Ballesteros MD\textsuperscript{a}, José María Rodríguez-Barbero MD\textsuperscript{b}

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Keywords:
Ventilator-associated pneumonia;
Clinical diagnosis;
Microbiological cultures;
Radiographic infiltrates;
Autopsy findings

Abstract

Methods: We studied patients requiring mechanical ventilation for more than 48 hours who died in the intensive care unit and whose bodies were autopsied. We evaluated 3 clinical definitions of ventilator-associated pneumonia: loose definition, defined as chest radiograph infiltrates and 2 of 3 clinical criteria (leukocytosis, fever, purulent respiratory secretions); rigorous definition, defined as chest radiograph infiltrates and all of the clinical criteria; and a clinical pulmonary infection score higher than 6 points. Sensitivity, specificity, and likelihood ratios were calculated by using pathology pattern as criterion standard.

Results: One hundred forty-two (56\%) of the 253 patients included had histological criteria of pneumonia. Patients who met the clinical criteria of ventilator-associated pneumonia were 163 (64\%) for the loose definition, 32 (13\%) for the rigorous definition, and 109 (43\%) for the clinical pulmonary infection score. The operative indexes (sensitivity and specificity) of each definition were as follows: loose definition, 64.8\% and 36\%; rigorous definition, 91\% and 15.5\%; and clinical pulmonary infection score higher than 6, 45.8\% and 60.4\%. The addition of microbiological data to the clinical definitions increased the specificity and decreased the sensitivity but not significantly.

Conclusions: Accuracy of 3 commonly used clinical definitions of ventilator-associated pneumonia was poor taking the autopsy findings as reference standard.

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The Clinical Pulmonary Infection Score (CPIS) uses a combination of CXR and clinical, physiological and microbiological information for the diagnosis of VAP.

Score > 6 correlates with VAP.

Respir Care. 2011;56(8):1087–94
<table>
<thead>
<tr>
<th>CPIS points</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tracheal secretions</td>
<td>Rare</td>
<td>Abundant</td>
<td>Purulent</td>
</tr>
<tr>
<td>Leukocyte count (mm$^3$)</td>
<td>&gt;4,000 and &lt;11,000</td>
<td>&lt;4,000 and &gt;11,000</td>
<td>&lt;4,000 or &gt;11,000 + band forms</td>
</tr>
<tr>
<td>Temperature ($^\circ$C)</td>
<td>&gt;36.5 and &lt;38.4</td>
<td>&gt;38.5 and &lt;38.9</td>
<td>&gt;39 or &lt;36</td>
</tr>
<tr>
<td>$\text{PaO}_2$/FIO$_2$ ratio (mmHg)</td>
<td>&gt;240 or ARDS</td>
<td>-</td>
<td>$\leq$240 and no ARDS</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>No infiltrate</td>
<td>Diffuse infiltrate</td>
<td>Localized infiltrate</td>
</tr>
<tr>
<td>Culture of tracheal aspirate</td>
<td>Negative</td>
<td>-</td>
<td>Positive</td>
</tr>
</tbody>
</table>

CPIS: Clinical pulmonary infection scoring
Diagnostic Accuracy of Clinical Pulmonary Infection Score for Ventilator-Associated Pneumonia: A Meta-analysis

Jun Shan MM RN, Hong-Lin Chen MM, and Jian-Hua Zhu MD

OBJECTIVE: To assess the diagnostic accuracy of the clinical pulmonary infection score in the diagnosis of ventilator-associated pneumonia in mechanically ventilated patients. METHODS: We searched PubMed and the Cochrane database, and included only studies that compared clinical pulmonary infection score with quantitative microbiological analysis of samples for diagnosing ventilator-associated pneumonia. We constructed 2-by-2 tables of diagnostic accuracy from each article, and meta-analyzed the results by pooling estimates of sensitivity, specificity, likelihood ratio for positive index test, likelihood ratio for negative index test, diagnostic odds ratio, and 95% confidence intervals. RESULTS: Thirteen studies met the inclusion criteria. The pooled estimates for sensitivity and specificity for clinical pulmonary infection score were 65% (95% CI 61–69%) and 64% (95% CI 60–67%), respectively. The combined diagnostic odds ratio was 4.85 (95% CI 2.42–9.71) and the area under the curve was 0.748 (95% CI 0.65–0.85). CONCLUSIONS: The diagnostic performance of the clinical pulmonary infection score for ventilator-associated pneumonia is moderate. However, the clinical pulmonary infection score is simple and easy to perform, and may still be useful in diagnosing ventilator-associated pneumonia. Key words: ventilator-associated pneumonia; clinical pulmonary infection score; diagnosis; meta-analysis. [Respir Care 2011;56(8):1087–1094. © 2011 Daedalus Enterprises]
Most accurate predictor for autopsy-proven VAP on CXR was the presence of air bronchograms but this was also low.

The Radiologic Diagnosis of Autopsy-proven Ventilator-associated Pneumonia*


An abnormal chest roentgenogram is essential for the diagnosis of ventilator-associated pneumonia. The diagnostic accuracy of various roentgenographic signs of pneumonia has not been assessed previously in the portable anteroposterior roentgenograms obtained in ventilated patients. Seven roentgenographic signs (air bronchograms, alveolar infiltrates, silhouette sign, cavities, fissure abutment, atelectasis, and asymmetric infiltrates superimposed on diffuse bilateral infiltrates) were evaluated for their accuracy in predicting pneumonia alone, in combination with other signs, or in combination with clinical parameters. The last roentgenogram prior to autopsy of 69 ventilated patients was interpreted by three reviewers and the above signs were correlated with autopsy evidence of pneumonia. Pneumonia was present in 24 (35 percent) of the 69 autopsies. No roentgenographic sign had a diagnostic efficiency of greater than 68 percent. By stepwise logistic regression, the presence of air bronchograms was the only roentgenographic sign that correlated with pneumonia in the total group, correctly predicting 64 percent of pneumonias. In patients without adult respiratory distress syndrome (ARDS), the presence of air bronchograms or alveolar infiltrates correlated with pneumonia, while in patients with ARDS, no roentgenographic sign and only the clinical parameter of purulent sputum correlated with pneumonia. Only a minority (7/22) of worsening alveolar infiltrates in all groups were due to pneumonia and were often confused with ARDS. Alveolar hemorrhage occurred with a surprising frequency (38 percent of autopsies), including 13/45 (29 percent) patients without pneumonia. Alveolar hemorrhage was associated with 29 percent of multiple air bronchograms and 30 percent of bilateral alveolar infiltrates in patients without pneumonia. We conclude that in intubated patients with diffuse bilateral roentgenographic infiltrates, no roentgenographic sign correlates well with pneumonia. No clinical parameter added to the accuracy of either an alveolar infiltrate or an air bronchogram in patients without diffuse infiltrates. Pulmonary hemorrhage and/or infarction are frequent autopsy findings in intubated patients and may be confused radiologically with pneumonia. (Chest 1992; 101:458-63)

VAP = ventilator-associated pneumonia
Respiratory tract sampling—routinely conducted when there is a clinical suspicion of VAP
non-bronchoscopic or bronchoscopic techniques
a recent Cochrane analysis found no change in mortality, days on mechanical ventilation, number of days in the ICU, or antibiotic utilization when compared to semi-quantitative cultures

Cochrane Database Syst Rev. 2014;10, CD006482
Quantitative versus qualitative cultures of respiratory secretions for clinical outcomes in patients with ventilator-associated pneumonia

Danilo Cortozi Berton¹, Andre C Kalil², Paulo José Zimermann Teixeira¹

¹Department of Pulmonary Medicine - Pavilhão Pereira Filho - Santa Casa de Porto Alegre, Federal University of Health Sciences of Porto Alegre (UFCSPA) and FEEVALE University, Porto Alegre, Brazil. ²Department of Internal Medicine, Infectious Diseases Division, University of Nebraska Medical Center, Omaha, Nebraska, USA

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Ventilator-Associated Events: New Terminology and Its Relationship to VAP

Why?
Background and rationale for VAE surveillance
Who?
Age, location
What?
Surveillance definitions
how?
Tools, pitfalls
Why VAE?: the problem

Ventilator-associated pneumonia (VAP) is an important complication of mechanical ventilation. But other bad things also happen to patients on ventilators.

No valid, reliable definition for VAP

Need more accurate diagnostics …to conduct surveillance and track prevention progress!

Commonly used definitions include subjective elements and are neither sensitive nor specific for VAP.

Not ideal in an era of public reporting of healthcare-associated infection (HAI) rates, comparisons among facilities, pay-for-performance programs.

