Nebulized Antibiotics in VAP: Don’t Hold Your Breath

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Learning Objectives

Following this presentation, the audience member will be able to:

1. Describe the definition, risk factors, and common organisms associated with ventilator-associated pneumonia (VAP)
2. Explain the current literature regarding nebulized antibiotics in VAP patients
3. Provide an evidenced-based recommendation on the appropriate use of nebulized antibiotics

Risk Factors for VAP

<table>
<thead>
<tr>
<th>Patient Specific</th>
<th>Preventable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60 years old</td>
<td>Reintubation, tracheostomy, or patient transport</td>
</tr>
<tr>
<td>COPD, ARDS, or coma</td>
<td>H2RA’s or PPI’s</td>
</tr>
<tr>
<td>Enteral nutrition, nasogastric tube</td>
<td>Head trauma</td>
</tr>
<tr>
<td>MDR risk</td>
<td>ICP Monitoring</td>
</tr>
</tbody>
</table>

Common Organisms

Gram Positive

- *S. aureus* (20-30% of isolates)
- 50% methicillin-resistant

Enteric Gram Negative

- 20-40% of isolates
- *E. coli*
- *Klebsiella pneumoniae*

Non-Enteric Gram Negative

- *P. aeruginosa* (10-20% of isolates)
- 19-35% resistant to cephalosporins
- 36-61% resistant to carbapenems
- 19-35% resistant to piperacillin-tazobactam
- 36-61% resistant to carbapenems

Conflicts of Interest

The author has no conflicts of interest to disclose

References

Risk Factors for MDR VAP

Prior intravenous antibiotic use within 90 days
Septic shock at the time of VAP
ARDS preceding VAP
5 or more days of hospitalization prior to the occurrence of VAP
Acute renal replacement therapy prior to the occurrence of VAP


Empiric Treatment Options for VAP

**Gram Positive Antibiotics (MRSA Activity)**
- Vancomycin
- Linezolid

**Gram Negative Antibiotics:**
- β-Lactam Based Agents:
  - Piperacillin-tazobactam
  - Cefepime, ceftazadime
  - Imipenem, meropenem
  - Aztreonam

**Gram Negative Antibiotics: Non-β-Lactam Based**
- Ciprofloxacin, levofloxacin
- Amikacin, gentamicin, tobramycin
- Colistin, polymyxin B


Current Treatment Options for MDR

- VAP due to: *Acinetobacter* spp sensitive to polymixins/colistin or carbapenem resistant pathogens
  - IV polymixin or colistin recommended
  - Adjunctive inhaled colistin suggested


Nebulization of Antibiotics

**Background**
- Up to 40% of cases caused by MDR *Pseudomonas* or *Acinetobacter* in ICU’s

**Rationale**
- Few antibiotic options
- PK changes in critically ill patients

**Benefits**
- Avoids high systemic IV concentrations
- Reduced systemic ADE’s/toxicities

**Disadvantage of IV Antibiotics**
- Poor lung penetration
- Ex: β-lactams, colistin, aminoglycosides, and glycopeptides


Benefits of Nebulized Antibiotics

- Higher drug concentrations (lungs)
- Decreased systemic toxicity
- Reduced need for systemic antibiotics


Types of Nebulizers: Advantages & Disadvantages

<table>
<thead>
<tr>
<th>Nebulizer</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jet</td>
<td>Easy to use</td>
<td>Low drug delivery rate (15%)</td>
</tr>
<tr>
<td></td>
<td>Low cost</td>
<td>Difficult to clean</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Particle size &gt;5 μm</td>
</tr>
</tbody>
</table>

Types of Nebulizers: Advantages & Disadvantages

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<th>Nebulizer</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound</td>
<td>• Good drug delivery (30-40%)</td>
<td>• Increases drug temperature</td>
</tr>
<tr>
<td></td>
<td>• Particle size 3.7-10.5 μm</td>
<td>• Inability to aerosolize viscous solutions</td>
</tr>
<tr>
<td></td>
<td>• Silent</td>
<td>• Large device size</td>
</tr>
</tbody>
</table>

