VAT or just VAP: When and how to treat?

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Universitat Autònoma de Barcelona, Spain
Overview

- Definition and epidemiology
- Pathogenesis
- Diagnosis
- Impact on outcome
- Management
Daily Problem

Does This Patient Have Ventilator-Associated Pneumonia?

Craven et al, Clin Inf Dis 2010;51(S1):S59–S66
Klompas M, JAMA2007; 297:1583-93
Resp Infect in MV Management

Important Milestones

• 1985: BAL: Intracellular Organisms
• 1990: Quantitative cultures
• 1993: ATS Guidelines
• 1999: Local Variability.
• 2003: The Tarragona Strategy
• 2006: One vs two weeks.
• 2009: EUVAP study
• 2012: VAT
Definition

“Lower respiratory infection involving the conducting zone of the lung sparing the gas exchange zone”.

Agrafiotis M, et al Respiratory Medicine 2010,104; 325-336
Risk Factors

- Oropharyngeal colonization.
- Bacteria/secretions.
- Leak around ETT cuff.
- ETT biofilm.
- Tracheostomy

In relation with:
- Bacterial pathogens: number, type and virulence.
- Lung Defenses: cilia, humoral, cellular.

Craven D et al, CHEST 2009;135:521-528
Prevention?

- Oral care.
- Stress ulcer prophylaxis?
- SDD?
- Coated ET tubes.
- Tracheotomy
- Liberation of vocal cords.\(^2\)

- None studied for VAT

Martin-Loeches, Clin Pulm Med 2010;17:117-121
When does it starts

- > 2 days.
TIMING: VAT Later than VAP!

- **VAT**: 7.5 days (IQR: 5.25-10)  \( p = 0.05 \)
- **VAP**: 5 days (IQR: 4-8)
Epidemiology in VH P-ICU

VAP = 4.12 x 1000 MV-days
VAT = 6.9 x 1000 MV-days

VAP = 6 VAP (5.8%)
VAT = 10 VAT (9.7%)

VAT + VAP rates: 11 x 1000 MV-days ≈ VAP rates in adult/children Spanish ICUs

Lower VAP rates because we treat VAT?

Epidemiology

- 2.7% German multicenter study.¹
- 3.7% Spain trauma patients.²
- 10% France ICU patients in MV.³
- 11% USA mixed ICU.⁴
- 9.7% Children’s VH ICU patients in MV
- 15.3% Lung transplant

¹ Kampf G et al, J Clin Epidemiol 1998;51:495-502
² Rello J et al, CHEST 1992;102:525-529
³ Nseir S et al, Eur Resp J 2002;20:1483-1489
Pathogenesis

Craven D et al, CHEST 2009;135:521-528
Gene Expression profiles in VAP vs VAT

- 5595 genes expressed differently in the pre-infection period!
- Significant depression of the complement system signalling pathway.
- cAMP & Calcium signalling pathways depressed in the pre-infection phase for VAP

Pathogenesis

Colonization

VAT

VAP

Dallas J, CHEST 2009;135:252-254
Pathogenesis

After an intervention…
(ventilator bundle)

VAT as own entity, too

Pathogenesis

Colonisation

VAT

VAP

Early VAP

VARI
## The challenge of Diagnosis

- No standard

### Variable

<table>
<thead>
<tr>
<th></th>
<th>VAP</th>
<th>VAT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td>Fever, cough, new or increased sputum production,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Worsening oxygen requirements (increasing FIO2) or PaO2/FIO2 ratio)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Or CPIS Score &gt;6</td>
<td></td>
</tr>
<tr>
<td><strong>Microbiology</strong></td>
<td>EA: ≥10⁵ CFU/ml</td>
<td>SQ-ETA: +++ /++++</td>
</tr>
<tr>
<td></td>
<td>BAL: ≥10⁴ CFU/ml</td>
<td>Q-ETA: ≥10⁶ CFU/ml</td>
</tr>
<tr>
<td></td>
<td>Lung Tissue: ≥10⁴ CFU/g</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Protected brush:≥10³ /ml</td>
<td></td>
</tr>
<tr>
<td><strong>Radiology</strong></td>
<td>New and progressive or persistent consolidation</td>
<td>No new infiltrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Craven D et al, CHEST 2009;135:521-528
Agrafiotis M, et al Respiratory Medicine 2010,104; 325-336
VAE – VENTILATOR-ASSOCIATED EVENT

VAC – Ventilator-Associated Condition

Period of stability or improvement on the ventilator, defined by ≥2 calendar days of stable or decreasing daily minimum FiO2 or PEEP values, and after has at least one of the following indicators of worsening oxygenation:

1. Increase in daily minimum FiO2 of ≥0.20 (20 points) over the daily minimum FiO2 in the baseline period, sustained for ≥2 calendar days

2. Increase in daily minimum PEEP values of ≥3 cmH2O over the daily minimum PEEP in the baseline period, sustained for ≥2 calendar days.
IVAC:
- Fever and leucocytosis/leucopenia
- New antimicrobial agent is started !!!
- Possible VAP.
- Probable VAP.