Need a new approach
Combination of x-ray, signs/symptoms and laboratory criteria

- Three sets of criteria: PNU1, PNU2, PNU3
- Chest imaging findings are required
- Signs and symptoms of pneumonia are required
  Laboratory evidence is optional—but should be used if available

To be “ventilator-associated” —

- Endotracheal tube (ETT)/ventilator must have been in place at some time during the 48 hours preceding or at time of PNEU onset
- No required amount of time that the ETT/ventilator must have been in place for a PNEU to count as a VAP

NHSN Manual: Patient Safety Component Protocol,
Cdc definitions

Ventilator-associated pneumonia (VAP):
A pneumonia where the patient is on mechanical ventilation for >2 calendar days on the date of event, with day of ventilator placement being Day 1, AND the ventilator was in place on the date of event or the day before.
<table>
<thead>
<tr>
<th>Imaging Test Evidence</th>
<th>Signs/Symptoms/Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two or more serial chest imaging test results with at least one of the following:</td>
<td>For ANY PATIENT, at least one of the following:</td>
</tr>
<tr>
<td>- New or progressive and persistent infiltrate</td>
<td>- Fever (&gt;38.0°C or &gt;100.4°F)</td>
</tr>
<tr>
<td>- Consolidation</td>
<td>- Leukopenia (&lt;4000 WBC/mm³) or leukocytosis (≥12,000 WBC/mm³)</td>
</tr>
<tr>
<td>- Cavitation</td>
<td>- For adults ≥70 years old, altered mental status with no other recognized cause</td>
</tr>
<tr>
<td>- Pneumatoceles, in infants ≤1 year old</td>
<td>And at least two of the following:</td>
</tr>
<tr>
<td>Note: In patients without underlying pulmonary or cardiac disease (e.g., respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary edema, or chronic obstructive pulmonary disease), one definitive imaging test result is acceptable.</td>
<td>- New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements</td>
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<td></td>
<td>- New onset or worsening cough, or dyspnea, or tachypnea</td>
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<td></td>
<td>- Rales or bronchial breath sounds</td>
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<td></td>
<td>- Worsening gas exchange (e.g., O₂ desaturations [e.g., PaO₂/FiO₂ &lt; 240], increased oxygen requirements, or increased ventilator demand)</td>
</tr>
<tr>
<td>ALTERNATE CRITERIA, for infants ≤1 year old:</td>
<td>Worsening gas exchange (e.g., O₂ desaturations [e.g., pulse oximetry &lt; 94%], increased oxygen requirements, or increased ventilator demand)</td>
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<td>And at least three of the following:</td>
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<td>- Temperature instability</td>
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<td>- Leukopenia (&lt;4000 WBC/mm³) or leukocytosis (≥15,000 WBC/mm³) and left shift (≥10% band forms)</td>
</tr>
<tr>
<td></td>
<td>- New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements</td>
</tr>
<tr>
<td></td>
<td>- Apnea, tachypnea, nasal flaring with retraction of chest wall or nasal flaring with grunting</td>
</tr>
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<td></td>
<td>- Wheezing, rales, or rhonchi</td>
</tr>
<tr>
<td></td>
<td>- Bradycardia (&lt;100 beats/min) or tachycardia (&gt;170 beats/min)</td>
</tr>
<tr>
<td>ALTERNATE CRITERIA, for child &gt;1 year old or ≤12 years old, at least three of the following:</td>
<td>Fever (&gt;38.0°C or &gt;100.4°F) or hypothermia (&lt;36.0°C or &lt;96.8°F)</td>
</tr>
<tr>
<td></td>
<td>- Leukopenia (&lt;4000 WBC/mm³) or leukocytosis (≥15,000 WBC/mm³)</td>
</tr>
<tr>
<td></td>
<td>- New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements</td>
</tr>
<tr>
<td></td>
<td>- New onset or worsening cough, or dyspnea, apnea, or tachypnea</td>
</tr>
<tr>
<td></td>
<td>- Rales or bronchial breath sounds</td>
</tr>
<tr>
<td></td>
<td>- Worsening gas exchange (e.g., O₂ desaturations [e.g., pulse oximetry &lt; 94%], increased oxygen requirements, or increased ventilator demand)</td>
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</tbody>
</table>
Table 2: Specific Site Algorithms for Pneumonia with Common Bacterial or Filamentous Fungal Pathogens and Specific Laboratory Findings (PNU2)

<table>
<thead>
<tr>
<th>Imaging Test Evidence</th>
<th>Signs/Symptoms</th>
<th>Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two or more serial chest imaging test results 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 (&gt;38.0°C or &gt;100.4°F)</td>
<td>- Positive growth in blood culture not related to another source of infection</td>
</tr>
<tr>
<td>- Consolidation</td>
<td>- Leukopenia (&lt;4000 WBC/mm³) or leukocytosis (≥12,000 WBC/mm³)</td>
<td>- Positive growth in culture of pleural fluid</td>
</tr>
<tr>
<td>- Cavitation</td>
<td>- For adults ≥70 years old, altered mental status with no other recognized cause</td>
<td>- Positive quantitative culture from minimally-contaminated LRT specimen (e.g., BAL or protected specimen brushing)</td>
</tr>
<tr>
<td>- Pneumatocoeles, in infants ≤1 year old</td>
<td>And at least one of the following:</td>
<td>- ≥5% BAL-obtained cells contain intracellular bacteria on direct microscopic exam (e.g., Gram’s stain)</td>
</tr>
<tr>
<td><strong>Note:</strong> In patients without underlying pulmonary or cardiac disease (e.g., respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary edema, or chronic obstructive pulmonary disease), one definitive chest imaging test result is acceptable.</td>
<td>- New onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements</td>
<td>- Positive quantitative culture of lung tissue</td>
</tr>
<tr>
<td></td>
<td>- New onset or worsening cough, or dyspnea or tachypnea</td>
<td>- Histopathologic exam shows at least one of the following evidences of pneumonia:</td>
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<tr>
<td></td>
<td>- Rales or bronchial breath sounds</td>
<td>- Abscess formation or foci of consolidation with intense PMN accumulation in bronchioles and alveoli</td>
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<td></td>
<td>- Worsening gas exchange (e.g., O₂ desaturations [e.g., PaO₂/FiO₂ ≤400], increased oxygen requirements, or increased ventilator demand)</td>
<td>- Evidence of lung parenchyma invasion by fungal hyphae or pseudohyphae</td>
</tr>
<tr>
<td>Imaging Test Evidence</td>
<td>Signs/Symptoms</td>
<td>Laboratory</td>
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</tr>
<tr>
<td>Two or more serial chest imaging test results with at least one of the following:</td>
<td>Patient who is immunocompromised (see definition in footnote) has 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 (&gt;38.0°C or &gt;100.4°F)</td>
<td>- Matching positive blood and sputum or endotracheal aspirate cultures with Candida spp.</td>
</tr>
<tr>
<td>- Consolidation</td>
<td>- For adults ≥70 years old, altered mental status with no other recognized cause</td>
<td>- Evidence of fungi from minimally-contaminated LRT specimen (e.g., BAL or protected specimen brushing) from one of the following:</td>
</tr>
<tr>
<td>- Cavitation</td>
<td>- New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements</td>
<td>- Direct microscopic exam</td>
</tr>
<tr>
<td>- Pneumatoceles, in infants ≤1 year old</td>
<td>- New onset or worsening cough, or dyspnea, or tachypnea</td>
<td>- Positive culture of fungi</td>
</tr>
<tr>
<td><strong>Note:</strong> In patients without underlying pulmonary or cardiac disease (e.g., respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary edema, or chronic obstructive pulmonary disease), one definitive chest imaging test result is acceptable.</td>
<td>- Rales or bronchial breath sounds</td>
<td>- Non-culture diagnostic laboratory test</td>
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<td></td>
<td>Any of the following from:</td>
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<td><strong>LABORATORY CRITERIA DEFINED UNDER PNU2</strong></td>
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</tbody>
</table>
Limitations of current definitions-
Current definitions (e.g., definitions used for surveillance in NHSN, Clinical Pulmonary Infection Score) all use combinations of criteria:

**Chest x-ray**-
Lack specificity for VAP1
Inter-observer variability2

**Clinical signs/symptoms**-
Lack sensitivity and specificity3
Some are highly subjective
Documentation varies

**Microbiological evidence**-
Lack sensitivity and specificity4
Practices vary among providers
Controversy about best practices5,6

Why VAP rates declining?

- Evidence-based prevention measures
- Other reasons—several ways to lower VAP rates without improving patient care (Klompas et al., *AJIC* 2012;40:408-10)

- Strict interpretation of clinical signs included in surveillance definitions
- Strict interpretation of chest x-ray findings included in surveillance definitions
- Practice of transferring out those patients needing prolonged mechanical ventilation
- Admission of uncomplicated, vented post-operative patients to unit.
Goals for Modifying Current NHSN Definitions-

- Achieve face validity/clinical credibility
- Improve reliability
- Reduce burden
VAE Surveillance Definition Algorithm—Tiered Approach

Tiers 1 and 2: Definitions suitable for potential use in public reporting
- Objective, general measures of Ventilator-Associated Conditions (VAC) and Infection-related, Ventilator-Associated Complications (IVAC)
- Definitions similar to Tier 1 VAC definition evaluated by Klompas et al. identified events associated with longer duration of mechanical ventilation, longer ICU stay, and increased mortality—and were more efficient to apply than current VAP definitions (*PLoS One* 2011;6:e18062, *Crit Care Med* 2012; in press)

Tier 3: Internal use definitions
- Possible VAP and Probable VAP, incorporating laboratory evidence
Who is eligible?

- ≥18 years of age
- Inpatients of acute care hospitals, long term acute care hospitals, inpatient rehabilitation facilities
Who is NOT eligible for VAE surveillance?

- Children are not eligible.
- Inpatients of facilities other than acute care hospitals, long-term acute care hospitals and inpatient rehabilitation facilities are not eligible.
- Patients on high frequency ventilation or extracorporeal life support are NOT ELIGIBLE for VAE surveillance.
“WHAT” IS VAE? REVIEW OF DEFINITIONS
**VAE Definition Algorithm Summary**

- **Respiratory status component**
  - Patient on mechanical ventilation > 2 days
  - Baseline period of stability or improvement, followed by sustained period of worsening oxygenation

- **Infection / inflammation component**
  - General evidence of infection/inflammation
  - Infection-Related Ventilator-Associated Complication (IVAC)

- **Additional evidence**
  - Positive results of microbiological testing
  - Possible or Probable VAP

No CXR needed!
VAE Definition Algorithm Summary

- **Respiratory status component**
  - Patient on mechanical ventilation > 2 days
  - Baseline period of stability or improvement, followed by sustained period of worsening oxygenation
    - \( \text{FiO}_2 \) or PEEP
  - Ventilator-Associated Condition (VAC)

- **Infection / inflammation component**
  - General evidence of infection/inflammation
  - Infection-Related Ventilator-Associated Complication (IVAC)

- **Additional evidence**
  - Positive results of microbiological testing
  - Possible or Probable VAP
VAE Definition Algorithm Summary

- **Respiratory status component**
  - Patient on mechanical ventilation > 2 days
  - Baseline period of stability or improvement, followed by sustained period of worsening oxygenation

- **Infection / inflammation component**
  - General evidence of infection/inflammation
  - Infection-Related Ventilator-Associated Complication (IVAC)

- **Additional evidence**
  - Positive results of microbiological testing
  - Possible or Probable VAP

- Temperature or WBC and New antimicrobial agent
VAE Definition Algorithm Summary

- Respiratory status component
  - Patient on mechanical ventilation > 2 days
  - Baseline period of stability or improvement, followed by sustained period of worsening oxygenation
  - Ventilator-Associated Condition (VAC)

- Infection / inflammation component
  - General evidence of infection/inflammation
  - Infection-Related Ventilator-Associated Condition (IVAC)
  - Purulent secretions and/or other positive laboratory evidence

- Additional evidence
  - Positive results of microbiological testing
  - Possible or Probable VAP
Tier 1: VAC

Patient has a baseline period of stability or improvement on the ventilator, defined by ≥ 2 calendar days of stable or decreasing daily minimum \( \text{FiO}_2 \) or PEEP values. The baseline period is defined as the two calendar days immediately preceding the first day of increased daily minimum PEEP or \( \text{FiO}_2 \).