Vibrating Mesh

<table>
<thead>
<tr>
<th>Nebulizer</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Best drug delivery (40-60%)</td>
<td>• Pores can clog</td>
</tr>
<tr>
<td></td>
<td>• Adjustable drug particle size (&lt;5 μm)</td>
<td>• High cost</td>
</tr>
<tr>
<td></td>
<td>• Pores can clog</td>
<td>• Difficult to clean</td>
</tr>
</tbody>
</table>

Ideal Properties of an Aerosolized Antibiotic Solution

- Particle Size
- Aerosolized Antibiotic Solution
- pH adjusted
- Osmolality Adjusted
- Preservative Free, Sterile, Non-Pyrogenic


Role of Inhaled Antibiotic Therapy in VAP

- Reserved as treatment of last resort in patients who are not responding to IV antibiotics alone
- Used as an adjunct to IV antibiotic therapy
- May be used whether or not infecting organism is MDR


Rationale

- Determine efficacy and safety of antibiotic nebulization
- Increased use of nebulized antibiotics
- Safety and efficacy unknown
- Hypothesis: Nebulized antibiotics are safe and effective therapy in invasively mechanically ventilated adult patients

Methods

Data
- Systematic review and meta-analysis data from June 2014, March 2015, and July 2016

Databases Included
- MEDLINE, PubMed, EMBASE, and Cochrane Library Database

Search Terms
- Aerosols, nebulizers and vaporizers, anti-bacterial agents, antimicrobial, pneumonia, ventilator associated

Size
- 826 patients

Inclusion Criteria
- Randomized control trials (RCT), observational studies, and case series
- Use of jet, ultrasonic, or vibrating-mesh nebulizers
- Reported at least one of the following:
  - Efficacy Outcome: Clinical resolution OR
  - Safety Outcomes: Systemic Toxicity, cardiorespiratory complications

Exclusion Criteria
- Children, colonized-but-not-infected adults, and cystic fibrosis patients
- Burn, renal replacement therapies, and/or cardiopulmonary support patients

1435 studies (duplicates removed)
1358 studies excluded
859 studies excluded
487 full-text articles excluded
11 articles included in qualitative/quantitative synthesis

Statistics
- Pooled Evaluation
- Majority of studies had small sample sizes
- Performed for each outcome
- Heterogeneity
- Higgins I^2 Test
- Funnel Plot
- Assessment of publication bias

Outcomes

Intervention
- Standard first-line IV antibiotics
- Nebulized antibiotics administered via adjunctive or substitution strategy

Comparator
- Standard first-line IV antibiotics + IV colistin or aminoglycosides (AG)

Primary Efficacy Outcome
- Clinical Resolution

Safety Outcomes
- Systemic Toxicity
- Cardiorespiratory complications
Adjunctive vs Substitution Strategy

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Intervention</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjunctive</td>
<td>First-line IV Antibiotics + IV colistin/aminoglycosides</td>
<td>First-line IV Antibiotics + IV colistin/aminoglycosides</td>
</tr>
<tr>
<td>Substitution</td>
<td>First-line IV Antibiotics + Nebulized colistin/aminoglycosides</td>
<td>Nebulized colistin/aminoglycosides</td>
</tr>
</tbody>
</table>

Observational Studies Included

<table>
<thead>
<tr>
<th>Study</th>
<th>Nebulized Antibiotic</th>
<th>Placebo</th>
<th>Nebulized Antibiotic</th>
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<th>Admin. Strategy</th>
<th>Primary Efficacy Outcomes</th>
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<tbody>
<tr>
<td>Niederman et al.</td>
<td>Tobramycin &amp; gentamicin</td>
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<td>Substitution</td>
<td>Clinical resolution (reduction in CDC, SNA &amp; CRB Score)</td>
<td>None</td>
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<td>None</td>
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<tr>
<td>Doshi et al.</td>
<td>Colistin + aminoglycosides</td>
<td>IV</td>
<td>Colistin + aminoglycosides</td>
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<td>Tobramycin + placebo</td>
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RCT’s Studies Included

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Clinical Result (Adjunctive Strategy)

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<th>Clinical Resolution</th>
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<tbody>
<tr>
<td>Results (continued)</td>
</tr>
<tr>
<td>OR 0.33 (95% CI: 0.36 to 0.81)</td>
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</tr>
</tbody>
</table>
### Clinical Result (Substitution Strategy)

