Update on Inhaled Antibiotics for Hospital-Acquired Pneumonia

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Conflict of Interest Statement

• G. Christopher Wood is currently:
  – A consultant for Bayer Pharmaceuticals
  – An investigator in the INHALE 1 study of an aerosolized amikacin product for HAP/VAP (sponsored by Bayer).
Objectives

• Understand a general history of the use of aerosolized antibiotics for treating hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP).

• Understand recent studies and trends in the literature on the use of aerosolized antibiotics for HAP/VAP.
  – Includes drug therapy as well as administration issues
Importance of HAP/VAP

- Health care associated infections are a major cause of death
  - VAP is the most common serious HAI
- Incidence in intubated patients: 9 – 27%
- Increases length of stay by 7 – 9 days
- Attributable mortality up to 50%
- Increases hospital charges by ~ $40,000 / patient
- VAP accounts for 50% of inpatient antibiotic use

Am J Respir Crit Care Med 2005;171:388-416
Why Aerosolize Antibiotics?

• VAP cure rates are poor in some settings
  – 63% overall (41 trials, n=7015)¹
• Bacterial resistance is worsening
• Poor pulmonary penetration of IV antibiotics
  – Need to optimize lung concentrations of antibiotics
• Potentially decreased toxicity

¹ Aarts MAW. Crit Care Med 2008;36-108-117
VAP Prevention with Aerosolized Antibiotics
## VAP Prevention – Positive Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>n</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klick 1975</td>
<td>Colistin/Placebo</td>
<td>744</td>
<td>↓ PA VAP 82%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No reduction overall</td>
</tr>
<tr>
<td>Vogel 1981</td>
<td>Gent/No tx</td>
<td>40</td>
<td>“Decreased” HAP</td>
</tr>
<tr>
<td>Rathgeber 1993</td>
<td>Tobra/No tx</td>
<td>69</td>
<td>↓ 58%</td>
</tr>
<tr>
<td>Rouby 1994</td>
<td>Colistin/No tx</td>
<td>598</td>
<td>↓ 30%</td>
</tr>
<tr>
<td>(retrospective)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wood 2002</td>
<td>Ceftaz/Placebo</td>
<td>40</td>
<td>↓ 54%</td>
</tr>
</tbody>
</table>

*Drugs 2007;67:903-14*
# VAP Prevention – Negative Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>n</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenfield 1973</td>
<td>Colistin/No tx</td>
<td>58</td>
<td>No benefit</td>
</tr>
<tr>
<td>Klastersky 1974</td>
<td>Gent/Placebo</td>
<td>85</td>
<td>↑ resistance</td>
</tr>
<tr>
<td>Klastersky 1975</td>
<td>AMG/AMG+colistin</td>
<td>47</td>
<td>↑ resistance</td>
</tr>
<tr>
<td>Feeley 1975</td>
<td>Colistin/No tx</td>
<td>292</td>
<td>↑ HAP mortality 33%</td>
</tr>
<tr>
<td></td>
<td>(retrospective)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levine 1978</td>
<td>Gent/Placebo</td>
<td>30</td>
<td>↑ resistance</td>
</tr>
<tr>
<td>Lode 1992</td>
<td>Gent/Placebo</td>
<td>199</td>
<td>No benefit</td>
</tr>
<tr>
<td>Claridge 2007</td>
<td>Ceftazidime/Placebo</td>
<td>105</td>
<td>No benefit</td>
</tr>
</tbody>
</table>
VAP Prevention

• Why did these studies fail?
  – Poor HAP/VAP diagnosis
  – Indiscriminate patient selection
  – Long-term prophylaxis
  – Poor administration technique
    • Use of ET instillation instead of aerosolization

• Conclusion: Not recommended by ATS/IDSA

Drugs 2007;67:903-14
VAP Treatment with Aerosolized Antibiotics: 1960s-2008
## VAP Treatment - Aerosolized AMGs

<table>
<thead>
<tr>
<th>Year</th>
<th>n</th>
<th>Drug</th>
<th>Cure (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1967</td>
<td>11</td>
<td>Gent</td>
<td>18%</td>
<td>IV nonresponders</td>
</tr>
<tr>
<td>1970</td>
<td>12</td>
<td>Gent</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>1972</td>
<td>15</td>
<td>Gent</td>
<td>100% vs 25%</td>
<td>Aero superior (p&lt;0.05)</td>
</tr>
<tr>
<td>1979</td>
<td>38</td>
<td>Siso</td>
<td>77% vs 45%</td>
<td>Aero superior (p&lt;0.05)</td>
</tr>
<tr>
<td>1980s</td>
<td>6</td>
<td>Tobra/Amik</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>22</td>
<td>Tobra/Amik</td>
<td>59%</td>
<td>PA, AB</td>
</tr>
<tr>
<td>2007</td>
<td>10</td>
<td>Tobra</td>
<td>100% vs 60%</td>
<td>PA, AB (p=NS)</td>
</tr>
</tbody>
</table>