AND

After a period of stability or improvement on the ventilator, the patient has at least one of the following indicators of worsening oxygenation:

1) Increase in daily minimum \( \text{FiO}_2 \) of ≥ 0.20 (20 points) over the daily minimum \( \text{FiO}_2 \) in the baseline period, sustained for ≥ 2 calendar days.

2) Increase in daily minimum PEEP values of ≥ 3 cmH\(_2\)O over the daily minimum PEEP in the baseline period, sustained for ≥ 2 calendar days.
Tier 2: IVAC

Patient meets criteria for VAC

AND

On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, the patient meets both of the following criteria:

1) Temperature > 38 °C or < 36 °C, OR white blood cell count ≥ 12,000 cells/mm³ or ≤ 4,000 cells/mm³.

AND

2) A new antimicrobial agent(s)* is started, and is continued for ≥ 4 calendar days.

*See Appendix for eligible agents.
Tier 3: Possible VAP

Patient meets criteria for VAC and IVAC

AND

On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, ONE of the following criteria is met:

1) Purulent respiratory secretions (from one or more specimen collections)
   - Defined as secretions from the lungs, bronchi, or trachea that contain \( \geq 25 \) neutrophils and \( \leq 10 \) squamous epithelial cells per low power field (lpf, x100).
   - If the laboratory reports semi-quantitative results, those results must be equivalent to the above quantitative thresholds.

2) Positive culture (qualitative, semi-quantitative or quantitative) of sputum*, endotracheal aspirate*, bronchoalveolar lavage*, lung tissue, or protected specimen brushing*

*Excludes the following:
- Normal respiratory/oral flora, mixed respiratory/oral flora or equivalent
- Candida species or yeast not otherwise specified
- Coagulase-negative Staphylococcus species
- Enterococcus species
Tier 3: Probable VAP

VAC, IVAC plus the following...

On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, ONE of the following criteria is met:

1) Purulent respiratory secretions (from one or more specimen collections—and defined as for possible VAP)

   AND one of the following (see Table 2):
   - Positive culture of endotracheal aspirate*, \( \geq 10^5 \text{ CFU/ml} \) or equivalent semi-quantitative result
   - Positive culture of bronchoalveolar lavage*, \( \geq 10^4 \text{ CFU/ml} \) or equivalent semi-quantitative result
   - Positive culture of lung tissue, \( \geq 10^4 \text{ CFU/g} \) or equivalent semi-quantitative result
   - Positive culture of protected specimen brush*, \( \geq 10^3 \text{ CFU/ml} \) or equivalent semi-quantitative result

*Same organism exclusions as noted for Possible VAP.

2) One of the following (without requirement for purulent respiratory secretions):
   - Positive pleural fluid culture (where specimen was obtained during thoracentesis or initial placement of chest tube and NOT from an indwelling chest tube)
   - Positive lung histopathology
   - Positive diagnostic test for *Legionella* spp.
   - Positive diagnostic test on respiratory secretions for influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, human metapneumovirus, coronavirus
Hierarchy of definitions:

- If a patient meets criteria for VAC and IVAC, report as IVAC.
- If a patient meets criteria for VAC, IVAC and Possible VAP, report Possible VAP.
- If a patient meets criteria for VAC, IVAC and Probable VAP, report Probable VAP.
- If a patient meets criteria for VAC, IVAC, Possible VAP and Probable VAP, report Probable VAP.
Ventilator associated events [VAE], Ventilator associated pneumonia [VAP]: Definition changes 2015

www.cdc.gov/nhsn/
VAE protocol change #1:
Third tier of the VAE algorithm is collapsed to include one specific event: PVAP.
PVAP replaces possible and probable VAP.
Provides simplification.
Three pathways for meeting PVAP definition

- Quantitative or semiquantitative equivalent culture WITHOUT purulent respiratory secretions
- Culture result with purulent secretions
- Other positive laboratory tests.
On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, ONE of the following criteria is met (taking into account organism exclusions specified in the protocol*):

1) Criterion 1: Positive culture of one of the following specimens, meeting quantitative or semi-quantitative thresholds as outlined in protocol, without requirement for purulent respiratory secretions:
   - Endotracheal aspirate, $\geq 10^5$ CFU/ml or corresponding semi-quantitative result
   - Bronchial wash, $\geq 10^4$ CFU/ml or corresponding semi-quantitative result
   - Lung tissue, $\geq 10^4$ CFU/g or corresponding semi-quantitative result
   - Protected specimen brush, $\geq 10^5$ CFU/ml or corresponding semi-quantitative result

2) Criterion 2: Purulent respiratory secretions (defined as secretions from the lungs, bronchi, or trachea that contain $>25$ neutrophils and $\leq 10$ squamous epithelial cells per low power field [1lpf, x100]) plus a positive culture of one of the following specimens (qualitative culture, or quantitative/semi-quantitative culture without sufficient growth to meet criterion #1):
   - Sputum
   - Endotracheal aspirate
   - Bronchial wash
   - Lung tissue
   - Protected specimen brush
   * If the laboratory reports semi-quantitative results, those results must correspond to the quantitative thresholds. See additional instructions for using the purulent respiratory secretions criterion in the VAE Protocol.

3) Criterion 3: One of the following positive tests:
   - Pleural fluid culture (where specimen was obtained during thoracentesis or initial placement of chest tube and NOT from an indwelling chest tube)
   - Lung histopathology, defined as: 1) abscess formation or foci of consolidation with intense neutrophil accumulation in bronchioles and alveoli; 2) evidence of lung parenchyma invasion by fungi (hyphae, pseudohyphae or yeast forms); 3) evidence of infection with the viral pathogens listed below based on results of immunohistochemical assays, cytology, or microscopy performed on lung tissue
   - Diagnostic test for Legionella species
   - Diagnostic test on respiratory secretions for influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, rhinovirus, human metapneumovirus,
VAE protocol change 2:
The following community acquired fungal pathogens rarely cause health care associated infections and therefore are no longer available for meeting the PVAP definition-
Cryptococcus
Histoplasma
Pneumocystis
Blastomyces
VAE protocol change #3:

- Daily minimum PEEP and FiO2 values are defined as the lowest value during the calendar day that is set on the ventilator and maintained for at least 1 hour.

- Provides simplification and consistency for determining the daily minimum PEEP and FiO2 in select circumstances.
VAE new denominator-
Episodes of mechanical ventilation [EMV] is introduced.
defined as a period of days during which the patient was mechanically ventilated for some portion of each consecutive day.
EMV is a total of the number of episodes occurring during a month.
EXAMPLE: On January 1, there are 5 patients on mechanical ventilation in the MICU (2 patients were started on mechanical ventilation on December 24, 2 patients on December 31, and 1 patient on January 1). During the rest of the month, the following are noted: 1 patient is started on mechanical ventilation on January 8; 2 patients are transferred to the MICU on mechanical ventilation on January 15, and 1 patient who was previously ventilated (from January 1 through January 12) goes back on mechanical ventilation on January 20. No other patients are on mechanical ventilation during the month of January. The number of EMV for January is nine. This is calculated as follows: 5 patients (on mechanical ventilation on the first day of the month) + 4 patients who were either started on mechanical ventilation, transferred into the MICU on mechanical ventilation, or re-initiated on mechanical ventilation after being off of the vent for at least 1 calendar day = 9 EMV.
Key points

- Key Take-Home Points: Patient must be ventilated more than 2 calendar days.
- Patient must have ≥2 calendar days of stability or improvement of oxygenation followed by ≥2 calendar days of worsening oxygenation.
- Earliest date of event for VAE is mechanical ventilation day 3 (first day of worsening oxygenation).
- First possible day that VAC criteria can be fulfilled is mechanical ventilation day 4.
Event Date defines the VAE Window Period:

- 2 days before, day of and 2 days after the Event Date – 5 days
- May be shorter if worsening occurs early in the course of ventilation

All other criteria (for IVAC, Possible VAP, Probable VAP) must be identified within the VAE Window Period.

The “VAE clock” starts over again when ...

- The patient begins a new episode of mechanical ventilation
- A new event period starts (i.e., 14 days have elapsed since previous VAE Event Date)
- The patient comes off of an excluded therapy (such as HFV or ECMO) and goes back on conventional mode of ventilation.
Prevention of VAP

VAP incidence is 25% of all critical care unit infectious diseases, and 10-25% of ventilated cases develop VAP, >25% of antibiotics prescribed in ICU are for VAP patients.

Craven et al., 2006 Chest 130: 251-260.
VAP increases the length on mechanical ventilation, and ICU stay, longer hospital length of stay, and increase the mortality rate by double.

Safdar et al., 2005 Care Med 33: 2184-2193.
The sources of the VAP have been identified in several places such as oral cavity, subglottic fluid, and the gastric mucosa. The endotracheal tube shows an important matter in the development of VAP, as a source of infection and as a reservoir of the infection from the formation of the biofilm on the inner surface of tube.