**Clinical Resolution**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Observational: Ghanntam et al. 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Nebulized Antibiotics, 16 IV Antibiotics</td>
</tr>
<tr>
<td>Results</td>
<td>Higher rates of clinical resolution in the NA group. OR 9.53 (95% CI: 1.85 to 49.2)</td>
</tr>
</tbody>
</table>


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### Safety Result (Adjunctive Strategy)

**Systemic Toxicity: Nephrotoxicity**

**Studies**
- 2 RCT’s:
  - Niederman et al. 2012
  - Rattanasupawan et al. 2010
- 3 Observational:
  - Kofteridis et al. 2010
  - Tumbarello et al. 2013
  - Arnold et al. 2007

**Patients** Nebulized Antibiotics, 288 IV Antibiotics, 265

**Results** No significant difference seen between both groups.


---

### Safety Result (Substitution Strategy)

**Systemic Toxicity: Cardiorespiratory Complications**

**Studies**
- 4 RCT’s:
  - Niederman et al. 2012
  - Rattanasupawan et al. 2010
  - Li et al. 2011
  - Hallal et al. 2007
- 2 Observational:
  - Kofteridis et al. 2010
  - Tumbarello et al. 2013
  - Arnold et al. 2007

**Patients** Nebulized Antibiotics, 212 IV Antibiotics, 189

**Results**
- RCT: 0.2% increase in respiratory complications
  - Risk difference, 0.02 (95% CI: -0.05 to 0.11)
- Observational: No difference in ADEs
  - Risk difference, 0.00 (95% CI: -0.04 to 0.04)
- Combined meta-analysis
  - Risk difference, 0.00 (95% CI: -0.02 to 0.02)

**Results: Risk of Bias**

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection Bias</th>
<th>Performance Bias</th>
<th>Detection Bias</th>
<th>Attrition Bias</th>
<th>Reporting Bias</th>
<th>Other Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hallal 2007</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
</tr>
<tr>
<td>Liu 2011</td>
<td>LOW</td>
<td>HIGH</td>
<td>HIGH</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
</tr>
<tr>
<td>Niederman 2012</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
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<tr>
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<td>LOW</td>
<td>LOW</td>
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<td>LOW</td>
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</tr>
<tr>
<td>Palmer 2014</td>
<td>LOW</td>
<td>LOW</td>
<td>MEDIUM</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
</tr>
<tr>
<td>Rattanaumpawan 2010</td>
<td>LOW</td>
<td>HIGH</td>
<td>HIGH</td>
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</tr>
</tbody>
</table>

**Critique**

**Strengths**
- Strict inclusion criteria
- Utilized PRISMA guidelines for meta-analysis

**Limitations**
- Use of jet nebulizers
- Only ½ of studies randomized
- Sub-therapeutic dosing in studies prior to 2014
- Heterogeneous populations

**Doses of Nebulized Antibiotics Used in Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Nebulized Antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmer et al. 2008</td>
<td>Vancomycin 120 mg Q8H/NS 2 mL, Gentamicin 80 mg Q8H/NS 2 mL</td>
</tr>
<tr>
<td>Palmer &amp; Smaldone et al. 2014</td>
<td>Vancomycin 120 mg Q8H, Gentamicin 80 mg Q8H, Amikacin 400 mg Q8H</td>
</tr>
<tr>
<td>Niederman et al. 2012</td>
<td>Amikacin 400 mg Q12 or Q24H</td>
</tr>
<tr>
<td>Liu et al. 2011</td>
<td>Ceftazadime 15 mg/kg Q12H, max: 120 mg/day Amikacin 25 mg/kg Q24H</td>
</tr>
<tr>
<td>Hallal et al. 2007</td>
<td>Tobramycin 300 mg/5 mL Q12H or Q24H</td>
</tr>
<tr>
<td>Rattanaumpawan et al. 2010</td>
<td>Colistin 75 mg Q2H/NS 4 mL</td>
</tr>
</tbody>
</table>

