Optimizing Antibiotic Therapy

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GENERAL ISSUES FOR ANTIBIOTIC USE IN THE CRITICALLY ILL

• General Considerations
  – Know local microbiology
  – Site of infection
  – Patient risk factors: recent hospitalization, prolonged hospitalization, recent antibiotic use, immune status, origin (community, nursing home, hospital)
  – Emphasis on proper dosing
  – Specific antibiotic issues
    • Avoid dual beta-lactam therapy
    • Limit use of third generation cephalosporins
    • Consider sequence of therapy: ? Limit quinolones to second episode of ICU infection
OTHER PRINCIPLES OF ANTIBIOTIC USE IN THE CRITICALLY ILL

- Limited need for combination therapy
  - Bacteremia, neutropenia, broad spectrum coverage
- Consider 5 day aminoglycoside therapy in combination with a beta-lactam when treating P. aeruginosa
- Use an empiric therapy regimen that includes agents different from what the patient has recently received
- Re-evaluate patient during therapy
  - Shorten duration of therapy
  - Stop therapy in some
  - Consider aerosolized therapy as an adjunct to reduce the duration of therapy
- Consider aerosolized antibiotics as adjunctive therapy for VAP with MDR pathogens
What Does “Optimizing” Mean?

- Choosing the right drug
- Avoiding delay in therapy
- Using the right dose/therapy regimen
- Choosing the correct duration
- Using an approach that does not promote resistance

- Nair GB, Niederman MS. Intensive Care Med 2015; 41:34-48
What Does “Optimizing” Mean?

• Choosing the right drug
  – Mono vs combination therapy
  – MDR pathogens: Acinetobacter, MRSA

• Avoiding delay in therapy

• Using the right dose/therapy regimen

• Choosing the correct duration

• Using an approach that does not promote resistance
Why EMPIRIC Combination Therapy in VAP?

- Combination therapy does NOT
  - Improve mortality overall
  - Prevent the emergence of resistance during therapy

- BUT combination therapy could reduce mortality IF
  - It increases the chance of appropriate therapy
    - Broader spectrum coverage than with one drug alone (gram negative and gram-positive)
    - Mixed infection: cover gram-positives and gram-negatives
  - It is used in Pseudomonal bacteremia
    - BUT adequate empiric monotherapy not as effective as adequate empiric combination therapy. Chamot E, et al. AAC 2003; 47:2756-6

- Does 1+1=3? Combination therapy may correct for relative mistakes of monotherapy: delay, delay in adding second agent, using less rapidly bactericidal agents
  - Niederman MS. Crit Care Med 2010; 38: 1906-8
Does Combination Therapy Lead To More Rapid Bacterial Killing Than Monotherapy?

- Retrospective, multi-center, propensity-matched cohort study of 4662 culture-positive patients with septic shock.
  - 1223 matched pairs of mono vs. combination therapy. ALL got appropriate therapy
- Combination with decreased mortality (HR= 0.77), ICU need, fewer days with ventilators or pressors. Effect greatest with shorter time to first appropriate rx, and shorter time to adding second agent.
- Applied to beta-lactams with aminoglycoside, quinolones, macrolides/clindamycin
- ESP applied to respiratory infections, but independent of bacteremia or gram + vs. gram –