Adair cg etal, 1995 Intensive care medicine 25: 1072-1076
Strategies for VAP prevention-

- Non-invasive positive-pressure ventilation (NIPPV)
- Semi-recumbent position to decrease aspiration of oropharyngeal secretions.
- Oral hygiene with chlorhexidine
- Specialized endotracheal tubes (subglottic secretion drainage; silver-coated)
Current modalities for the prevention of VAP and the evidence for these modalities, are based on the traditional definition of VAP. It is unknown if VACs and iVACs are preventable with the VAP prevention modalities.
Non-invasive Positive Pressure Ventilation (NIPPV)

- Avoiding intubation and limiting the duration of mechanical ventilation reduces the occurrence of VAP.
- Use of NIPPV avoids the need for intubation or terminates mechanical ventilation as early as possible by extubation to NIPPV.

Hess Dr, Respir Care. 2005;50(7):924–9
Burns KE et al, Cochrane Database Syst Rev. 2013;12, CD004127
Noninvasive Positive-Pressure Ventilation and Ventilator-Associated Pneumonia

Dean R Hess PhD RRT FAARC

Introduction
Methods
NPPV and Ventilator-Associated Pneumonia
Observations
Continuous Positive Airway Pressure and Pneumonia
Summary

There is much interest in the use of noninvasive positive-pressure ventilation (NPPV) to prevent intubation and afford a survival benefit for patients. The risk of pneumonia in patients receiving NPPV has been reported in 12 studies. Compared to patients receiving invasive mechanical ventilation (4 studies), the pneumonia rate is lower with the use of NPPV (relative risk [RR] 0.15, 95% confidence interval [CI] 0.04 to 0.58, p = 0.006). Compared to patients assigned to invasive mechanical ventilation (3 studies), in which some of the patients assigned to NPPV did not respond and were eventually intubated, there was also a benefit for the use of NPPV (RR 0.24, 95% CI 0.08 to 0.73, p = 0.01). In studies in which patients assigned to NPPV were compared to patients assigned to standard therapy (5 studies), in which some of the patients in each group were eventually intubated, there was benefit shown for the use of NPPV (RR 0.56, 95% CI 0.31 to 1.02, p = 0.06). When this meta-analysis is repeated without the results of the negative study for NPPV (extubation failure), there is a stronger benefit in support of NPPV to decrease the risk of pneumonia in the remaining 4 studies (RR 0.38, 95% CI 0.20 to 0.73, p = 0.003). A meta-analysis combining the results from the 12 studies reviewed shows a strong benefit for NPPV (RR 0.31, 95% CI 0.16 to 0.57, p = 0.0002). One randomized controlled trial of continuous positive airway pressure compared with standard treatment in patients who developed acute hypoxemia after elective major abdominal surgery reported a lower rate of pneumonia with continuous positive airway pressure (2% vs 10%, RR 0.19, 95% CI 0.04 to 0.88, p = 0.02). In patients who are appropriate candidates for NPPV or continuous positive airway pressure, the available evidence suggests a benefit in terms of a lower risk of pneumonia. Perhaps “endotracheal-tube-associated pneumonia” is a better term than “ventilator-associated pneumonia.”  

Keywords: continuous positive airway pressure, mechanical ventilation, noninvasive positive-pressure ventilation, ventilator-associated pneumonia.  

[Respir Care 2005;50(7):924-929. © 2005 Daedalus Enterprises]
Fig. 1. Pooled analysis of pneumonia in studies comparing non-invasive positive-pressure ventilation (NPPV) with invasive mechanical ventilation. p = 0.13 for heterogeneity. p = 0.006 for overall effect. RR = relative risk. CI = confidence interval.

Fig. 2. Pooled analysis of pneumonia in studies where patients were assigned to noninvasive positive-pressure ventilation (NPPV) or invasive mechanical ventilation. p = 0.25 for heterogeneity. p = 0.01 for overall effect. RR = relative risk. CI = confidence interval.
Noninvasive positive-pressure ventilation as a weaning strategy for intubated adults with respiratory failure

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Fig. 3. A: Pooled analysis of pneumonia in studies comparing patients assigned to noninvasive positive-pressure ventilation (NPPV) or assigned to standard therapy. $p = 0.19$ for heterogeneity. $p = 0.06$ for overall effect. B: Pooled analysis of pneumonia in studies comparing patients assigned to NPPV or assigned to standard therapy after removal of the study showing no benefit for noninvasive positive-pressure ventilation (NPPV) (failed extubation). $p = 0.96$ for heterogeneity. $p = 0.003$ for overall effect. RR = relative risk. CI = confidence interval.
Main results

We identified 16 trials, predominantly of moderate to good quality, involving 994 participants, most with chronic obstructive pulmonary disease (COPD). Compared with IPPV weaning, NPPV weaning significantly decreased mortality. The benefits for mortality were significantly greater in trials enrolling exclusively participants with COPD (risk ratio (RR) 0.36, 95% confidence interval (CI) 0.24 to 0.56) versus mixed populations (RR 0.81, 95% CI 0.47 to 1.40). NPPV significantly reduced weaning failure (RR 0.63, 95% CI 0.42 to 0.96) and ventilator-associated pneumonia (RR 0.25, 95% CI 0.15 to 0.43); shortened length of stay in an intensive care unit (mean difference (MD) -5.59 days, 95% CI -7.90 to -3.28) and in hospital (MD -6.04 days, 95% CI -9.22 to -2.87); and decreased the total duration of ventilation (MD -5.64 days, 95% CI -9.50 to -1.77) and the duration of endotracheal mechanical ventilation (MD -7.44 days, 95% CI -10.34 to -4.55) amidst significant heterogeneity. Noninvasive weaning also significantly reduced tracheostomy (RR 0.19, 95% CI 0.08 to 0.47) and reintubation (RR 0.65, 95% CI 0.44 to 0.97) rates. Noninvasive weaning had no effect on the duration of ventilation related to weaning. Exclusion of a single quasi-randomized trial did not alter these results. Subgroup analyses suggest that the benefits for mortality were significantly greater in trials enrolling exclusively participants with COPD versus mixed populations.

Authors’ conclusions

Summary estimates from 16 trials of moderate to good quality that included predominantly participants with COPD suggest that a weaning strategy that includes NPPV may reduce rates of mortality and ventilator-associated pneumonia without increasing the risk of weaning failure or reintubation.
Positioning

• Limiting aspiration of oropharyngeal secretions is a strategy to prevent VAP. done in part by maintaining a semi-recumbent position to maintain the head of the bed between 30 and 45°.

• Is a simple intervention and it is worth implementing unless there are contraindications in the specific patient.

Impact of patient position on the incidence of ventilator-associated pneumonia: A meta-analysis of randomized controlled trials

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\textsuperscript{c}Department of Medicine, Henry Dunant Hospital, Athens, Greece
\textsuperscript{d}Department of Medicine, Tufts University School of Medicine, Boston, MA, USA
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<th>First author/Reference</th>
<th>Study design/Year of publication</th>
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<td>Van Nieuwenhoven [15]</td>
<td>MC RCT/12 2006</td>
<td>Netherlands</td>
<td>Semi-recumbent position; 45° of the head and back vs supine position; standard care; 10° of the head and back</td>
<td>Patients treated in 3 ICUs intubated within 24 h of ICU admission and with duration of ventilation for at least 48 h</td>
<td>221</td>
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<td>Drakulovic [16]</td>
<td>SC RCT/13 1999</td>
<td>Spain</td>
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<td>Intubated and mechanically ventilated patients of one medical and one respiratory ICU at a tertiary university hospital</td>
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<td>Keeley [17]</td>
<td>SC RCT/14 2007</td>
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<td>Critical care patients intubated within 12 h from ICU admission</td>
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<td>Veggemeier [18]</td>
<td>MC RCT/15 2005</td>
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<td>Multiple trauma patients with ALI/ARDS and receiving mechanical ventilation treated in 2 trauma ICU</td>
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<td>Beuret [20]</td>
<td>SC RCT/17 2002</td>
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<td>Comatose patients who needed mechanical ventilation for at least 48 h</td>
<td>51</td>
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<td>Guerin [12]</td>
<td>MC RCT/18 2004</td>
<td>France</td>
<td>Prone position for at least 8 h daily vs supine position (30° of the head and back)</td>
<td>Patients with acute respiratory failure treated in 21 general ICUs with ( P_{a}O_{2}/FiO_{2} ) ratio at most 300</td>
<td>791</td>
<td>2</td>
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MC: Multi Center, SC: Single Center.
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<tr>
<td>Semirecumbent position</td>
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<td>Prone position in patients with ARDS/ALI</td>
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<td>Prone position in patients without ARDS/ALI</td>
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<td>VAP clinically suspected</td>
<td>16/112 vs 20/109</td>
<td>3/39 vs 16/47</td>
<td>5/17 vs 7/13</td>
<td>13/21 vs 17/19</td>
<td>14/76 vs 9/60</td>
<td>11/25 vs 14/26</td>
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<td>VAP microbiologically documented</td>
<td>13/112 vs 8/109</td>
<td>2/39 vs 11/47</td>
<td>4/17 vs 5/13</td>
<td>N/A</td>
<td>N/A</td>
<td>4/25 vs N/A</td>
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<tr>
<td>Mortality</td>
<td>29/112 vs 39/112 (ICU)</td>
<td>7/39 vs 13/47 (ICU)</td>
<td>3/17 vs 4/17 (ICU)</td>
<td>1/21 vs 3/19 (day 90)</td>
<td>33/76 vs 35/60 (ICU)</td>
<td>38/76 vs 37/60 (hospital)</td>
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<td>30/109 (ICU)</td>
<td>13/47 (ICU)</td>
<td>4/13 (ICU)</td>
<td>4/13 (hospital)</td>
<td>12/26 (day 28)</td>
<td>134/413 vs 119/378 (day 28)</td>
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<td>Mean duration of ventilation in days (SD)</td>
<td>6 vs 6 median</td>
<td>6(6.2) vs 7.1 (7)</td>
<td>N/A</td>
<td>30 (17) vs 33 (23)</td>
<td>N/A</td>
<td>12.7 (10) vs 14.6 (17.7)</td>
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<td>Mean duration of ICU stay in days (SD)</td>
<td>9 vs 10 median</td>
<td>9.3 (7.2) vs 9.7 (7.8)</td>
<td>N/A</td>
<td>N/A</td>
<td>20.5 (18.2) vs 19.1 (23.1)</td>
<td>16.5 (12.9) vs 19.4 (24.1)</td>
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<td>Mean duration of antibiotic therapy in days (SD)</td>
<td>4 (N/A) vs 4 (N/A)</td>
<td>N/A</td>
<td>N/A</td>
<td>20.8 (8.9) vs 18.2 (8.7)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
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</table>
This meta-analysis provides additional evidence that the usual practice of back-rest elevation of 15° to 30° is not sufficient to prevent VAP in mechanically ventilated patients. Patients positioned semi recumbently 45° have significantly lower incidence of clinically diagnosed VAP compared to patients positioned supinely. On the other hand, the incidence of clinically diagnosed VAP among patients positioned pronely does not differ significantly from the incidence of clinically diagnosed VAP among patients positioned supinely.
Probiotics are living microbial agents of human origin that are able to tolerate the hostile gastrointestinal environment (acid and bile) such that they ultimately persist in the lower alimentary tract to confer health benefits to the host.

