When to start treatment: VAT (ventilator-associated tracheobronchitis) or VAP (pneumonia)?

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Conflict of interest

NONE RELATED TO THIS PRESENTATION
Overview of the presentation
Ventilator-Associated Tracheobronchitis/VAT

1. What is VAT
   1. Definition,
   2. Pathophysiology
   3. Diagnosis

2. Why treat VAT
   1. Clinical consequences
   2. Mortality of untreated VAT

3. Current therapeutic approaches

4. Current challenges and considerations
Biofilm lining the foreign body (ET)

10^7 bacteria/mL of oral secretions

Purulent secretions

(Multidrug-resistant) Bacteria

Planktonic? Biofilm?

Aerosolized antibiotics

Systemic antibiotics

VAP

Purulent secretions in alveoli

• >10^4 bacteria/mL

The multifactorial process that leads to VAT and VAP

• Subglottic secretions
• Disturbed mucociliary clearance
• Damaged mucosa
• Bacterial biofilm

Adapted from Palmer LB
Curr Opin Pulm Med
2015, 21:239–249
A model of descending infection for VAT proposed by Craven DE et al

Critical Care 2014, 18:627

Figure 1 Pathogenesis and routine antibiotic therapy for urinary tract infections versus ventilator-associated pneumonia and tracheobronchitis. (A) The pathogenesis of ‘ascending’ urinary tract infection due to cystitis or pyelonephritis or both, which are currently treated with antibiotics as a ‘standard of care’. (B) The pathogenesis of ‘descending’, primarily ‘one-way’ respiratory tract infection manifests as ventilator-associated tracheobronchitis or pneumonia, for which we would recommend treatment with intravenous or aerosolized antibiotic therapy or both. Reprinted with permission from Lippincott Williams & Wilkins [12].
Rationale for treating VAT and/or VAP

- VAT and VAP are ‘descending, one-way infections
- Impaired tracheobronchial clearance
- Bacteria-loaded secretions constantly fight the gravity
- Reflux of ventilator tubing concentrate may also wash bacteria down into the bronchioles and alveoli
- Removal of bacteria is limited to suctioning through the ETT lumen. This procedure is blind, and may dislodge pathogens or biofilm-encased bacteria into the lower airway.
- Age, comorbidities, concurrent medications, and nutrition are representative risk factors that may further increase total bacterial lung burden
General concepts
...debated

- Ventilator-associated tracheobronchitis (VAT) is believed to be an intermediate stage between colonization of the lower respiratory tract and VAP.

- However, more recent data suggests that VAT may be a separate entity that may contribute to increased length of ICU stay and longer duration of MV.

Craven DE, Chest. 2009;1352:521-528
Dallas J, Chest. 2011;139(3):513-518
Ventilator-Associated Tracheobronchitis in a Mixed Surgical and Medical ICU Population

Is VAT really a precursor of VAP?

- Incidence of VAT was 1.4%, and the overall incidence of VAP was 4.0%
- Rate of 3.2 cases of VAT per 1,000 mechanical ventilator days and 9.4 cases of VAP per 1,000 mechanical ventilator days
- The mean onset of VAT was 8.3 ± 4.8 days (median 7.5 days; interquartile range, 5.25-10.0 days), and the mean onset of VAP was 6.7 ± 4.1 days (P = .052) (median 5.0 days; interquartile range, 4.0-8.0 days).

Dallas J, Chest. 2011;139(3):513-518
Are VAT and VAP really a continuum? Comparison of VAP/VAT gene expression "signatures" using genomewide oligonucleotide microarrays

Translational study, 8 patients

Gene expression profiles in the pre-infection period identified a significant depression of the complement system pathway in the VAP group compared to the VAT group, affecting the classical pathway along with the final common pathway:

- red, upregulated; blue, downregulated

- This suggests that intubation by itself is associated with different degrees of immunocompromise
- Early development of immunocompromise in the post-intubation period suggests that not all episodes of VAP are preventable

I. Martin-Loeches et al Med Intensiva 2012
Incidence of VAT in the literature

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence %</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nseir/2002</td>
<td>10</td>
<td>Mixed</td>
</tr>
<tr>
<td>Hortal/2010</td>
<td>10</td>
<td>CVS</td>
</tr>
<tr>
<td>Ninan/2010</td>
<td>16</td>
<td>Respiratory stepdown unit</td>
</tr>
<tr>
<td>Dallas/2011</td>
<td>1.4</td>
<td>Mixed</td>
</tr>
<tr>
<td>Craven/2013</td>
<td>11</td>
<td>Mixed</td>
</tr>
<tr>
<td>Karvouniaris/2014</td>
<td>18</td>
<td>Mixed</td>
</tr>
</tbody>
</table>
Frequency, prevention, outcome and treatment of ventilator-associated tracheobronchitis: Systematic review and meta-analysis

- 10 randomized controlled trials (RCTs), 5 cohorts, and 2 case control studies involving 7056 patients
- VAT affected 386 (11.5%) out of 3,362 patients (5 reports)

Agrafiotis M et al, Respiratory Medicine (2010) 104, 325e336
Incidence may vary according to the patient population

• 236 patients observed; 42 patients (18%) presented with VAT
• Patients with a neurosurgical admission presented with VAT significantly more often than did other ICU patients (28.5% vs 14.1%; $P = .02$).