<table>
<thead>
<tr>
<th>Disease Code</th>
<th>MT Deaths</th>
<th>MT Total</th>
<th>CT Deaths</th>
<th>CT Total</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSSI</td>
<td>33/68</td>
<td>(51.5%)</td>
<td>31/70</td>
<td>(44.3%)</td>
<td>0.89 (0.55-1.44)</td>
<td>.02</td>
</tr>
<tr>
<td>CRIP</td>
<td>15/50</td>
<td>(32.0%)</td>
<td>13/52</td>
<td>(25.0%)</td>
<td>0.75 (0.36-1.65)</td>
<td>.45</td>
</tr>
<tr>
<td>RTI</td>
<td>182/449</td>
<td>(40.5%)</td>
<td>136/439</td>
<td>(31.0%)</td>
<td>0.71 (0.57-0.89)</td>
<td>.003</td>
</tr>
<tr>
<td>UTI</td>
<td>46/224</td>
<td>(20.5%)</td>
<td>35/229</td>
<td>(15.3%)</td>
<td>0.72 (0.47-1.12)</td>
<td>.15</td>
</tr>
<tr>
<td>IA</td>
<td>107/272</td>
<td>(39.3%)</td>
<td>97/275</td>
<td>(35.3%)</td>
<td>0.89 (0.68-1.18)</td>
<td>.42</td>
</tr>
<tr>
<td>CNSI</td>
<td>8/13</td>
<td>(61.5%)</td>
<td>4/12</td>
<td>(33.3%)</td>
<td>0.46 (0.14-1.52)</td>
<td>.20</td>
</tr>
<tr>
<td>SSTI</td>
<td>39/119</td>
<td>(32.8%)</td>
<td>30/116</td>
<td>(25.9%)</td>
<td>0.76 (0.47-1.22)</td>
<td>.25</td>
</tr>
<tr>
<td>SSI</td>
<td>6/16</td>
<td>(37.5%)</td>
<td>1/16</td>
<td>(6.3%)</td>
<td>0.15 (0.02-0.21)</td>
<td>.07</td>
</tr>
<tr>
<td>ITI</td>
<td>5/7</td>
<td>(71.4%)</td>
<td>6/8</td>
<td>(75.0%)</td>
<td>1.33 (0.40-4.40)</td>
<td>.64</td>
</tr>
</tbody>
</table>
Pseudomonal VAP: Outcome and Mortality Risk Factors and Combination Rx

- 110 patients with ICU P. aeruginosa pneumonia: 71 VAP, 28 HAP, 11 HCAP.
- 81 ICU-AP, 29 not ICU-AP
- 38% with MDR pathogens
- 59% monotherapy. 50.9% got IIAT
  - Sig less if combination rx.
- ICU mortality risks: IIAT, diabetes, higher SAPS II, older age, no empiric combination rx.
- IIAT and MDR pathogens increase duration MV
Combination Therapy for Acinetobacter VAP

• For XDR Acinetobacter, colistin in combination is better than monotherapy for microbiologic eradication and mortality. 47% with carbapenem, 32% with sulbactam, 20% with tigecycline. Results similar with any of the combinations.


• 33 patients with carbapenem-resistant Acinetobacter (19 VAP)
  – 31 got tigecycline combination rx (with AG or cefperazone/sulbactam)
  – 21 clinical success
  – 57.6% 30 day mortality, 24.2% attributable mortality
Tigecycline for Acinetobacter VAP: in a Combination Regimen

- Prospective observational data of Tigecycline in ICU
  - 156 patients in 26 French ICUs (83 with SOFA score > 7), in combination therapy in 67%, not always improved mortality
  - 76% HAIs, 56% intra-abdominal, 19% SSTI. 24% lung. 12% had bacteremia.
  - 60% overall success, 76% if > 9 days duration
  - Less success with more severe illness, bacteremia, obesity, immune suppression
  - 85% survival at 28 days.

[Diagram: Anti-infective agents combined with tigecycline]
Vancomycin vs. Linezolid for MRSA

- **Vancomycin**. Glycopeptide, disrupts cell wall/peptidoglycan synthesis
  - **Pros**: low resistance rates, years of experience
  - **Cons**: slow increase in MICs (w/i “sensitive” range); poor lung penetration (12% serum levels); slowly bactericidal; nephrotoxicity
    - May overcome poor penetration by synergy with rifampin

- **Linezolid**
  - **Pros**: good lung penetration; IV/oral available; high bioavailability orally; no renal dose adjustment
  - **Cons**: thrombocytopenia, optic neuritis, lactic acidosis (prolonged therapy); drug interactions (serotonin syndrome)
  - Linezolid, but not vancomycin reduces MRSA bacterial burden in ETT biofilm, in a pig model of MRSA pneumonia.
Linezolid vs. Vancomycin For MRSA VAP

- Multicenter retrospective analysis of 188 with MRSA VAP (IMPACT-HAP)
- 101 linezolid, 87 vancomycin
- Higher APACHE II with linezolid (21 vs 19, p=0.04)
- Higher clinical success with linezolid (85% vs 69%, p<0.010), even after propensity adjustment
- In multivariate model, 24% more likely clinical success with linezolid. Similar toxicity, mortality
### A. Clinical Response

#### Linezolid vs. Vancomycin: Randomized Double-Blind

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Linezolid</th>
<th>Vancomycin</th>
<th>Weight</th>
<th>Risk Difference M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin 2008 *</td>
<td>19</td>
<td>26</td>
<td>18</td>
<td>33 8.8% 0.19 [-0.06, 0.43]</td>
</tr>
<tr>
<td>Wunderink 2003</td>
<td>36</td>
<td>61</td>
<td>22</td>
<td>62 17.4% 0.24 [0.06, 0.41]</td>
</tr>
<tr>
<td>Wunderink 2012</td>
<td>95</td>
<td>185</td>
<td>81</td>
<td>174 45.7% 0.11 [0.00, 0.22]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>252</td>
<td>269</td>
<td>71.8%</td>
<td>0.15 [0.07, 0.23]</td>
</tr>
<tr>
<td>Total events</td>
<td>150</td>
<td>121</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.58, df = 2 (P = 0.45); I^2 = 0%
Test for overall effect: Z = 3.48 (P = 0.0005)

#### Linezolid vs. Vancomycin: Randomized Open-Label

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Linezolid</th>
<th>Vancomycin</th>
<th>Weight</th>
<th>Risk Difference M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wunderink 2008</td>
<td>15</td>
<td>23</td>
<td>10</td>
<td>19 5.8% 0.13 [-0.17, 0.42]</td>
</tr>
<tr>
<td>Kohno 2007</td>
<td>21</td>
<td>35</td>
<td>9</td>
<td>19 6.7% 0.13 [-0.15, 0.40]</td>
</tr>
<tr>
<td>Stevens 2002</td>
<td>21</td>
<td>35</td>
<td>9</td>
<td>19 6.7% 0.13 [-0.15, 0.40]</td>
</tr>
<tr>
<td>Kaplan 2003</td>
<td>9</td>
<td>10</td>
<td>10</td>
<td>10 9.1% -0.10 [-0.34, 0.14]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>66</td>
<td>38</td>
<td></td>
<td>0.05 [-0.08, 0.19]</td>
</tr>
<tr>
<td>Total events</td>
<td>103</td>
<td>67</td>
<td>28.2%</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau^2 = 0.00; Chi^2 = 2.79, df = 3 (P = 0.43); I^2 = 0%
Test for overall effect: Z = 0.78 (P = 0.44)

Total events: 355 (95% CI)

Heterogeneity: Tau^2 = 0.00; Chi^2 = 5.50, df = 6 (P = 0.48); I^2 = 0%
Test for overall effect: Z = 3.36 (P = 0.0008)
Test for subgroup differences: Chi^2 = 1.41, df = 1 (P = 0.23), I^2 = 29.2%
Therapy Algorithm for VAP

• Nair GB, Niederman MS. Intensive Care Med 2015; 41:34-48

Step 3. Initiate antibiotic therapy as soon as possible

No MDR risk factors
Monotherapy with any of the following agents (normal renal function):
- Ampicillin/Subactam: 1.5 to 3 g intravenously every 6 hours
- Ceftriaxone: 1-2 g intravenously every 24 hours
- Ertapenem: 1 g intravenously every 24 hours
- Levofloxacin: 750 mg intravenously every 24 hours
- Moxifloxacin: 400 mg intravenously every 24 hours

Plus any one of the following:
- Ciprofloxacin: 400 mg intravenously every 8-12 hours
- Levofloxacin: 750 mg intravenously every 24 hours
- Amikacin: 20 mg/kg intravenously every 24 hours
- Gentamicin: 7 mg/kg intravenously every 24 hours
- Tobramycin: 7 mg/kg intravenously every 24 hours

MDR risk factors present
Combination therapy with:
Any one of the following (normal renal function):
- Cefepime: 1-2 g intravenously every 8 to 12 hours
- Ceftazidime sodium: 2 g intravenously every 8 hours
- Imipenem/Cilastatin: 500 mg intravenously every 6 hours; or 1000 mg intravenously every 8 hours
- Meropenem: 1 g intravenously every 8 hours
- Piperacillin/Tazobactam: 4.5 g intravenously every 6 hours

If MRSA is suspected, add one of the following:
- Linezolid: 600 mg intravenously every 12 hours
- Vancomycin HCl: 15 mg/kg intravenously every 12 hours
What Does “Optimizing” Mean?

• Choosing the right drug
• Avoiding delay in therapy
• Using the right dose/ therapy regimen
• Choosing the correct duration
• Using an approach that does not promote resistance
Defining Delay In Appropriate Therapy by CPIS

- 76 patients with bacteriologic dx of VAP
  - 24 appropriate therapy (AT)
  - 52 Inadequate therapy: either IT or DIAT

- DIAT even if AT within 24 hours of clinical dx (VAP 0), IF CPIS was >5 on day VAP -1

- Mortality 29.2% for adequate vs. 75% IT, 58.3% DIAT

- IT and DIAT with a more gradual increase in CPIS that AT group

- May need to define VAP earlier in order to affect outcome with rx


**FIGURE 1.** The clinical pulmonary infection score (CPIS) evolution between the ventilator associated pneumonia (VAP)-3 and the VAP+3 time points. There was a significant worsening at the VAP day compared with the CPIS 3 days before, then CPIS improved significantly during the following 3 days. The data were analysed by two-way repeated measures ANOVA. Post hoc analyses showed significant differences for the VAP-2 and VAP-1 time points, adequate therapy (●) versus inappropriate therapy-delayed initiation of appropriate therapy (■; p=0.0083 and 0.0051, respectively). After VAP onset, the CPIS was the same at the VAP+3 time point for both groups.
What Does “Optimizing” Mean?

- Choosing the right drug
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Can We Use Pharmacokinetic/Pharmacodynamic Principles To Improve Adequacy of Therapy?

T > MIC to be bactericidal: 60-70% cephalosporins; 50% PCNs; 40% carbapenems
Target a steady state concentration of 4X MIC during continuous infusion
Factors Affecting Clinical Success In Pneumonia Therapy

Lippman et al. Curr Opin Infect Dis 2013, in press

**Antibiotic administration**
- Protein binding
- Intra-pulmonary penetration
- Drug $V_d$
- Drug CL

**ELF concentrations**
- PK-PD characteristics
- Bacterial susceptibility

**Microbiological success (bacterial kill)**
- Admission diagnosis
- Functional reserve
- Associated non-pulmonary organ dysfunction
- Immune mediated lung damage
- Ventilator induced lung injury
- Ancillary interventions
- Non-pulmonary complications

**Clinical Success**
FACTORS AFFECTING ANTIBIOTIC CONCENTRATIONS IN THE LUNG

- Penetration, Protein Binding, Volume of Distribution (Vd), Clearance
  - Often enhanced renal clearance (beta-lactams) in hyperdynamic septic patients (ARC, augmented renal clearance)
  - Volume of distribution > 3L means concentration outside of plasma
    - Lipophilic drugs have a high Vd
    - Hydrophilic drugs expand their Vd with sepsis and “leaky capillaries” (can underdose)
    - Obesity: If use IBW can underdose (esp lipophilic drugs). Generally use TBW, BUT if calculate dose on TBW can overdose hydrophilic drugs (extracellular water does not expand as much).
  - Free drug is active and thus with low serum proteins, may increase BOTH Vd and Clearance
Meta-Analysis of CI or Extended Infusion vs. Intermittent Infusion

- 14 studies of Pip/tazobactam or carbapenems
- Mostly non-randomized, but a mortality benefit overall and for pneumonia
- Greater benefit for pip/taz than carbapenems by CI or EI

Falagas ME, et al. CID 2013; 56:272-282
Using Pk/PD Principles DID NOT Reduce VAP Therapy Duration

- 227 patients in prospective, randomized, double blind study of 7 days of 1 gram doripenem over 4 hours q 8h vs. 10 days of 1 gram imipenem over 1 hour q 8h

- 7 day therapy with sig less clinical cure and higher 28 day mortality, esp with P. aeruginosa

No Benefit From Prolonged Infusion When Dose NOT Optimized and Little Resistance

- Before and after comparison of two time periods with 30 minute infusion vs. 3 hour infusion of pip/taz, cefepime, carbapenem
- Same dosing with prolonged inf.
- Few highly resistant organisms
- 242 intermittent, 261 prolonged infusion
- Treatment success the same in both groups (56% vs 51%). Same mortality
High Dose Tigecycline: Proof of Concept

• Tigecycline monotherapy for HAP/VAP: 100 mg load and 50 mg q 12 not comparable to imipenem. Freire et al. Diag Microbiol Infect Dis 2010; 68: 140-51
  – Maybe need higher dose

• Phase 2 study of tigecycline 200 mg load and 100 mg q12h vs. 150 mg load and 75 mg q12h vs. imipenem 1 gm q 8h
  – 75 sites, 105 patients, 68 clin eval.
  – 5 Tigecycline pts with Acinetobacter
  – 41 VAP, others HAP
  – Clinical response 10-21 days post rx: 85% vs. 69% vs. 75% No safety signal

• Ramirez J, et al. AAC 2013; 57:1756

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Tigecycline (75 mg)</th>
<th>Tigecycline (100 mg)</th>
<th>Imipenem/ cilastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-VAP</td>
<td>11/16 (68.8)</td>
<td>11/13 (84.6)</td>
<td>11/15 (73.3)</td>
</tr>
<tr>
<td>VAP</td>
<td>5/7 (71.4)</td>
<td>6/7 (85.7)</td>
<td>7/9 (77.8)</td>
</tr>
</tbody>
</table>
What Does “Optimizing” Mean?

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Is Shorter Better?? Sometimes
Using Procalcitonin To Reduce Duration of CAP, VAP and ICU Infection Therapy

- **PRORATA trial**: Prospective, multicenter, open label trial of PCT to guide duration of therapy for infection in the ICU
  - 307 PCT with algorithm: < 0.25, < 0.5, < 1.0, > 1.0 mcg/L
  - 314 control. Recommended 15 days rx. for VAP due to P. aeruginosa or if inappropriate initial therapy or immune suppressed

- PCT with similar mortality but more days without antibiotics. Absolute difference of 2.7 days.

<table>
<thead>
<tr>
<th>Days without antibiotics/number of patients</th>
<th>Absolute difference (days; 95% CI)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control group</strong></td>
<td><strong>Procalcitonin group</strong></td>
<td></td>
</tr>
<tr>
<td>Overall population</td>
<td>11.6/314</td>
<td>14.3/307</td>
</tr>
<tr>
<td>Prespecified analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community-acquired</td>
<td>12.0/173</td>
<td>15.3/153</td>
</tr>
<tr>
<td>Hospital-acquired</td>
<td>11.0/141</td>
<td>13.3/154</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12.0/248</td>
<td>14.8/232</td>
</tr>
<tr>
<td>No</td>
<td>9.7/66</td>
<td>12.8/75</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9.4/51</td>
<td>13.0/47</td>
</tr>
<tr>
<td>No</td>
<td>12.0/263</td>
<td>14.5/260</td>
</tr>
<tr>
<td>Algorithm adherence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10.4/173</td>
<td>13.6/145</td>
</tr>
<tr>
<td>No</td>
<td>13.0/141</td>
<td>15.0/162</td>
</tr>
</tbody>
</table>

* p values for each subgroup comparison to PCT group
Meta-Analysis of Duration of Therapy for VAP

- 4 RCTs of short (7-8 days) vs. long (10-15 days) rx VAP
  - No mortality difference
  - More antibiotic free days with short duration (3.4 days)
  - Trend to more relapse (non-fermenting GNB) with short duration

![Study or Subgroup Cochrane Review Table]

**FIGURE 2. ORs of mortality. Vertical line is the “no difference” point in mortality between the two arms.**
What Does “Optimizing” Mean?

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Antimicrobial Stewardship

• Multidisciplinary approach: ID, pharmacy, microbiology, epidemiology, (CRITICAL CARE: NOT MENTIONED)

• 2 CORE STRATEGIES
  – Prospective audit with intervention and feedback (A-I)
  – Formulary restriction and preauthorization to control resistance (B-II)

• Supplemental strategies
  – Education
  – Guidelines with local microbiology (A-I)
  – Antimicrobial cycling (C-II)
  – Antibiotic order forms (B-II), Combination therapy (C-II)
  – De-escalation (A-II)
  – Dose optimization (A-II)
  – IV to oral conversion (A-III)

• Dellit TH, et al. CID 2007; 44: 159-77
Correlates of De-Escalation Frequency

- Reported rates in VAP vary from 22% to 74%
  - Highest rates with a protocol vs. usual care
  - Higher rates if initial therapy appropriate
  - Unclear if diagnostic method has any impact on de-escalation
  - Rates are often higher if cultures are positive vs. negative
  - Lower rates of de-escalation with initial monotherapy/limited spectrum/early onset vs. broad spectrum / multidrug/late onset
  - Lower rates of de-escalation if high frequency of MDR pathogens

Benefits of De-Escalation in Septic Shock: Mortality as an Effect

- 712 with sepsis or septic shock, 628 evaluable (no early death)
- 34.9% de-escalation
- Mortality predictors: septic shock, SOFA score, inadequate rx. De-escalation was PROTECTIVE.
- De-escalation also protective if apply propensity score or if only look at those with appropriate rx.

<table>
<thead>
<tr>
<th></th>
<th>Total cohort (n = 628)</th>
<th>Cohort with adequate empirical antimicrobial therapy (n = 403)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted by PS OR (95 % CI)</td>
<td>p</td>
</tr>
<tr>
<td>SOFA day of culture results</td>
<td>1.11 (1.04–1.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Septic shock</td>
<td>1.70 (1.03–2.84)</td>
<td>0.043</td>
</tr>
<tr>
<td>Inadequate empirical treatment</td>
<td>2.03 (1.06–3.84)</td>
<td>0.030</td>
</tr>
<tr>
<td>De-escalation</td>
<td>0.55 (0.32–0.98)</td>
<td>0.022</td>
</tr>
</tbody>
</table>
Optimizing Therapy after Culture Data Are Available (72 hours)

- Nair GB, Niederman MS. Intensive Care Med 2015; 41:34-48
Combination with Aerosolized Amikacin To Reduce Duration of Systemic Antibiotics?

- Prospective randomized, controlled trial of ADJUNCTIVE aerosolized amikacin 400 mg BID vs. QD vs. placebo, all with systemic antibiotics
- 49.1% with P. aeruginosa or Acinetobacter baumanii.
- Use of proprietary Pulmonary Dose Delivery System (Nektar)
- Up to day 7: antibiotics were added (escalated) in 14%, 38% and 58% of the patients in the q12 h, q24h, and placebo groups, The remainder in each group had antibiotics either stopped or subtracted (de-escalated).

End= Mean of 7 days
Can Use of Inhaled Antibiotics REDUCE MDR Pathogen Rates?

- Double –blind placebo-controlled trial for therapy of RTI (CPIS >6, purulent secretions: VAT + VAP) of aerosol antibiotics (AA) x 14 days or until extubation
- Inhaled vanco, gent or both per Gram stain. All AA pts got systemic therapy also. Same amount both groups.
- Aerosol (n=24) or Placebo (n=18)
- AA with more eradication of initial organisms and of resistant organisms at EOT; more drop in CPIS and secretion volume
- At EOT, no new resistance to aerosol, more to systemic in placebo than AA group
- Palmer LB, Smaldone GC. AJRCCM 2014; 189:1225-1233

<table>
<thead>
<tr>
<th>Table 5: Systemic Antibiotics and New Resistance during Aerosol Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with New Resistance during Treatment</strong></td>
</tr>
<tr>
<td><strong>Patients</strong></td>
</tr>
<tr>
<td>AA (n = 16)</td>
</tr>
<tr>
<td>1 Placebo (n = 11)</td>
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*P value*, 0.03

Definition of abbreviations: AA = aerosolized antibiotics; MRSA = methicillin-resistant Staphylococcus aureus; PA = Pseudomonas aeruginosa; VRE = vancomycin-resistant enterococcus. Data from patients with serial cultures throughout the study. *Fisher exact test.*
Conclusions

- Optimizing current therapies (no real new therapies)
  - Use the right drug: Guidelines (local modifications), empiric combination therapy, specific therapy for Acinetobacter MRSA
  - Avoiding delays in therapy
  - Optimal doses
    - Prolonged infusions, high doses for MDR pathogens (eg. Tigecycline)
  - Correct duration of therapy: ? biomarkers
- Avoid resistance promotion
  - De-escalation
    - More evidence that it can be done if negative cultures
  - Adjunctive aerosol therapy in VAP