decrease the inflammatory reaction and improve both the immunological response (the balance between T-helper 1 and T-helper 2 cells), and immunological barrier of the gut.


Probiotics for preventing ventilator-associated pneumonia

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Editorial group: Cochrane Acute Respiratory Infections Group.
Review content assessed as up-to-date: 17 September 2014.


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Figure 1. Study flow diagram: 2014 search

362 records identified through database searching
0 additional records identified through other sources

276 records after duplicates removed

276 records screened
262 records excluded

14 full-text articles assessed for eligibility
5 full-text articles excluded, with reasons

8 studies included in qualitative synthesis

8 studies included in quantitative synthesis (meta-analysis)
# Summary of Findings for the Main Comparison

**Per-protocol analysis: probiotics versus control for preventing ventilator-associated pneumonia**

**Patient or population:** patients receiving mechanical ventilation  
**Settings:** inpatient: China, France, Greece, Slovenia, Sweden, UK and USA  
**Intervention:** per-protocol analysis: probiotics versus control

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<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
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<td><strong>Incidence of VAP</strong></td>
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<tr>
<td>Follow-up: mean 37 days</td>
<td>Moderate(^1)</td>
<td>OR 0.7</td>
<td>1018 (8 studies)</td>
<td>low(^2,3)</td>
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<tr>
<td></td>
<td>309 per 1000 (189 to 298)</td>
<td>(0.52 to 0.95)</td>
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<tr>
<td></td>
<td>Per-protocol analysis: probiotics versus control</td>
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<tr>
<td><strong>ICU mortality</strong></td>
<td></td>
<td>OR 0.84</td>
<td>703 (5 studies)</td>
<td>very low(^5,6)</td>
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</tr>
<tr>
<td>Follow-up: mean 35 days</td>
<td>Moderate(^4)</td>
<td>(0.58 to 1.22)</td>
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<tr>
<td></td>
<td>214 per 1000 (136 to 249)</td>
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<tr>
<td><strong>Hospital mortality</strong></td>
<td></td>
<td>OR 0.78</td>
<td>524 (4 studies)</td>
<td>very low(^5,6,8)</td>
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</tr>
<tr>
<td>Follow-up: median 37 days</td>
<td>Moderate(^7)</td>
<td>(0.54 to 1.14)</td>
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<td></td>
<td>306 per 1000 (192 to 335)</td>
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</tr>
<tr>
<td><strong>Diarrhoea</strong></td>
<td></td>
<td>OR 0.72</td>
<td>618 (4 studies)</td>
<td>very low(^5,6,8)</td>
<td></td>
</tr>
<tr>
<td>Follow-up: mean 40 days</td>
<td>Moderate(^9)</td>
<td>(0.47 to 1.09)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>435 per 1000 (266 to 456)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Analysis 1.1. Comparison 1 Per-protocol analysis: probiotics versus control, Outcome 1. Incidence of VAP.

Review: Probiotics for preventing ventilator-associated pneumonia

Comparison: 1 Per-protocol analysis: probiotics versus control

Outcome: 1 Incidence of VAP

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Probiotics</th>
<th>Control</th>
<th>Odds Ratio</th>
<th>Weight</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H Fixed 95% CI</td>
<td></td>
<td>M-H Fixed 95% CI</td>
</tr>
<tr>
<td>Barral 2010</td>
<td>23/78</td>
<td>15/71</td>
<td>1.56 [ 0.74, 3.30 ]</td>
<td>10.9%</td>
<td>1.56 [ 0.74, 3.30 ]</td>
</tr>
<tr>
<td>Forrest 2008</td>
<td>24/102</td>
<td>24/106</td>
<td>1.05 [ 0.55, 2.00 ]</td>
<td>17.8%</td>
<td>1.05 [ 0.55, 2.00 ]</td>
</tr>
<tr>
<td>Klarin 2008</td>
<td>1/23</td>
<td>3/21</td>
<td>0.27 [ 0.03, 2.85 ]</td>
<td>3.0%</td>
<td>0.27 [ 0.03, 2.85 ]</td>
</tr>
<tr>
<td>Knight 2009</td>
<td>12/130</td>
<td>17/129</td>
<td>0.67 [ 0.31, 1.47 ]</td>
<td>15.3%</td>
<td>0.67 [ 0.31, 1.47 ]</td>
</tr>
<tr>
<td>Kotrampalli 2006</td>
<td>15/36</td>
<td>16/36</td>
<td>0.89 [ 0.35, 2.27 ]</td>
<td>9.2%</td>
<td>0.89 [ 0.35, 2.27 ]</td>
</tr>
<tr>
<td>Morrow 2010</td>
<td>17/68</td>
<td>33/70</td>
<td>0.37 [ 0.18, 0.77 ]</td>
<td>24.1%</td>
<td>0.37 [ 0.18, 0.77 ]</td>
</tr>
<tr>
<td>Spindler-Vesel 2007</td>
<td>4/26</td>
<td>34/87</td>
<td>0.09 [ 0.01, 0.73 ]</td>
<td>13.1%</td>
<td>0.09 [ 0.01, 0.73 ]</td>
</tr>
<tr>
<td>Tan 2011</td>
<td>7/16</td>
<td>13/19</td>
<td>0.36 [ 0.09, 1.43 ]</td>
<td>6.6%</td>
<td>0.36 [ 0.09, 1.43 ]</td>
</tr>
</tbody>
</table>

Total (95% CI)     479 | 539 | 100.0% | 0.70 [ 0.52, 0.95 ] |

Total events: 103 (Probiotics), 155 (Control).

Heterogeneity: CHI² = 12.99, df = 7 (P = 0.07); I² = 46%

Test for overall effect: Z = 2.30 (P = 0.02)

Test for subgroup differences: Not applicable
Endotracheal tubes represent a foreign body in the upper airway and are prone to bacterial colonization and the development of biofilms.

The formation of the biofilm is early after the intubation. The biofilm is a source and reservoir of infection to the lower respiratory tract, and a source of the contamination of the respiratory circuits, and it is resistance to the effect of the antibiotic.

Rello J etal, 2010 Crit Care Med 38: 1135-1140.
The silver coated tubes have an effect in reduction of the formation of the biofilm, as after 16h of intubation there is no formation of the biofilm in the coated tubes, while the biofilm is formed on a non-coated tubes just after 8h.

Berra L etal, 2004 Anesthesiology 100: 1446-1456
The use of the silver coated tubes has no additional adverse effects on the patients and shows a decrease in the incidence of VAP (in both early onset and late onset pneumonia), comparing with noncoated tubes, that decrease is around 50%.

Kollef MH, 2008 the NASCENT randomized trial. JAMA: the journal of the American Medical Association 300: 805-813
Reduced burden of bacterial airway colonization with a novel silver-coated endotracheal tube in a randomized multiple-center feasibility study.*
Rello, Jordi; MD, PhD; Kollef, Marin; Diaz, Emili; MD, PhD; Sandiumenge, Albert; del Castillo, Yolanda; Corbella, Xavier; Zachskorn, Regina

DOI: 10.1097/01.CCM.0000242154.49682.B0
Recruitment and randomization
(N = 155)
Spain (n = 99)
USA (n = 56)

Allocation
RIC device (n = 78)
(n = 3) No intubation
(n = 3)

Control device (n = 77)

Intubation
Safety analysis (n = 75)
(n = 14) Intubation < 24 h
(n = 14)

Safety analysis (n = 74)

Intubation ≥ 24 h
Full analysis set (n = 61)
(n = 24) Protocol violation
(n = 30)

Full analysis set (n = 60)

No protocol violations
Per-protocol set (n = 37)

Per-protocol set (n = 30)
### Table 2. Colonization rates on endotracheal tube in the full analysis set

<table>
<thead>
<tr>
<th>Threshold</th>
<th>RIC Group</th>
<th>Control Group</th>
<th>Relative Risk Reduction (95% CI)</th>
<th>p Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients with colonization/</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest</td>
<td>23/61 (38)</td>
<td>33/60 (55)</td>
<td>0.31 (-0.008 to 0.610)</td>
<td>.07</td>
</tr>
<tr>
<td>Intermediate</td>
<td>20/61 (33)</td>
<td>28/60 (47)</td>
<td>0.30 (-0.074 to 0.646)</td>
<td>.14</td>
</tr>
<tr>
<td>Highest</td>
<td>18/61 (30)</td>
<td>25/60 (42)</td>
<td>0.29 (-0.115 to 0.677)</td>
<td>.19</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Threshold</th>
<th>RIC Group</th>
<th>Control Group</th>
<th>Relative Risk Reduction (95% CI)</th>
<th>p Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of days with colonization/</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest</td>
<td>54/242 (22)</td>
<td>86/226 (38)</td>
<td>0.41 (0.195 to 0.625)</td>
<td>.04</td>
</tr>
<tr>
<td>Intermediate</td>
<td>50/242 (21)</td>
<td>76/226 (34)</td>
<td>0.39 (0.146 to 0.620)</td>
<td>.09</td>
</tr>
<tr>
<td>Highest</td>
<td>45/242 (19)</td>
<td>71/226 (31)</td>
<td>0.41 (0.159 to 0.653)</td>
<td>.14</td>
</tr>
</tbody>
</table>

RIC, respiratory infection control; 95% CI, 95% confidence interval; lowest threshold, ++, ++++, or ≥10^4 colony-forming units (cfu)/mL; intermediate threshold, ++, ++++, or ≥10^5 cfu/mL; highest threshold, ++, ++++, or ≥10^6 cfu/mL.