But… No mention to VAT.
Does VAC, IVAc and VAP correlates?

FIGURE 1. The relationship between VAP, VAC, and iVAC. iVAC = infection-related ventilator-associated complication; VAC = ventilator-associated condition; VAP = ventilator-associated pneumonia.

Muscedere J et al; CHEST 2013; 144(5):1453–1460
Does VAC, IVAc and VAP correlates?

![VAP as the Comparison Standard (n = 148)](image)

<table>
<thead>
<tr>
<th>Condition as compared w/ VAP</th>
<th>Presence of both VAP and VAC or iVAC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAC (n=139)</td>
<td>39/148 (26.4%)</td>
<td>26%</td>
<td>91%</td>
<td>28%</td>
<td>91%</td>
</tr>
<tr>
<td>iVAC (n=65)</td>
<td>26/148 (17.6%)</td>
<td>18%</td>
<td>97%</td>
<td>40%</td>
<td>90%</td>
</tr>
</tbody>
</table>

Muscedere J et al; CHEST 2013; 144(5):1453–1460
Effect of ventilator-associated tracheobronchitis on outcome in patients without chronic respiratory failure: a case-control study

Saad Nseir¹, Christophe Di Pompeo², Stéphane Soubrier¹, Hélène Lenzi³, Pierre Delour³, Thierry Onimus¹, Fabienne Saulnier¹, Daniel Mathieu³ and Alain Durocher¹

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cases (n = 55)</th>
<th>Controls (n = 55)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of mechanical ventilation (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>7.0 (1-95)</td>
<td>8.0 (3-81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>21.6 ± 16.0</td>
<td>13.3 ± 13.1</td>
<td></td>
</tr>
<tr>
<td>Length of ICU stay (days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>24.5 (5-85)</td>
<td>12.0 (4-74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>28.0 ± 15.7</td>
<td>17.6 ± 16.6</td>
<td></td>
</tr>
<tr>
<td>ICU mortality (n [%])</td>
<td>16 (29)</td>
<td>20 (36)</td>
<td>0.284</td>
</tr>
</tbody>
</table>

Results by univariate analysis. ICU, intensive care unit; SD, standard deviation.

Outcome

Frequency, prevention, outcome and treatment of ventilator-associated tracheobronchitis: Systematic review and meta-analysis

Michalis Agrafiotis a, Ilias I. Siempos a, Matthew E. Falagas a,b,c,*

Antimicrobial treatment

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment</th>
<th>Events</th>
<th>Total</th>
<th>Control</th>
<th>Events</th>
<th>Total</th>
<th>OR Total (95% CI)</th>
<th>OR M-H (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neur 2002</td>
<td>54</td>
<td>150</td>
<td>214</td>
<td>34</td>
<td>100</td>
<td>134</td>
<td>0.60 (0.33, 1.09)</td>
<td></td>
</tr>
<tr>
<td>Neur 2003</td>
<td>30</td>
<td>74</td>
<td>102</td>
<td>16</td>
<td>50</td>
<td>64</td>
<td>0.25 (0.07, 0.86)</td>
<td></td>
</tr>
<tr>
<td>Palmer 2003</td>
<td>4</td>
<td>19</td>
<td>229</td>
<td>14</td>
<td>67</td>
<td>81</td>
<td>1.33 (0.29, 6.21)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>62</td>
<td>55</td>
<td>177</td>
<td>125</td>
<td>100</td>
<td>225</td>
<td>9.56 (3.27, 27.14)</td>
<td></td>
</tr>
</tbody>
</table>

Agrafiotis M, et al Respiratory Medicine 2010, 104; 325-333
VAP / VAT Management

- Key questions to address:
  - when to start antibiotics
  - how microbiological tests determine antibiotic changes (de-escalate)
  - what microorganisms should be covered
  - the choice of the initial agent
  - dose and duration

Figure 3  Outcomes of patients who developed heavy colonization only, defined as quantitative endotracheal aspirates (Q-ETA) ≥ 10^5 cfu/mL, versus no or light colonization, ventilator-associated tracheobronchitis (tracheobronchitis [VAT]) versus no tracheobronchitis, and ventilator-associated pneumonia (pneumonia [VAP]) versus no pneumonia. Outcomes included median ventilator days, intensive care unit days, and hospital days.
VAT and VAP in Lung Transplant
MV days and LOS

Riera et al, 2014; submitted
Rationale for treatment

- May VAT be a precursor to VAP?
- Increases in lower respiratory tract colonization over time with a peak about 2 days before the onset of clinical signs of VAP. ²
- Increased length of ICU stay, more mechanical ventilator days.