Total aerosolized n = 114  
Mean cure = 80%

*Expert Rev Anti Infect Ther 2011;9:993-1000*
## VAP Treatment - Aerosolized Colistin

<table>
<thead>
<tr>
<th>Year</th>
<th>n</th>
<th>Cure (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1967</td>
<td>17</td>
<td>24%</td>
<td>IV Nonresponders</td>
</tr>
<tr>
<td>2000s</td>
<td>24</td>
<td>88%</td>
<td>MDR PA, AB</td>
</tr>
<tr>
<td>2005</td>
<td>21</td>
<td>86%</td>
<td>MDR PA, AB</td>
</tr>
<tr>
<td>2005</td>
<td>71</td>
<td>92%</td>
<td>Included floor pts.</td>
</tr>
<tr>
<td>2006</td>
<td>16</td>
<td>100%</td>
<td>All AB, all MV</td>
</tr>
<tr>
<td>2006</td>
<td>9</td>
<td>85%</td>
<td>MDR PA, AB</td>
</tr>
<tr>
<td>2007</td>
<td>14</td>
<td>93%</td>
<td>IV Nonresponders, MDR PA</td>
</tr>
<tr>
<td>2008</td>
<td>60</td>
<td>83%</td>
<td>PA, AB, Kleb</td>
</tr>
</tbody>
</table>

Total aerosolized n = 232  
Mean cure = 84%

*Expert Rev Anti Infect Ther* 2011;9:993-1000
<table>
<thead>
<tr>
<th>Year</th>
<th>n</th>
<th>Drug</th>
<th>Cure (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970</td>
<td>15</td>
<td>Carbenicillin</td>
<td>47%</td>
<td>PA</td>
</tr>
<tr>
<td>1986</td>
<td>25</td>
<td>Cefotaxime/</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ceftazidime</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Expert Rev Anti Infect Ther 2011;9:993-1000*
Conclusions – Treatment of VAP

• ATS/IDSA Guidelines 2005:

  – “Aerosolized antibiotics have not been proved to have value in the therapy of VAP. However, they may be considered as adjunctive therapy in patients with MDR Gram-negatives and who are not responding to systemic therapy.”

*Am J Respir Crit Care Med* 2005;171:388-416
Conclusions – Treatment of VAP

• SIDP Guidelines 2010:
  – Expanded on ATS/IDSA recommendations
  – Adding aerosolized antibiotics to systemic antibiotics may be considered in the following situations:
    • Nonresponders
    • Recurrent VAP
    • MDR VAP
    • Aminoglycosides are preferred when possible
VAP Treatment with Aerosolized Antibiotics:
Newer Studies
What’s New?

• Optimal dosing and administration technique

• Larger studies, control groups
  – Most studies have been retrospective, no control group

• Data with aerosolized monotherapy
  – Most studies compared IV alone vs. IV + aerosolized
Update on Administration Issues

• Vibrating plate (mesh) nebulizers are superior to jet nebulizers
  – Still require proper technique!
  – Proper technique includes:
    • D/C humidification
    • Placement ~15 cm from ET tube
    • Pretreat with albuterol if needed

Update on Administration Issues

• Colistin issues
  – 80 mg Q8h is inadequate – optimal dosing unclear
  – Ventilators need filters to avoid clogging
  – Use colistin immediately after reconstitution
    • Degredation products can be fatal
  – Overall more toxic than aminoglycosides
    • Use AMGs when sensitivity allows

Dosing

- **Aminoglycosides**
  - Gent/Tobra: 300 mg Q12h
  - WIDELY variable in studies
  - Amikacin: 500 mg Q12 (up to 1000 mg Q12)

- **Colistin**
  - 1 million units = 80 mg colistimethate ~ 33 colistin
  - SIDP recommendation: 150 mg Q12
  - Insert recommendation: 25-50 mg Q8-Q12

- **Ceftazidime**
  - 15 mg/kg Q3 or 250 mg Q12h

References:
- Pharmacother 2010;30:562-84
- Am J Respir Crit Care Med 2011;184:106-15
- Surg Infect 2007;8:83-90
Aerosolized Colistin – Lin et al.

- Design: Retrospective, observational
- Patients:
  - Mixed ICU pts
  - All VAP
  - Colistin 66 mg Q8-Q12
  - Also received IV abx
- Outcomes: Clinical/micro success
Aerosolized Colistin – Lin et al.

• Results:
  • 45 episodes in 45 pts.
  • All Acinetobacter
  • Clinical cure 58%

• Notable points:
  • Less rigorous culture technique
  • Large series of high acuity/VAP patients
Aerosolized Colistin – Kofteridis et al.

• Design: Retrospective, observational, case-matched
• Patients:
  • Mixed ICU pts
  • All VAP
  • Aero plus IV vs. IV alone: age/APACHE II matching
  • Colistin 33 mg Q12
  • Also received IV abx
• Outcomes: Clinical/micro success

Clin Infect Dis 2010;51:1238-44
Aerosolized Colistin – Kafteridis et al.

• Results:
  • 43 aero/IV vs. 43 IV only
  • Acinetobacter (77%), Klebsiella (14%), Pseudomonas (9%)
  • Clinical cure: 54% vs. 33% (p=0.05)
  • Micro cure: 45% vs. 50% (p=0.6)

• Notable points:
  • BAL-confirmed VAP
  • Matched control group
  • Relatively large study

Clin Infect Dis 2010;51:1238-44
Aerosolized Ceftazidime – Lu et al.

- Design: Prospective, randomized
- Patients:
  - Mixed ICU pts: ~90% surgery/trauma
  - All VAP
  - All Pseudomonas
  - Aero group: CTZ 15 mg/kg Q3, amikacin 25 mg/kg/d
  - IV group: CTZ 90 mg/kg/d continuous, amikacin 15 mg/kd/d
- Outcomes: Clinical/micro success

Am J Respir Crit Care Med 2011;184:106-15
Aerosolized Ceftazidime – Lu et al.

- Results:
  - Aero group n=20, IV group n=20
  - Clinical cure: 70% vs. 55% (p=0.33)
  - Micro cure: 85% vs. 70% (p=0.26)

- Notable points:
  - Prospective, randomized data (finally!)
  - No IV therapy in aero group
  - VAP confirmed by quantitative cultures
  - Vibrating plate nebulizers
  - Very high dosing

*Am J Respir Crit Care Med 2011;184:106-15*
Aerosolized Aminoglycosides

• Czosnowski et al:¹
  – Case series, high-quality diagnosis, good technique
  – n = 44 tobramycin, 9 amikacin (all adjunctive)
  – Clinical cure 73%

• Arnold et al:²
  – Retrospective cohort, high-quality diagnosis, good technique
  – n = 74 (IV) vs. 10 (IV+aero tobra)
  – 30 day survival improved with IV/aero if APACHE II > 16 (p = 0.004)

¹. Pharmacother 2009;29:1054-60
². Respir Care 2012;57:1226-33
Aerosolized Aminoglycosides

• Niederman et al:¹
  – RCT, Phase II amikacin PK study, weak diagnosis, VP nebulizers
  – n = 16 (IV), n = 16 (IV/Aero Q12), n = 16 (IV/Aero Q24)
  – Clinical cure: 88 vs. 94 vs. 75% (p = 0.467)

• Palmer et al:²
  – RCT, weak diagnosis, excellent technique
  – n = 11 (IV) vs. 16 (IV+aero)
  – Microbiologic eradication: 9 vs. 88% (p < 0.001)

¹. Intensive Care Med 2012;38:263-71
². Am J Respir Crit Care Med 2014;189:1225-33
Colistin: IV vs. IV/Aero

• Study design:
  – Randomized controlled trial, low dose (75 mg Q12)
  – No vibrating plate nebulizers, medium-quality diagnosis
  – n = 51 (IV) vs. 49 (IV/Aero)

• Results:
  – Favorable outcome: 53 vs. 51%, p = 0.84

• Key points:
  – Randomized controlled trial – but no benefit
  – Did dosing/nebulizer/diagnostic technique affect results?

Colistin: IV vs. IV/Aero

• Study design:
  – Retrospective, low dose (80 mg Q12)
  – Jet nebulizer, high-quality diagnosis
  – n = 43 (IV) vs. 78 (IV/Aero)

• Results:
  – Clinical cure: 61 vs. 80%, p = 0.025

• Key points:
  – Lower quality design, but aero was beneficial (also on multivariate)

Colistin: IV vs. IV/Aero

• Study design:
  – Retrospective, 3 centers, various nebs/dosing, MDR VAP
  – n = 51 (IV) vs. 44 (IV/Aero)

• Results:
  – VAP mortality: 70 vs. 40%, p = 0.055
  – VAP cure if BAL verified: 31 vs. 57%, p=0.033

• Key points:
  – Relatively large n
  – IV/aero better if high-quality diagnosis

Doshi et al. *BMC Anesthesiol* 2013;13:45
Colistin: IV vs. IV/Aero

• **Study design:**
  – Retrospective, case matched, dose not reported
  – Medium-quality cultures, no vibrating plate nebulizers
  – n = 104 (IV) vs. 104 (IV/Aero)

• **Results:**
  – Clinical cure: 55 vs. 69%, p = 0.03

• **Key points:**
  – Large n, good design
  – IV/aero was more effective

Tumbarello et al. Chest 2013;144:1768-75
Colistin: IV vs. IV/Aero – The Verdict

• Study design:
  – Meta-analysis, 8 studies, total n = 690
  – n = 322 (IV) vs. 368 (IV/Aero)

• Results:
  – Clinical success: OR 1.57 (1.14-2.15)
  – Microbiologic success: OR 1.61 (1.11-2.35)
  – Pneumonia-related mortality: OR 0.58 (0.34-0.96)

• Key points:
  – IV/aero was more effective

Valachis et al.  *Crit Care Med* 2014 DOI:10.1097/CCM.00000000000000771
Aerosolized Monotherapy: Colistin

- **Rationale:** 10/11 pts. cured in two case series\(^1,2\)
- **Study design:**\(^3\)
  - Retrospective, higher dosing (167 mg Q8)
  - Vibrating plate nebulizer, high-quality diagnosis
  - \(n = 122\) (IV) vs. 28 (Aero) + 15 (Aero/IV x 3 days)
- **Results:**
  - Clinical cure: 66 vs. 67%, \(p = \text{NS}\)
- **Key points:**
  - High dose aero alone (or with 3d IV) was effective

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Aero Monotherapy: Ceftaz/Amikacin

• Study design:
  – RCT, very high dosing (CTZ: 15 mg/kg Q3h, Amik: 25 mg/kg QD)
  – VP nebulizer, high-quality diagnosis, all Pseudomonas VAPs
  – n = 20 (IV) vs. 20 (Aero)

• Results:
  – Clinical cure: 55 vs. 70%, p = 0.33

• Key points:
  – High dose aero alone was effective, RCT
  – Dosing is very unusual

Lu et al. *Am J Respir Crit Care Med* 2011;184:106-115
Safety - Aminoglycosides

• Nephrotoxicity
  – Aero ~3% vs. IV ~10%
  – Serum concentrations are undetectable/very low
  – Can accumulate in renal failure

• Ototoxicity
  – Aero ~3% vs. IV ~5%
  – Poorly documented, often not reported

• Pulmonary adverse events
  – Cough, bronchospasm, bad taste, vocal changes

Safety - Colistin

• Nephrotoxicity
  – Not well documented
  – Seems no worse than 10-15% in modern IV use

• Pulmonary adverse events
  – Cough, bronchospasm, bad taste
  – Seems more common than with AMGs
  – Potentially fatal reactions
  – MUST mix immediately prior to use

Safety – Beta-lactams

• No adverse events reported
• Allergy risk for health care workers/visitors
  – Likely less if pt. mechanically ventilated
  – Don’t enter room when administering
• Don’t aerosolize carbapenems
  – Imipenem – poor delivery
  – Doripenem – poorly tolerated

Prescribing information: Doribax
Optimizing Safety

• Pre-treat with albuterol
• Use AMGs over colistin if possible
  – Tobi vs. IV tobramycin?
• Compounding issues
  – Use colistin immediately after preparation
  – Reconstitute in ½NS or NS
  – Target osmolarity 150-1200 mOsm/L
  – pH 4.0-8.0

Conclusions – Treatment of VAP

• My opinions:
  – Comparative data are extremely limited but positive
    • High success rates in difficult patients is suggestive of a benefit
    • Colistin meta-analysis suggests a benefit
  – Still use AMGs over colistin when possible
  – Emerging role for beta-lactams?
  – Vibrating plate nebulizers now preferred
  – Upcoming comparative trials will add greatly to this literature
    • Amikacin, amikacin/fosfomycin