<sup>a</sup>p value determined by Fisher’s exact test for rates by patients and Wilcoxon’s test for rates by days.
Silver-Coated Endotracheal Tubes and Incidence of Ventilator-Associated Pneumonia
The NASCENT Randomized Trial

Marin H. Kollef, MD
Bekele Afessa, MD
Antonio Anzueto, MD
Christopher Veremakis, MD
Kim M. Kerr, MD
Benjamin D. Margolis, MD
Donald E. Craven, MD
Pamela R. Roberts, MD
Alejandro C. Arrolgiga, MD
Rolf D. Habmayr, MD
Marcos L. Restrepo, MD
William R. Auger, MD
Regina Schinner, Dipl-Stat
for the NASCENT Investigation Group

Context Ventilator-associated pneumonia (VAP) causes substantial morbidity. A silver-coated endotracheal tube has been designed to reduce VAP incidence by preventing bacterial colonization and biofilm formation.

Objective To determine whether a silver-coated endotracheal tube would reduce the incidence of microbiologically confirmed VAP.

Design, Setting, and Participants Prospective, randomized, single-blind, controlled study conducted in 54 centers in North America. A total of 9417 adult patients (≥18 years) were screened between 2002 and 2006. A total of 2003 patients expected to require mechanical ventilation for 24 hours or longer were randomized.

Intervention Patients were assigned to undergo intubation with 1 of 2 high-volume, low-pressure endotracheal tubes, similar except for a silver coating on the experimental tube.

Main Outcome Measures Primary outcome was VAP incidence based on quantitative bronchoalveolar lavage fluid culture with 10^6 colony-forming units/mL or greater in patients intubated for 24 hours or longer. Other outcomes were VAP incidence in all intubated patients, time to VAP onset, length of intubation and duration of intensive care unit and hospital stay, mortality, and adverse events.

Results Among patients intubated for 24 hours or longer, rates of microbiologically confirmed VAP were 4.8% (37/766 patients; 95% confidence interval [CI], 3.4%-6.6%) in the group receiving the silver-coated tube and 7.5% (56/743; 95% CI, 5.7%-9.7%) (P = .03) in the group receiving the uncoated tube (all intubated patients, 3.8% [37/968; 95% CI, 2.7%-5.2%] and 5.8% [56/964; 95% CI, 4.4%-7.5%] [P = .04]), with a relative risk reduction of 35.9% (95% CI, 3.6%-69.0%; all intubated patients, 34.2% [95% CI, 1.2%-67.9%]). The silver-coated endotracheal tube was associated with delayed occurrence of VAP (P = .005). No statistically significant between-group differences were observed in durations of intubation, intensive care unit stay, and hospital stay; mortality; and frequency and severity of adverse events.

Conclusion Patients receiving a silver-coated endotracheal tube had a statistically significant reduction in the incidence of VAP and delayed time to VAP occurrence compared with those receiving a similar, uncoated tube.
Figure 1. Flow of Participants Through the Trial

9417 Patients screened

7414 Excluded (no informed consent or unlikely to be intubated ≥24 h)

2009 Randomized

998 Randomized to receive silver-coated endotracheal tube
968 Received coated tube as assigned

0 Lost to follow-up

766 Included in primary efficacy analysis
232 Excluded
  30 Not intubated
  202 Intubated < 24 h
968 Included in safety analysis
30 Excluded (not intubated)

1005 Randomized to receive uncoated endotracheal tube
964 Received uncoated tube as assigned

0 Lost to follow-up

743 Included in primary efficacy analysis
262 Excluded
  41 Not intubated
  221 Intubated < 24 h
964 Included in safety analysis
41 Excluded (not intubated)
<table>
<thead>
<tr>
<th>Table 2. Incidence of Microbiologically Confirmed Ventilator-Associated Pneumonia (VAP)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evaluable Patients With VAP, No./Total (%) [95% CI]</strong></td>
</tr>
<tr>
<td><strong>RR Reduction, % [95% CI]</strong></td>
</tr>
<tr>
<td><strong>Silver-Coated Tube</strong></td>
</tr>
<tr>
<td>VAP at any time Intubated ≥24 h</td>
</tr>
<tr>
<td>All intubated</td>
</tr>
<tr>
<td>VAP within 10 d of intubation Intubated ≥24 h</td>
</tr>
<tr>
<td>All intubated</td>
</tr>
<tr>
<td><strong>Microbiology</strong></td>
</tr>
<tr>
<td><strong>Staphylococcus aureus</strong></td>
</tr>
<tr>
<td><strong>Methicillin-resistant S aureus</strong></td>
</tr>
<tr>
<td><strong>Pseudomonas aeruginosa</strong></td>
</tr>
<tr>
<td><strong>Enterobacteriaceae</strong></td>
</tr>
<tr>
<td><strong>Yeast</strong></td>
</tr>
<tr>
<td><strong>Streptococcus species</strong></td>
</tr>
<tr>
<td><strong>Haemophilus influenzae</strong></td>
</tr>
<tr>
<td><strong>Acinetobacter baumannii</strong></td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.

a Patients with at least 10⁶ colony-forming units/mL in bronchoalveolar lavage fluid.

b Twenty patients had polymicrobial infections. In the group receiving the silver-coated endotracheal tube, 6 patients had 2 microorganisms and 1 patient had 3. In the group receiving the uncoated tube, 11 patients had 2 microorganisms and 2 patients had 3.

c Other microorganisms in the group receiving the silver-coated endotracheal tube were normal flora in 14 and Staphylo...
Subglottic secretion drainage-SSD
The presence of secretion in the subglottic space is a source of aspiration in the intubated patients. The subglottic secretion leakage occurs between the cuff and the trachea through the longitudinal folds towards the lungs or through the micro aspiration of the subglottic secretions.

Subglottic secretion drainage for the prevention of ventilator-associated pneumonia: A systematic review and meta-analysis *.
Muscedere, John; MD, FRCPC; Rewa, Oleksa; McKechnie, Kyle; Jiang, Xuran; Laporta, Denny; MD, FRCPC; Heyland, Daren; MD, FRCPC