<table>
<thead>
<tr>
<th>Organism</th>
<th>VAT Pathogens (n = 32)</th>
<th>VAP Pathogens (n = 90)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MDR pathogen</strong></td>
<td>9 (28.1%)</td>
<td>31 (34.4%)</td>
</tr>
<tr>
<td><strong>Gram positive</strong></td>
<td>12 (37.5%)</td>
<td>25 (27.8%)</td>
</tr>
<tr>
<td>MRSA</td>
<td>6 (18.8%)</td>
<td>10 (11.1%)</td>
</tr>
<tr>
<td>MSSA</td>
<td>4 (12.5%)</td>
<td>9 (10.0%)</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>2 (6.3%)</td>
<td>5 (5.6%)</td>
</tr>
<tr>
<td>“Non-pneumococcal”</td>
<td>2 (6.3%)</td>
<td>7 (7.8%)</td>
</tr>
<tr>
<td><strong>Streptococci</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Corynebacterium striatum</em></td>
<td>1 (3.1%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>Gram negative</strong></td>
<td>16 (50.0%)</td>
<td>58 (64.4%)</td>
</tr>
<tr>
<td><em>Acinetobacter baumanii</em></td>
<td>5 (15.6%)</td>
<td>10 (11.1%)</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>3 (9.4%)</td>
<td>11 (12.2%)</td>
</tr>
<tr>
<td><em>Haemophilus influenza</em></td>
<td>3 (9.4%)</td>
<td>3 (3.3%)</td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em></td>
<td>2 (6.3%)</td>
<td>2 (2.2%)</td>
</tr>
<tr>
<td><em>Klebsiella pneumonia</em></td>
<td>1 (3.1%)</td>
<td>6 (6.7%)</td>
</tr>
<tr>
<td><em>Enterobacter aerogenes</em></td>
<td>1 (3.1%)</td>
<td>6 (6.7%)</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>1 (3.1%)</td>
<td>3 (3.3%)</td>
</tr>
<tr>
<td><em>Serratia odoriferae</em></td>
<td>1 (3.1%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><em>Haemophilus parainfluenza</em></td>
<td>0 (0.0%)</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td><em>Enterobacter cloacae</em></td>
<td>0 (0.0%)</td>
<td>6 (6.7%)</td>
</tr>
<tr>
<td><em>Citrobacter freundii</em></td>
<td>0 (0.0%)</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td><em>Citrobacter koseri</em></td>
<td>0 (0.0%)</td>
<td>2 (2.2%)</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>0 (0.0%)</td>
<td>3 (3.3%)</td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
<td>0 (0.0%)</td>
<td>4 (4.4%)</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>0 (0.0%)</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td><strong>Polymicrobial infections</strong></td>
<td>7 (25.0%)</td>
<td>16 (19.3%)</td>
</tr>
</tbody>
</table>

*p > 0.05*
How to treat: Targets

- Gram negative bacteria:
  - *Pseudomonas aeruginosa*
  - *Acinetobacter baumannii*
  - *Klebsiella spp.*

- Gram positive bacteria:
  - MRSA
  - MSSA

Nseir S et al, Eur Resp J 2002;20:1483-1489
Craven D et al, CHEST 2009;135:521-528
Treatment Decision Tree for VAP & VAT

Suspected

Microbiological investigation

Empiric antibiotics based on risk factors

Cultures and Gram stain

G+ stain – if MRSA, start anti-MRSA coverage
G- stain – if Acinetobacter, start carbapenem
– if Pseudomonas, start 2 anti-Ps agents
If none of above, start antibiotics and consider local epidemiology

Re-assess 72 hours

IMPACT OF ANTIMICROBIAL TREATMENT ON OUTCOME

Nosocomial tracheobronchitis in mechanically ventilated patients: incidence, aetiology and outcome

Prospective, observational, cohort study

Table 5. – Impact of antibiotics on outcomes of surgical and medical patients with nosocomial tracheobronchitis (NTB)