Karvouniaris M et al, Infect Control Hosp Epidemiol 2013;34(8):800-808
# Rate of progression of VAT to VAP

<table>
<thead>
<tr>
<th>Study</th>
<th>Rate %</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nseir 2002</td>
<td>9</td>
<td>Mixed</td>
</tr>
<tr>
<td>Nseir 2008</td>
<td>34</td>
<td>Mixed</td>
</tr>
<tr>
<td>Dallas 2011</td>
<td>32.1</td>
<td>Mixed</td>
</tr>
<tr>
<td>Craven 2013</td>
<td>29</td>
<td>Mixed</td>
</tr>
<tr>
<td>Karvouniaris 2014</td>
<td>16.7</td>
<td>Mixed</td>
</tr>
</tbody>
</table>
Diagnostic criteria for ventilator-associated tracheobronchitis and ventilator-associated pneumonia

They vary significantly among studies!

<table>
<thead>
<tr>
<th>Clinical signs and symptoms</th>
<th>Chest radiograph or CT scan</th>
<th>Microbiology lung culture methods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VAT</strong></td>
<td>Temperature &gt;38° C WBC &gt;12,000/µl or &lt;4000/µl purulent sputum&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No new lung infiltrate</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
</tbody>
</table>

| **VAP**                    | Temperature >38° C WBC >12,000/µl or <4000/µl purulent sputum<sup>a</sup> | New and persistent lung infiltrate | B-BAL or N-BAL ≥ 10<sup>4</sup> cfu/ml | SQ-ETA: ≥ +++   |
|                            | OR                          |                                  | B-PSB ≥ 10<sup>3</sup> cfu/ml | OR             |
|                            | OR                          |                                  | Q-ETA ≥ 10<sup>5</sup> cfu/ml |                |

<sup>a</sup> B-BAL: bronchoalveolar lavage; N-BAL: nasotracheal aspirate; B-PSB: bronchial aspirate; Q-ETA: quantitative endotracheal aspirate; VAT: ventilator-associated tracheobronchitis; VAP: ventilator-associated pneumonia.
DIAGNOSIS OF VAT: a difficult task

- Diagnosis of VAT and/or VAP requires similar clinical signs and microbiologic criteria
- VAP requires evidence of a new and persistent infiltrate on chest X-ray or computed tomography scan
- Portable chest X-rays often lack sensitivity and specificity, making it difficult for clinicians to differentiate VAP from noninfectious causes, such as congestive heart failure, pulmonary emboli or neoplastic disease

Wunderink RG, Chest 2000; 117 (4 Suppl 2):191S–194S
A novel approach to VAP definition

- The Centers for Disease Control’s (CDC) National Health Safety Network has proposed new surveillance definitions for possible and probable ventilator-associated pneumonia.
- The new definitions rely on changes in oxygenation, clinical signs, and microbiologic criteria.
- Chest radiograph criteria were not included for the diagnosis of “probable or possible VAP.”
- They focus on ventilator-associated infections and would not discriminate between ventilator-associated tracheobronchitis and pneumonia.

http://www.cdc.gov/nhsn
Incidence and diagnosis of ventilator-associated tracheobronchitis in the intensive care unit: an international online survey

- 288 ICUs from 16 countries answered the survey: 51% from the Latin American (LA) group and 49% from Spain, Portugal, and France (SPF group)
- The majority of respondents (n = 228; 79.2%) make the diagnosis of VAT on the basis of both clinical and microbiological criteria
- 13.9% reported diagnosis using clinical criteria alone
Techniques used for the diagnosis of ventilator-associated tracheobronchitis

<table>
<thead>
<tr>
<th>Technique</th>
<th>Global</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 288</td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Endotracheal aspirate (ETA)</td>
<td>171 (59.4)</td>
</tr>
<tr>
<td>Bronchoalveolar lavage (BAL)</td>
<td>40 (13.9)</td>
</tr>
<tr>
<td>ETA plus other techniques</td>
<td>35 (12.2)</td>
</tr>
<tr>
<td>Mini-BAL</td>
<td>21 (7.3)</td>
</tr>
<tr>
<td>Protected specimen brush</td>
<td>4 (1.4)</td>
</tr>
<tr>
<td>No response</td>
<td>17 (5.9)</td>
</tr>
</tbody>
</table>

- Endotracheal aspirates were reported to be the most frequently used technique followed by bronchoalveolar lavage (BAL).
- BAL and mini-BAL techniques were more frequently employed by the LA group, whereas multiple sample techniques were more commonly used by the SPF group.
Diagnosis of VAT according to an international survey

Diverse use of laboratory parameters

- More than 50% of physicians requested a computed tomography (CT) scan, 48.3% of them when CXR is inconclusive
- Although the majority of respondents ($n = 276; 95.8\%$) use microbiological findings to guide ATB treatment, more than half ($59.0\%$) do not perform a Gram stain on the respiratory sample
- $22.9\%$ do not routinely request quantitative cultures of respiratory secretions
Diverse methods of microbiologic diagnosis and criteria

- In 16 of the included studies the authors used tracheal aspirates
- Bronchoscopic cultures (bronchoalveolar lavage and protected specimen brush) have additionally been employed in 5 studies
- Cultures were quantitative in 10 studies
- Cutoff point of bacterial concentration for positivity in tracheal aspirates was $10^6$ cfu/ml in 6 studies, $10^5$ in 2 studies, $10^3$ cfu/ml in 1 study and $10^2$ cfu/ml in one study
How feasible and easy is to obtain optimal imaging?

- The diagnosis of a NEW infiltrate on CT scan precludes a baseline examination in suspicion of VAP
- Intrahospital transport can be a life-threatening endeavor
- A recent case–control study identified intrahospital transport (OR 2.9; 95% CI 1.4–5.7) as an independent risk factor for VAP
- Cost effectiveness of CT scan for all VAP suspected patients has not been thoroughly evaluated


Is VAT associated with increased mortality?

Be cautious about comparator arms...

- In two case-control studies excluding patients who eventually developed VAP, the presence, as opposed to the absence of VAT was not associated with higher attributable mortality (OR: 1.02, 95% CI: 0.57-1.81)

- In an observational cohort crude mortality was significantly higher in VAT patients, but this difference disappeared after exclusion of patients who subsequently developed VAP

- In another report by Bouza et al, in which patients who also developed VAP were not excluded, crude mortality of VAT was significantly higher compared to non-colonized patients

Agrafiotis M et al, Respiratory Medicine (2010) 104, 325e336
Ventilator-associated tracheobronchitis attributable mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>VAT</th>
<th>Control</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Nseir 2004</td>
<td>33</td>
<td>81</td>
<td>28</td>
</tr>
<tr>
<td>Nseir 2005</td>
<td>16</td>
<td>55</td>
<td>20</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>136</td>
<td>136</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>49</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.04; Chi² = 1.30, df = 1 (P = 0.25);</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I² = 23%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.06 (P = 0.95)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VAT and patients’ outcomes

Table 2 Impact of ventilator-associated tracheobronchitis on outcome in medical and surgical patients

<table>
<thead>
<tr>
<th></th>
<th>Medical patients (n = 1655)</th>
<th>Surgical patients (n = 234)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 165)</td>
<td>No (n = 1490)</td>
<td></td>
</tr>
<tr>
<td>Duration of MV</td>
<td>26 ± 17 (22)</td>
<td>8 ± 7 (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of ICU stay</td>
<td>33 ± 20 (28)</td>
<td>12 ± 19 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>64 (38)</td>
<td>479 (32)</td>
<td>0.051</td>
</tr>
<tr>
<td></td>
<td>Yes (n = 36)</td>
<td>No (n = 198)</td>
<td></td>
</tr>
<tr>
<td>Duration of MV</td>
<td>32 ± 31 (23)</td>
<td>13 ± 12 (10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of ICU stay</td>
<td>39 ± 31 (31)</td>
<td>18 ± 15 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>20 (55)</td>
<td>112 (56)</td>
<td>&gt;0.999</td>
</tr>
</tbody>
</table>

Data are numbers (%) or mean ± SD (median). MV, mechanical ventilation. Adapted from [3].

Table 3 Impact of ventilator-associated tracheobronchitis on outcome in matched case–control studies

<table>
<thead>
<tr>
<th></th>
<th>COPD patients</th>
<th>Patients without chronic respiratory disease</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 81)</td>
<td>No (n = 81)</td>
<td></td>
</tr>
<tr>
<td>Duration of MV</td>
<td>21 ± 12 (20)</td>
<td>19 ± 15 (12)</td>
<td>0.015</td>
</tr>
<tr>
<td>Length of ICU stay</td>
<td>27 ± 13 (25)</td>
<td>24 ± 20 (18)</td>
<td>0.022</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>33 (40)</td>
<td>28 (34)</td>
<td>0.480</td>
</tr>
<tr>
<td></td>
<td>Yes (n = 55)</td>
<td>No (n = 55)</td>
<td></td>
</tr>
<tr>
<td>Duration of MV</td>
<td>21 ± 16 (17)</td>
<td>13 ± 13 (8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of ICU stay</td>
<td>28 ± 15 (24)</td>
<td>17 ± 16 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU-mortality</td>
<td>16 (29)</td>
<td>20 (36)</td>
<td>0.294</td>
</tr>
</tbody>
</table>

Data are numbers (%) or mean ± SD (median). COPD, chronic obstructive pulmonary disease; MV, mechanical ventilation. Adapted from [32,33].

Eur Respir J 2002; 20:1483–1489
Crit Care 2005; 9:R238–R245
Ventilator-Associated Tracheobronchitis Increases the Length of Intensive Care Unit Stay

The occurrence of VAT was a significant risk factor for increased duration of ICU stay but not of mortality.
Outcomes of patients

Prescribing behaviours about VAT according to an international survey

- Half of physicians reported prescribing broad-spectrum systemic antibiotics for the treatment of VAT

Rodríguez et al. Critical Care 2014, 18:R32
Prescribing behaviours about VAT according to an international survey

- Intravenous (IV) monotherapy (62.5%) is the first choice of ATB treatment for VAT, followed by IV ATB combination (20.8%) and then IV and nebulized ATB.
- The use of nebulized ATB is more frequently reported by the LA group compared with the SPF group.

Rodríguez et al. Critical Care 2014, 18:R32
Prescribing behaviours about VAT according to an international survey

- More than half (66.7%) favored ATB treatment with a duration of between 7 and 10 days.
- Half of the respondents preferred to de-escalate therapy when the results of microbiology tests are available.
- Surprisingly, only 24% indicated a preference for a short course of ATB treatment (<7 days).

Rodríguez et al. Critical Care 2014, 18:R32
Response of VAT to Abx treatment is not always predictable

- Concentrations in the airway may be lower than in the bloodstream.
- The bacteria in this environment may require 10–25 times the minimum inhibitory concentration for bactericidal activity.
- The presence of biofilm may decrease the efficacy of systemic antibiotics due to lack of penetration.

Gil-Perotin S, Crit Care 2012; 16:R93
Mendleman PM, Am Rev Respir Dis 1985; 132:761–765
Untreated VAT progresses to VAP?  
Timely treated VAT prevents VAP?  
Treated VAP eliminates VAT?

- When VAP is present and treated with systemic antibiotics, this more proximal area of infection may persist and lead to a vicious cycle of recurrent infections.

- Alternatively, early treatment of ventilator-associated tracheobronchitis may prevent progression to VAP.
Preventive measures of VAP may not be effective on VAT

Application of SDD as opposed to placebo, standard or no treatment did not reduce VAT frequency

The same stands true for automatic regulation of tracheal cuff pressure, oral cavity decontamination or bacterial filter in the ventilator circuit

Aerds SJ, Chest 1991;100:783-91
Rodriguez-Roldan JM, Crit Care Med 1990;18:1239-42
New therapeutic approaches

- Better understanding of pharmacokinetics of commonly used antibiotics in critically ill patients
  - Colistin (new treatment algorithms)
  - Aminoglycosides
  - β-lactams (continuous infusion, etc)
- An explosion of data with applications of nebulized antibiotics
- New devices to deliver antibiotics locally
Aerosolized antibiotics used in mechanically ventilated patients for respiratory infection

1. Amikacin and Amikacin with proprietary pulmonary drug delivery system (phase 3 study)
2. Amikacin/fosfomycin proprietary preparation (phase 1 completed; delivered with Pari investigational eFlow inline nebulizer)
3. Colistin and Colistin methanesulfonate (prodrug of colistin)
4. Ceftazidime
5. Gentamicin
6. Tobramycin and Tobramycin proprietary preparation (approved for spontaneous breathing cystic fibrosis patients)
7. Sisomycin
8. Vancomycin
Concern #1
Increase in overall antibiotic consumption

1. Diagnostic criteria need to be defined
2. Diagnostic techniques need to be confirmed
3. Imaging requirements should be defined
4. Impact on resistance trends should be investigated
Concern #2
What kind of treatment and for how long?

1. Intravenous
2. Intravenous + nebulized
3. Nebulized only
4. How to evaluate response to treatment?
Other Questions to be answered

1. What are the surrogates of success in this story apart from resolution of fever?

2. What are the concentrations of antibiotics needed to eradicate MDROs in the proximal airway in areas of thick purulent secretion?

3. What are the best delivery devices to achieve the concentrations necessary to treat VAT and VAP?

4. Can inhaled antibiotics reduce or eliminate systemic antibiotic use and/or decrease the emergence of resistant organisms?
Thank you

ESCMID Study Group for Infections in Critically Ill Patients - ESGCIP

Apply for a membership
https://www.escmid.org/research_projects/study_groups/critically_ill_patients/