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Population Size</th>
<th>Inclusion Criteria</th>
<th>Clinical Susceptibility to VP*</th>
<th>VP*</th>
<th>Intervention*</th>
<th>Score a</th>
<th>MD b</th>
<th>Control b</th>
<th>Rate of VP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mathl, 1995</td>
<td>140</td>
<td>Expected duration of MV &gt;3 days</td>
<td>Chest radiograph</td>
<td>RAL</td>
<td>None specified</td>
<td>0</td>
<td>a. 9/1000 a. 17/5/1000 a. &lt;0.001</td>
<td>b. W/O b. 31/75 b. NR</td>
<td></td>
</tr>
<tr>
<td>Folioo, 1995</td>
<td>151</td>
<td>Expected duration of MV &gt;3 days</td>
<td>Chest radiograph plus temp &gt;38.5°C, WBC &gt;12 or &lt;4, purulent secretions</td>
<td>RAL or PFB</td>
<td>None specified</td>
<td>9</td>
<td>a. 9/1000 a. 28/6/1000 a. NR</td>
<td>b. 14/75 b. 27/77 b. NR</td>
<td></td>
</tr>
<tr>
<td>Fotis, 1998</td>
<td>24</td>
<td>Expected duration of MV &gt;3 days</td>
<td>Chest radiograph, temp &gt;38.5°C, WBC &gt;12 or &lt;3, purulent secretions</td>
<td>ETA or RAL</td>
<td>None specified</td>
<td>7</td>
<td>a. 31/1000 a. 41/3/1000 a. NR</td>
<td>b. 3/10 b. 9/14 b. NR</td>
<td></td>
</tr>
<tr>
<td>Saffad, 1999</td>
<td>241</td>
<td>Need for MV after cardiac surgery</td>
<td>Chest radiograph plus pulmonary abscess or histology or positive blood or pleural cultures or 2 of 3 of the following: fever, leukocytosis, purulent secretions</td>
<td>ETA or no more</td>
<td>None specified</td>
<td>11</td>
<td>a. 24/5/1000 a. 41/2/1000 a. NR</td>
<td>b. 8/100 b. 13/162 b. 0.16</td>
<td></td>
</tr>
<tr>
<td>Nix, 2000</td>
<td>68</td>
<td>Expected duration of MV &gt;12 hrs</td>
<td>Chest radiograph (temp &gt;38.5°C, WBC &gt;12 or &lt;4 or purulent secretions)</td>
<td>RAL or PFB</td>
<td>None specified</td>
<td>9</td>
<td>a. 31/1000 a. 31/1000 a. NR</td>
<td>b. 4/25 b. 8/33 b. NR</td>
<td></td>
</tr>
<tr>
<td>Saunder, 2002</td>
<td>150</td>
<td>Expected duration of MV &gt;12 hrs</td>
<td>Chest radiograph or evidence for chest pain, histology, positive blood culture, a positive pleural fluid culture, or any of the 2 following symptoms (age or 19, purulent tracheal aspirate &gt;25 WBC per field)</td>
<td>ETA</td>
<td>None specified</td>
<td>9</td>
<td>a. 9/2/1000 a. 22/3 a. NR</td>
<td>b. 3/75 b. 12/75 b. 0.03</td>
<td></td>
</tr>
<tr>
<td>Gera, 2006</td>
<td>14</td>
<td>Expected duration of MV &gt;10 days</td>
<td>Chest radiograph, temp &gt;38.5°C or WBC &gt;12, or purulent secretions</td>
<td>PFB or RAL</td>
<td>None specified</td>
<td>9</td>
<td>a. 31/1000 a. 31/1000 a. NR</td>
<td>b. 4/25 b. 8/33 b. NR</td>
<td></td>
</tr>
<tr>
<td>Liu, 2006</td>
<td>46</td>
<td>Age older than 60 yrs, expected MV &gt;40 hrs</td>
<td>Chest radiograph plus 3 of 4: temp &gt;38.5°C or &lt;25.5°C, WBC &gt;10 or &lt;2, &gt;10 WBC high powered field in ETA, or a positive ETA culture</td>
<td>PFB or ETA</td>
<td>None specified</td>
<td>9</td>
<td>a. 31/1000 a. 31/1000 a. NR</td>
<td>b. 4/25 b. 8/33 b. NR</td>
<td></td>
</tr>
<tr>
<td>Laurens, 2007</td>
<td>250</td>
<td>Expected MV &gt;24 hrs</td>
<td>Chest radiograph, purulent secretions, temp &gt;38°C or &lt;30.5°C, WBC &gt;10 or &lt;4</td>
<td>Quantitative ETA</td>
<td>None specified</td>
<td>12</td>
<td>a. 17/3/1000 a. 18/8/1000 a. 0.001</td>
<td>b. 17/3/1000 b. 31/310 b. 0.005</td>
<td></td>
</tr>
<tr>
<td>Bosni, 2008</td>
<td>71</td>
<td>Major heart surgery</td>
<td>Chest radiograph plus 2 of temp &gt;38.5°C, WBC &gt;12, purulent secretions, reduction in PFO &gt;15% or CPRS &gt;5</td>
<td>Quantitative ETA or PFB</td>
<td>None specified</td>
<td>12</td>
<td>a. 17/3/1000 a. 27/3 a. 7</td>
<td>b. 12/30 b. 19/311 b. 0.18</td>
<td></td>
</tr>
<tr>
<td>Fang, 2009</td>
<td>18</td>
<td>MV &gt;48 hrs</td>
<td>Chest radiograph and 2 of temp &gt;38°C, WBC &gt;12, purulent secretions</td>
<td>Quantitative ETA or PFB</td>
<td>None specified</td>
<td>12</td>
<td>a. 17/3/1000 a. 27/3 a. 7</td>
<td>b. 12/30 b. 19/311 b. 0.18</td>
<td></td>
</tr>
<tr>
<td>Author, Year</td>
<td>Population</td>
<td>Inclusion Criteria</td>
<td>Clinical Suspicion of VAP ( ^a )</td>
<td>VAP ( ^b )</td>
<td>Co-interventions ( ^c )</td>
<td>Score ( ^d )</td>
<td>SSD</td>
<td>Control</td>
<td>( p )</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
<td>-------------------</td>
<td>---------------------------------</td>
<td>----------------</td>
<td>------------------</td>
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<td>------</td>
<td>--------</td>
<td>-----</td>
</tr>
<tr>
<td>Zheng, 2009</td>
<td>61</td>
<td>MV &gt;48 hrs</td>
<td>Chest radiograph + temp &gt;38°C or WBC &gt;12 or &lt;4.0 or altered mental status + 2 of purulent sputum, cough, abnormal physical examination, or worsening gas exchange</td>
<td>No micro</td>
<td>None specified</td>
<td>7</td>
<td>a. NA/1000</td>
<td>a. NA/1000</td>
<td>a. NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>b. 9/30</td>
<td>b. 16/31</td>
<td>b. &lt;.05</td>
</tr>
<tr>
<td>Lacherade, 2010</td>
<td>333</td>
<td>Expected MV &gt;48 hrs</td>
<td>Chest radiograph and 2 of: temp &gt;38.5°C or &lt;36°C, WBC &gt;10 or &lt;4 and purulent tracheal secretions</td>
<td>PSB or BAL</td>
<td>None specified</td>
<td>12</td>
<td>a. 17/1000</td>
<td>a. 34/1000</td>
<td>a. .002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>b. 25 cases</td>
<td>b. 42 cases</td>
<td>b. .02</td>
</tr>
</tbody>
</table>

*B. M., broncho-alveolar lavage; CPS, clinical pulmonary infection score; ETA, endotracheal aspirate; MV, mechanical ventilation; NA, not applicable; No micro, microbiological; NR, not reported; NS, not significant; PF, PaO\textsubscript{2}/FiO\textsubscript{2} ratio; PSB, protected specimen brush; SSD, subglottic secretion drainage; Temp, temperature; VAP, ventilator-associated pneumonia; WBC, white blood cell count.

*Chest radiograph. Requirement for new or persistent pulmonary infiltrate on a chest radiograph for suspicion of VAP. WBC per 10\textsuperscript{9} ml.; \(^a\) microbiological criteria for VAP. This refers to the minimum microbiological criteria for the diagnosis of VAP. BAL or PSB = quantitative invasive cultures. No micro = microbiological culture not required for VAP diagnosis; \(^c\) co-interventions. When described, this refers to imbalances between SSD group and control in measures that may have an effect on VAP; \(^d\) methodological score. Refer to SDC Table 1 (see Supplemental Digital Content 1, http://links.lww.com/CCM/A247) for components.
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSD</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Mahul 1992</td>
<td>9</td>
<td>70</td>
<td>21</td>
<td>75</td>
</tr>
<tr>
<td>Valles 1995</td>
<td>14</td>
<td>76</td>
<td>25</td>
<td>77</td>
</tr>
<tr>
<td>Metz 1998</td>
<td>5</td>
<td>10</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Kollef 1999</td>
<td>8</td>
<td>160</td>
<td>15</td>
<td>183</td>
</tr>
<tr>
<td>Bo 2000</td>
<td>8</td>
<td>35</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td>Smulders 2002</td>
<td>3</td>
<td>75</td>
<td>12</td>
<td>75</td>
</tr>
<tr>
<td>Girou 2004</td>
<td>5</td>
<td>8</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Liu 2006</td>
<td>14</td>
<td>41</td>
<td>30</td>
<td>45</td>
</tr>
<tr>
<td>Lorente 2007</td>
<td>11</td>
<td>140</td>
<td>31</td>
<td>140</td>
</tr>
<tr>
<td>Yang 2008</td>
<td>12</td>
<td>48</td>
<td>20</td>
<td>43</td>
</tr>
<tr>
<td>Bouza 2008</td>
<td>12</td>
<td>331</td>
<td>19</td>
<td>359</td>
</tr>
<tr>
<td>Zheng 2008</td>
<td>9</td>
<td>30</td>
<td>16</td>
<td>31</td>
</tr>
<tr>
<td>Lacherade 2010</td>
<td>25</td>
<td>169</td>
<td>42</td>
<td>164</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>1193</td>
<td>1249</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total events**
- SSD: 135
- Control: 262

**Heterogeneity:** $\tau^2 = 0.00$; $\chi^2 = 7.78$, df = 12 ($P = 0.80$); $I^2 = 0\%$

**Test for overall effect:** $Z = 6.57$ ($P < 0.000001$)
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>SSD Events</th>
<th>SSD Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouza 2008</td>
<td>12</td>
<td>331</td>
<td>19</td>
<td>359</td>
<td>18.4%</td>
<td>0.69 [0.34, 1.39]</td>
<td></td>
</tr>
<tr>
<td>Kollef 1999</td>
<td>8</td>
<td>160</td>
<td>15</td>
<td>183</td>
<td>13.3%</td>
<td>0.61 [0.27, 1.40]</td>
<td></td>
</tr>
<tr>
<td>Lacherade 2010</td>
<td>25</td>
<td>169</td>
<td>42</td>
<td>164</td>
<td>46.3%</td>
<td>0.58 [0.37, 0.90]</td>
<td></td>
</tr>
<tr>
<td>Lorente 2007</td>
<td>11</td>
<td>140</td>
<td>31</td>
<td>140</td>
<td>22.0%</td>
<td>0.35 [0.19, 0.68]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>56</strong></td>
<td><strong>800</strong></td>
<td><strong>107</strong></td>
<td><strong>846</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.54 [0.40, 0.73]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 2.23, df = 3 (P = 0.53); I² = 0%

Test for overall effect: Z = 3.99 (P < 0.0001)
Prevention of Ventilator-Associated Pneumonia and Ventilator-Associated Conditions: A Randomized Controlled Trial With Subglottic Secretion Suctioning*

Damasis, Pierre MD, PhD 1; Fripiat, Frederic MD, PhD 2; Ancion, Arnaud MD 3; Canivet, Jean-Luc MD, PhD 1; Lambermont, Bernard MD, PhD 2; Layios, Nathalie MD 1; Massioni, Paul MD, PhD 1; Morimont, Philippe MD, PhD 2; Nys, Monique PhD 1; Piret, Sonia MD 1; Lancellotti, Patrizio MD, PhD 2; Wiesen, Patricia MD 1; D’orio, Vincent MD, PhD 2; Samalea, Nicolas 1; Ledoux, Didier MD, PhD 1

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3Department of Emergency Medicine, University Hospital of Liege, Liège, Belgium.

* See also p. 227.
This work was performed at University Hospital of Liege, Liège, Belgium.
Teleflex furnished the endotracheal tubes with subglottic secretion suctioning necessary for the whole study.
The authors have disclosed that they do not have any potential conflicts of interest.
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Abstract

Objectives: Ventilator-associated pneumonia diagnosis remains a debatable topic. New definitions of ventilator-associated conditions involving worsening oxygenation have been recently proposed to make surveillance of events possibly linked to ventilator-associated pneumonia as objective as possible. The objective of the study was to confirm the effect of subglottic secretion suctioning on ventilator-associated pneumonia prevalence and to assess its concomitant impact on ventilator-associated conditions and antibiotic use.

Design: Randomized controlled clinical trial conducted in five ICUs of the same hospital.
Oral chlorhexidine

- there are over 700 bacterial species identified in the oral cavity, with more than 400 are present in periodontal pocket.
- Absence of adequate salivary flow in intubated patients in ICU contributes with the development of oropharyngeal colonization and by molecular analysis of the oral and respiratory bacteria in VAP patients, it is shown that 88% of the cases of VAP had an overlap of pathogens in the lung and the oral cavity.

Bahrani et al., 2007 J Clin Microbiol 45: 1588-1593.
Paster bj, 2006 Periodontol 2000 42: 80-87
Oral hygiene care for critically ill patients to prevent ventilator-associated pneumonia

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Oral decontamination for prevention of pneumonia in mechanically ventilated adults: systematic review and meta-analysis

Ee Yuen Chan, nurse educator,1 Annie Ruest, infectious diseases consultant,2 Maureen O Meade, associate professor,2 Deborah J Cook, professor2

ABSTRACT
Objective To evaluate the effect of oral decontamination on the incidence of ventilator associated pneumonia and mortality in mechanically ventilated adults.

Design Systematic review and meta-analysis.

Data sources Medline, Embase, CINAHL, the Cochrane Library, trials registers, reference lists, conference proceedings, and investigators in the specialty.

Review methods Two independent reviewers screened studies for inclusion, assessed trial quality, and extracted data. Eligible trials were randomised controlled trials enrolling mechanically ventilated adults that compared the effects of daily oral application of antibiotics or antisepsics with no prophylaxis.

Results Eleven trials totalling 3242 patients met the inclusion criteria. Among four trials with 1098 patients, oral application of antibiotics did not significantly reduce the incidence of ventilator associated pneumonia (relative risk 0.69, 95% confidence interval 0.41 to 1.18). In seven trials with 2144 patients, however, oral application of antisepsics significantly reduced the incidence of ventilator associated pneumonia (0.55, 0.39 to 0.81). When the results of the 11 trials were pooled, rates of ventilator associated pneumonia were lower among patients receiving either method of oral decontamination (0.43, 0.45 to 0.65). Mortality was not influenced by prophylaxis with either antibiotics (0.94, 0.73 to 1.22) or antisepsics (0.96, 0.69 to 1.33) nor was duration of mechanical ventilation or stay in the intensive care unit.

Conclusions Oral decontamination of mechanically ventilated adults using a decontaminant is associated with a lower risk of ventilator associated pneumonia. Neither antibiotic nor antibiotic oral decontamination reduced mortality or duration of mechanical ventilation or stay in the intensive care unit.

INTRODUCTION
Ventilator associated pneumonia remains a leading cause of morbidity and mortality among mechanically ventilated patients, with the incidence ranging from 0% to 27% and a crude mortality that may exceed 50%. Aspiration of bacteria from the upper digestive tract is the main source of bacterial load. Antimicrobial prophylaxis is a promising strategy to prevent ventilator associated pneumonia. Several studies have shown that selective decontamination of the digestive tract, involving administration of non-absorbable antibiotics by mouth and through a nasogastric tube, and oral decontamination, which is limited to topical oral application of antibiotics or antisepsics.

Previous meta-analyses of selective decontamination of the digestive tract found a significant reduction in rates of ventilator associated pneumonia among treated patients. The use of this intervention is, however, limited by concerns about the emergence of antibiotic resistant bacteria. Oral decontamination alone therefore may be more attractive because it requires only a fraction of the antibiotics used in selective decontamination of the digestive tract. To date, trials of oral decontamination using antibiotics have generated conflicting results, some suggesting benefit and others showing no benefit.

One alternative to oral decontamination with antibiotics is to use antisepsics, such as chlorhexidine gluconate or povidone iodine. In contrast to antibiotics, antisepsics act rapidly at multiple target sites and accordingly may be less prone to induce drug resistance. Observational studies suggest that antisepsic oral decontamination can reduce ventilator associated pneumonia, but randomised controlled trials are not convincing. Recently a meta-analysis of four trials on chlorhexidine failed to show a significant reduction in rates of ventilator associated pneumonia. Two subsequent randomised controlled trials, however, suggested benefit from this approach.

Current guidelines from the Centers for Disease Control and Prevention recommend topical chlorhexidine 0.12% during the perioperative period for adults undergoing cardiac surgery (grade II evidence). The routine use of antibiotic or antisepic oral decontamination for the prevention of ventilator associated pneumonia, however, remains unresolved. Despite the lack of evidence favouring this preventive intervention, a recent survey across 50 European intensive care units from five countries showed that the use of oral decontamination with chlorhexidine was widespread. Therefore, further research is needed to evaluate the efficacy and safety of oral decontamination using chlorhexidine.
Fig 3 | Forest plot showing effect of oral decontamination prophylaxis compared with no prophylaxis on overall mortality
Preintubation Application of Oral Chlorhexidine Does Not Provide Additional Benefit in Prevention of Early-Onset Ventilator-Associated Pneumonia

Cindy L. Munro, PhD, RN, ANP; Mary Jo Grap, PhD, RN; Curtis N. Sessler, MD, FCCP; Ronald K. Elswick Jr, PhD; Devanand Mangar, MD; Rachel Karlnoski-Everall, PhD; and Paula Cairns, BSN, RN

BACKGROUND: Daily application of oral chlorhexidine gluconate (CHX) following intubation to reduce the risk of ventilator-associated pneumonia (VAP) is now the standard of care in many ICUs. This randomized clinical trial evaluated the benefit of adding a preintubation CHX dose to the known benefit of postintubation CHX to reduce the risk of early-onset VAP. A secondary aim was to test the effect of a preintubation oral application of CHX on early endotracheal tube (ETT) colonization.

METHODS: Subjects (N = 314) were recruited from two teaching hospitals and were randomly assigned to oral application of 5 mL CHX 0.12% solution before intubation (intervention group, n = 157), or to a control group (n = 157) who received no CHX before intubation. All subjects received CHX bid after intubation. Groups were compared using a repeated-measures model with Clinical Pulmonary Infection Score (CPIS) as the response variable. In a planned subset of subjects, ETTs were cultured at extubation.

RESULTS: Application of a preintubation dose of CHX did not provide benefit over the intervention period beyond that afforded by daily oral CHX following intubation. ETT colonization at extubation was <20% in both groups (no statistically significant difference). Mean CPIS remained below 6 (VAP threshold score) in both groups.

CONCLUSIONS: Although it is feasible to deliver CHX prior to intubation (including emergent or urgent intubation), the results suggest that preintubation CHX may be inconsequential when the ventilator bundle, including daily oral CHX, is in place. During the preintubation period, providers should focus their attention on other critical activities.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT00893763; URL: www.clinicaltrials.gov

CHEST 2015; 147(2):328-334
Key take home points-

the oral hygiene is effective in decreasing the incidence of early VAP but not the late onset VAP, while comparing the use of chlorhexidine and the toothbrush in the oral care to the regular oral care has shown no statistical difference prevention of VAP.
the use of the probiotic in prevention of VAP is still under analysis, as the results are controversial, and statistics did not show a clear results about different parameters such as the incidence, the days in the hospital, the use of the antibiotics.

Use of NIPPV is one important way to either avoid the need for intubation or terminate mechanical ventilation as early as possible by extubation to NIPPV.
SSD has proved the efficacy in decreasing the early VAP incidence, days on ventilations and use of antibiotics. Both continuous and intermittent suction have proved their efficacy in decreasing the VAP incidence
**Table 18: Preventive strategies for VAP**

The following strategies are recommended in prevention of VAP:

- Oral cavity decontamination with 2% chlorhexidine (1A)\(^{[412-415]}\)
- Hand hygiene preferably using alcohol-based hand rubs or soap and water (1A)\(^{[416]}\)
- Use of sedation and weaning protocols (1A)\(^{[419,420]}\)
- Use of NIV to avoid intubation, where feasible (1A)\(^{[264,421]}\)
- Subglottic secretion drainage (2A)\(^{[422,423]}\)
- Heat moisture exchangers in place of heated humidifiers (2A)\(^{[424-428]}\)
- Closed suction systems (2A)\(^{[429-431]}\)
- Use of orotracheal intubation as opposed to nasotracheal intubation (2A)\(^{[432,433]}\)
- Proper and timely disposal of condensates (3A)\(^{[434,435]}\)
- Maintaining tracheal cuff pressures <25 cm H\(_2\)O (2A)\(^{[436]}\)
- Wipe stethoscopes with alcohol rubs (2A)\(^{[437]}\)
- Regular postural mobilization to prevent stasis of secretions (2A)
- Use of only normal saline for suctioning (3A)
- Proper sterilization of nebulizer and other chambers (2A)
- Head end elevation to 30°–45° (2A)

The following strategies are not recommended in prevention of VAP:

- Antibiotics for prevention of VAP (2A)
- Selective digestive tract decontamination (2A)\(^{[438]}\)
- Routine ventilator circuit changes (2A)\(^{[439,440]}\)
- Early tracheostomy (2A)
Conclusion-

VAP is associated with significant morbidity and mortality in critically ill mechanically ventilated patients and has deleterious economic impact on the health care system. The most important step in the approach to VAP is therefore its prevention.
There are many preventative modalities which have been demonstrated to be effective. These include the utilization of NIPPV, oral hygiene measures, modification of ETTs (subglottic secretion drainage or silver-coated) and positioning.
The management of VAP relies upon its prompt diagnosis and involves clinical signs, laboratory investigations, chest radiography, and microbiological data from lung cultures. Unfortunately, a reference standard for VAP remains elusive.
There has been significant evolution for the surveillance of VAP. These terms, VAC and iVACs, do not replace the traditional diagnosis of VAP but capture a broader variety of pathologies including pneumonia that may impair gas exchange in mechanically ventilated patients.