<table>
<thead>
<tr>
<th></th>
<th>Surgical NTB patients</th>
<th>Medical NTB patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ATB</td>
<td>No ATB</td>
</tr>
<tr>
<td>Subjects n</td>
<td>26</td>
<td>10</td>
</tr>
<tr>
<td>ICU LOS days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>36.6±27.6</td>
<td>46.6±43.5</td>
</tr>
<tr>
<td>Median (range)</td>
<td>30.5 (10–148)</td>
<td>31.0 (11–134)</td>
</tr>
<tr>
<td>Length of MV days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>30.6±28.9</td>
<td>37.0±38.4</td>
</tr>
<tr>
<td>Median (range)</td>
<td>23.0 (3–127)</td>
<td>28.0 (11–132)</td>
</tr>
<tr>
<td>Mortality %</td>
<td>50.0</td>
<td>70.0</td>
</tr>
</tbody>
</table>
Figure 4: Effect of antimicrobial treatment on the crude mortality of ventilator-associated tracheobronchitis.

OR 0.56 (95% CI: 0.27-1.14)
INHALED ANTIMICROBIAL THERAPY

Double-blind, randomized, placebo controlled study

43 VAT

<table>
<thead>
<tr>
<th>Aerosolized antibiotics [13•]</th>
<th>Yes (n = 19)</th>
<th>No (n = 24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days free of MV, median (range)</td>
<td>10 (26)</td>
<td>0 (27)</td>
<td>0.069</td>
</tr>
<tr>
<td>Subsequent VAP, (%)</td>
<td>35.7</td>
<td>78.6</td>
<td>0.007</td>
</tr>
<tr>
<td>ICU-mortality, (%)</td>
<td>21.1</td>
<td>16.7</td>
<td>0.990</td>
</tr>
<tr>
<td>MDR bacteria emergence, (%)</td>
<td>0</td>
<td>16.6</td>
<td>0.005</td>
</tr>
</tbody>
</table>

✓ Lower rates of VAP at the end of treatment  
✓ Reduced use of systemic antibiotics  
✓ Increased weaning  

p< 0.05

Figure 3. Potential advantages of a model based on the diagnosis and early, targeted antibiotic treatment of VAT include reduction in VAP and improved patient outcomes. This model may also help in the management of early VAP (too early for chest radiograph changes) and possible VAP that includes patients with preexisting chest radiographs with prior diffuse infiltrates that prevent confirmation of new infiltrate needed to diagnose VAP.
Therapeutic Management of VARI

Risk factors for specific organism?
Known organism colonization? GenExpert

YES

EMPIRIC THERAPY

Baseline MDR? MV > 5 days, COPD?
IC, Vasopressors, Severe hypoxemia?

YES

Broad Spectrum

NO

Narrow Spectrum

FAVORABLE

CLINICAL RESPONSE

DELAyED

De-escalate

Combo therapy to Monotherapy

Culture negative -> stop antibiotic

Other: adapt antibiotic

Switch to broader spectrum

-Add second agent

-Optimize Dosage

-Rule out EMPYEMA, ABSCESS..

Modified from Rello et al, Lancet Resp Dis 2014
DURATION OF ANTIMICROBIAL TREATMENT

Probably shorter courses of treatment because therapy is initiated early and before there is extensive tissue damage or when there are fewer bacteria.
What's missing: Unmet clinical needs

- Consensus definition if needed.
- Impact / Stratification of severity
- ET = Tracheostomy?
- RCT on Duration of treatment.
- Nebulized vs intravenous vs double therapy
Conclusions

- VAT is more frequent than VAP in MV.
- No gold standard for diagnosis.
- Increase LOS and MV period.
- Further studies and new paradigms are needed.
Clinical suspicion

Microbiologic investigation

Empiric ATB

Reasses 48-72h

Clinical Resolution

DOSAGE & Duration ATB

• Adjust ATB therapy: de-escalation?
• Clinical response: Fever and hypoxemia
• Biomarkers: CRP

• Gram (+): If RF for MRSA start anti-MRSA agent
• Gram (-): If RF for AB start Carbapenem
  If RF for PA start 2 anti-PA agents
• If none, start ATB according to epidemiological data

• Gram
• Quantitative cultures
• Blood cultures

• SIRS
• Radiologic infiltrates
• Purulent secretions
What’s New in VAP?
Rello et al. Intensive Care Med 2015
VENTILATOR RESPIRATORY INFECTION

A NEW TREATMENT PARADIGM?

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