**Doses of Nebulized Antibiotics Used in Studies**

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<thead>
<tr>
<th>Study</th>
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<tbody>
<tr>
<td>Ghanam et al. 2009</td>
<td>Colistin 100 mg Q8H, Tobramycin 300 mg Q12H, Gentamicin 100 mg Q8H, Amikacin 100 mg Q12H or Q24H</td>
</tr>
<tr>
<td>Kotaeridis et al. 2010</td>
<td>Colistin 80 mg Q12H</td>
</tr>
<tr>
<td>Dushi et al. 2013</td>
<td>Colistin 75 mg Q2H or Colistin 150 mg Q2H</td>
</tr>
<tr>
<td>Tumbarello et al. 2013</td>
<td>Colistin 80 mg Q12H</td>
</tr>
<tr>
<td>Arnold et al. 2007</td>
<td>Colistin 150 mg Q8H/NS 5 mL or Tobramycin 300 mg/3 mL Q12H</td>
</tr>
</tbody>
</table>

**Authors’ Conclusion**

- **Efficacy**
  - Nebulized antibiotics might increase likelihood of clinical resolution (especially for VAP caused by MDR pathogens)
  - Protective effect on development of MDR pathogens
- **Safety**
  - Reduced risk of nephrotoxicity with nebulized antibiotics
  - ~10% increased risk for respiratory complications
Summary

• Efficacy
  • Studies showed that nebulized antibiotics may be associated with potentially higher cure rates

• Safety
  • Studies showed that overall, nebulized antibiotics showed reduced systemic toxicity
  • The most serious adverse effect associated with nebulized antibiotics was respiratory failure


Potential Future Therapies

• Vancomycin Inhalation Powder (AeroVanc®)
• Amikacin Inhale (Proprietary Preparation)
• Aerosolized Amikacin/Fosfomycin
• Ciprofloxacin Dry Powder Inhalation
• Inhaled Levofloxacin (Quinsair®)
• Inhaled Liposomal Amikacin (Arikayce®)


Recommendation: Target Population

No clinical improvement after 48-72 hrs on standard IV antibiotics for VAP

Patient has risk factors for MDR gram negative pathogens

Cultures positive for MDR pathogens (if available)

Past medical history negative for pulmonary conditions such as asthma, COPD, or ARDS

Utilization of ultrasonic nebulizers or vibrating mesh nebulizers

Recommendation:

Target Population

• No clinical improvement after 48-72 hrs on standard IV antibiotics for VAP
• Patient has risk factors for MDR gram negative pathogens
• Cultures positive for MDR pathogens (if available)
• Past medical history negative for pulmonary conditions such as asthma, COPD, or ARDS
• Utilization of ultrasonic nebulizers or vibrating mesh nebulizers

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Nebulized Antibiotics in VAP: Don’t Hold Your Breath

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Appendix A:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADE</td>
<td>Adverse Drug Events</td>
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<tr>
<td>AG</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>ARDS</td>
<td>Acute Respiratory Distress Syndrome</td>
</tr>
<tr>
<td>CDC-NNS</td>
<td>Centers for Disease Control-National Nosocomial Infections Surveillance</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>CPIS</td>
<td>Clinical Pulmonary Infections Score</td>
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<tr>
<td>H2RA</td>
<td>H2-antagonists</td>
</tr>
<tr>
<td>ICP</td>
<td>Intracranial Pressure</td>
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<tr>
<td>IDSA</td>
<td>Infectious Diseases Society of America</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>MDR</td>
<td>Multi-Drug Resistant</td>
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<tr>
<td>MDRO</td>
<td>Multi-Drug Resistant Pathogens</td>
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<tr>
<td>MRSA</td>
<td>Methicillin-Resistant Staphylococcus aureus</td>
</tr>
<tr>
<td>NA</td>
<td>Nebulized Antibiotics</td>
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<tr>
<td>NS</td>
<td>Normal Saline</td>
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<tr>
<td>PK/PD</td>
<td>Pharmacokinetics/Pharmacodynamics</td>
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<tr>
<td>PPI</td>
<td>Proton Pump Inhibitors</td>
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<tr>
<td>PRISMA</td>
<td>Preferred Reporting Items for Systematic Reviews and Meta-analyses</td>
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<tr>
<td>RCT</td>
<td>Randomized Control Trial</td>
</tr>
<tr>
<td>VAP</td>
<td>Ventilator Associated Pneumonia</td>
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Appendix B:


