Objectives

• Identify a dose and frequency of administration to optimize benefit and minimize toxicity of anti-pseudomonal antibiotics
• List two pharmacokinetic (PK)/pharmacodynamic (PD) advantages of continuous infusion (CI) versus intermittent antibiotics
• Describe an antibiotic dosing regimen to treat non-pseudomonal CF pathogens
Defective CF gene → Defective CFTR → Thick viscous secretions → Bronchial Obstruction → Activation of airway inflammatory cells (PMNs) → Infection → Inflammation → Bronchiectasis

Acute Pulmonary Exacerbations

**Symptoms**
- Increased frequency and duration of cough
- Increased sputum production
- Change in appearance of sputum
- Increased shortness of breath
- Decreased exercise tolerance
- Decreased appetite
- Feeling of increased congestion in the chest

**Signs**
- Increased respiratory rate
- Use of accessory muscles for breathing
- Intercostal retractions
- Change in results of auscultatory examination of chest
- Decline in measures of pulmonary function consistent with the presence of obstructive airway disease
- Fever and leukocytosis
- Weight loss
- New infiltrate on chest radiograph

Cystic Fibrosis Module #3: Management of Acute Pulmonary Exacerbations: Pseudomonas and Beyond

Acute Pulmonary Exacerbations

- Most common cause of morbidity and mortality
- Lead to hospital admissions and treatment with IV antibiotics
- Standard therapy is treatment with two IV antibiotics for 10-14 days


Pseudomonas aeruginosa

- Non-lactose fermenting gram negative bacillus (rod)
- 2 subtypes
  - Non-mucoid
  - Mucoid (forms biofilms)
- Lives in moist environments and hospitals
Acute Pulmonary Exacerbation due to *Pseudomonas aeruginosa*

- Inpatient management
  - Intravenous anti-pseudomonal antibiotics
- Outpatient management
  - Oral and inhaled antibiotics
Inpatient Antibiotic Strategies

• Combination therapy (Beta lactam + aminoglycoside) that targets *P. aeruginosa* is recommended for empiric treatment of pulmonary exacerbations
  – Enhance activity
  – Reduce selection of resistance
• Combination ≠ Single agent in treatment of exacerbations


What is a Beta-Lactam?

- Aztreonam
- Cefepime
- Ceftazidime
- Doripenem
- Imipenem
- Meropenem
- Piperacillin
- Ticarcillin*
Anti-Pseudomonal Antibiotic Mechanisms of Action

Pharmacodynamics (PD) of Anti-pseudomonal Antibiotics

Cystic Fibrosis Module #3: Management of Acute Pulmonary Exacerbations: Pseudomonas and Beyond

FDA-approved Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Class</th>
<th>Dose (mg/kg/day)</th>
<th>Dose Interval (hrs)</th>
<th>Adult Maximum Dose (gm/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam</td>
<td>Monobactam</td>
<td>90-120</td>
<td>6-8</td>
<td>8</td>
</tr>
<tr>
<td>Cefepime</td>
<td>Cephalosporin</td>
<td>150</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Cephalosporin</td>
<td>150</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Ceftolozane</td>
<td>Cephalosporin</td>
<td>1000 mg</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Doripenem</td>
<td>Carbapenem</td>
<td>500 mg</td>
<td>8</td>
<td>1.5</td>
</tr>
<tr>
<td>Imipenem-cilastatin</td>
<td>Carbapenem</td>
<td>60-100</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Meropenem</td>
<td>Carbapenem</td>
<td>60-120</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>Penicillin</td>
<td>240-300</td>
<td>6-8</td>
<td>12-16</td>
</tr>
<tr>
<td>Ticarcillin-clavulanate</td>
<td>Penicillin</td>
<td>200-300</td>
<td>4-6</td>
<td>12-18</td>
</tr>
</tbody>
</table>

Anti-Pseudomonal Beta-Lactam Utilization in CF

A Survey of the Utilization of Anti-Pseudomonal Beta-Lactam Therapy in Cystic Fibrosis Patients

Cystic Fibrosis Module #3: Management of Acute Pulmonary Exacerbations: Pseudomonas and Beyond

Anti-Pseudomonal Beta-Lactam Utilization in CF

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosing Strategy</th>
<th>Pediatric Dose</th>
<th>Adult Dose</th>
<th>Maximum Daily Dose (grams/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam</td>
<td>Intermittent</td>
<td>150 mg/kg/day div every 8 hrs</td>
<td>2 grams every 8 hrs</td>
<td>8</td>
</tr>
<tr>
<td>Cefepime</td>
<td>Intermittent</td>
<td>150-200 mg/kg/day div every 6-8 hrs</td>
<td>1.5-2 grams every 6-12 hrs</td>
<td>8</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Intermittent</td>
<td>100-300 mg/kg/day div every 6-12 hrs</td>
<td>2-3 grams every 4-12 hrs</td>
<td>12</td>
</tr>
</tbody>
</table>
### Doses Utilized in U.S.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosing Strategy</th>
<th>Pediatric Dose</th>
<th>Adult Dose</th>
<th>Maximum Daily Dose (grams/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meropenem</td>
<td>Intermittent</td>
<td>60-120 mg/kg/day div every 8 hrs</td>
<td>1-2 grams every 8 hrs</td>
<td>6</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>Intermittent</td>
<td>200-600 mg/kg/day div every 6-8 hrs</td>
<td>3-4 grams every 6-8 hrs</td>
<td>24</td>
</tr>
<tr>
<td>Ticarcillin-clavulanate</td>
<td>Intermittent</td>
<td>300-400 mg/kg/day div every 4-6 hrs</td>
<td>3 grams every 6 hrs</td>
<td>24</td>
</tr>
</tbody>
</table>


### Intermittent Beta-lactams in CF

- WHY are CF recommended > FDA-approved doses?
PK of Intermittent Beta-lactams in CF

- Larger volume of distribution
- Shorter half-life
- Increased total body clearance
- Increased renal clearance
- Smaller Area under the Curve
- Lower peak concentrations

### Evidence-Based Dosing Summary

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Class</th>
<th>Dose (mg/kg/day)</th>
<th>Dose Interval (hrs)</th>
<th>Adult Maximum Dose (gm/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam</td>
<td>Monobactam</td>
<td>200-300</td>
<td>6</td>
<td>8-12</td>
</tr>
<tr>
<td>Cefepime</td>
<td>Cephalosporin</td>
<td>150-200</td>
<td>6-8</td>
<td>6-8</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Cephalosporin</td>
<td>200-400 CI: 100-200</td>
<td>6-8</td>
<td>8-12</td>
</tr>
<tr>
<td>Doripenem</td>
<td>Carbapenem</td>
<td>90</td>
<td>8, infused over 4 hrs</td>
<td>6</td>
</tr>
<tr>
<td>Imipenem-cilastatin*</td>
<td>Carbapenem</td>
<td>100</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Meropenem</td>
<td>Carbapenem</td>
<td>120</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Piperacillin-tazobactam*</td>
<td>Penicillin</td>
<td>350-600</td>
<td>4</td>
<td>18-24</td>
</tr>
<tr>
<td>Ticarcillin-clavulanate</td>
<td>Penicillin</td>
<td>400-750</td>
<td>6</td>
<td>24-30</td>
</tr>
</tbody>
</table>

*Major limitations for routine use

*Zobell JT et al., Pediatr Pulmonol. 2013*
Question?

• Will these dosing recommendations be effective in the treatment of a CF patient with a higher MIC isolate?

Efficacy Evidence of CI Beta-lactams in CF

• CFF Pulmonary Guidelines do not recommend routine use
Cystic Fibrosis Module #3: Management of Acute Pulmonary Exacerbations: Pseudomonas and Beyond

Anti-Pseudomonal Beta-Lactam Utilization in CF

### TABLE 2—Dosing Regimens for Each Anti-Pseudomonal Beta-Lactam

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosing Strategy</th>
<th>Pediatric Dose</th>
<th>Adult Dose</th>
<th>Maximum Daily Dose (grams/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefepime</td>
<td>Continuous</td>
<td>200 mg/kg/day</td>
<td>6 grams</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Extended</td>
<td>NR</td>
<td>2 grams over 4 hrs every 8 hrs</td>
<td>6</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Continuous</td>
<td>150 mg/kg/day</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Extended</td>
<td>2 grams over 3 hrs every 8 hrs</td>
<td>2 grams over 3 hrs every 8 hrs</td>
<td>6</td>
</tr>
</tbody>
</table>

1 Antibiotic administered at a dose lower than CFF and European recommendations.
2 Antibiotic administered at a dose equal or greater than CFF and European recommendations.

Cystic Fibrosis Module #3: Management of Acute Pulmonary Exacerbations: Pseudomonas and Beyond

Doses Utilized in U.S.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosing Strategy</th>
<th>Pediatric Dose</th>
<th>Adult Dose</th>
<th>Maximum Daily Dose (grams/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meropenem</td>
<td>Extended</td>
<td>NR</td>
<td>2 grams over 3 hrs every 8 hrs</td>
<td>6</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>Extended</td>
<td>NR</td>
<td>3 grams over 4 hrs every 8 hrs</td>
<td>12-16</td>
</tr>
<tr>
<td>Ticarcillin-clavulanate</td>
<td>Continuous</td>
<td>NR</td>
<td>18.6-55.8</td>
<td>55.8</td>
</tr>
</tbody>
</table>

Studies with CI/EI Beta-Lactams in CF

- Ceftazidime (n=9)
- Cefepime (n=1; PK only)
- Piperacillin/tazobactam (n=2)
- Aztreonam (n=1)
- Ticarcillin/clavulanate (n=1)
- Meropenem (n=2)
- Doripenem (n=1)

Ceftazidime CI

- Multicenter, randomized, cross-over study
  - Comparing CI Ceftazidime + tobramycin vs. Short Infusions (SI) Ceftazidime (q 8 hrs) + tobramycin for acute exacerbations of chronic *P. aeruginosa* (PA) infection
- 70 patients (≥ 8 years of age, chronic PA, ≥ 2 IV courses of antibiotics for exacerbations) randomized

Ceftazidime CI

• Conclusion
  – The combo of CI Ceftazidime & OD Tobramycin appears safe and as effective as 3 x's/day ceftazidime SI.
Cystic Fibrosis Module #3: Management of Acute Pulmonary Exacerbations: Pseudomonas and Beyond

Anti-Pseudomonal Beta-Lactam Utilization in CF: Follow-up

Follow-Up Survey of the Utilization of Anti-Pseudomonal Beta-Lactam Antibiotics at U.S. Cystic Fibrosis Centers

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Cefepime</td>
<td>3</td>
<td>2</td>
<td>20</td>
<td>18</td>
<td>3</td>
<td>4</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>56</td>
<td>38</td>
<td>14</td>
<td>12</td>
<td>4</td>
<td>10</td>
<td>74</td>
<td>60</td>
</tr>
<tr>
<td>Meropenem</td>
<td>9</td>
<td>0</td>
<td>11</td>
<td>5</td>
<td>1</td>
<td>7</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>Piperacillin- tazobactam</td>
<td>18</td>
<td>8</td>
<td>14</td>
<td>10</td>
<td>3</td>
<td>10</td>
<td>35</td>
<td>28</td>
</tr>
<tr>
<td>Ticarcillin- clavulanate</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>90</td>
<td>51</td>
<td>65</td>
<td>47</td>
<td>12</td>
<td>33</td>
<td>167</td>
<td>130</td>
</tr>
</tbody>
</table>
Cystic Fibrosis Module #3: Management of Acute Pulmonary Exacerbations: Pseudomonas and Beyond

**Antibiotic Dosing Strategy**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Pediatric Dosing</th>
<th>Adult Dosing</th>
<th>Maximum Daily Dose (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam</td>
<td>NR</td>
<td>NR</td>
<td>8</td>
</tr>
<tr>
<td>Cefepime</td>
<td>150-200 mg/kg/day div every 6-8 hr</td>
<td>2 g every 8-12 hr</td>
<td>2-6</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>100-300 mg/kg/day div every 6-8 hr</td>
<td>2-4 g every 8 hr</td>
<td>12</td>
</tr>
<tr>
<td>Meropenem</td>
<td>NR</td>
<td>2 g every 8 hr</td>
<td>6</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>100-600 mg/kg/day div every 6-8 hr</td>
<td>100-600 mg/kg/day every 4-6 hr</td>
<td>12-24</td>
</tr>
<tr>
<td>Ticarcillin-clavulanate</td>
<td>300-600 mg/kg/day div every 6-8 hr</td>
<td>NR</td>
<td>24</td>
</tr>
</tbody>
</table>


**Anti-Pseudomonal Beta-Lactam Utilization in CF: Follow-up**

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Cefepime</td>
<td>3</td>
<td>2</td>
<td>20</td>
<td>18</td>
<td>3</td>
<td>4</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>56</td>
<td>39</td>
<td>14</td>
<td>12</td>
<td>4</td>
<td>10</td>
<td>74</td>
<td>60</td>
</tr>
<tr>
<td>Meropenem</td>
<td>9</td>
<td>0</td>
<td>11</td>
<td>5</td>
<td>1</td>
<td>7</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>18</td>
<td>8</td>
<td>14</td>
<td>10</td>
<td>3</td>
<td>10</td>
<td>35</td>
<td>28</td>
</tr>
<tr>
<td>Ticarcillin-clavulanate</td>
<td>3</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>51</td>
<td>65</td>
<td>47</td>
<td>12</td>
<td>33</td>
<td>167</td>
<td>130</td>
</tr>
</tbody>
</table>

**25% vs. 7% of respondents utilize “extended infusion” dosing (p<0.004)**

Cystic Fibrosis Module #3: Management of Acute Pulmonary Exacerbations: Pseudomonas and Beyond

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosing strategy</th>
<th>Pediatric dose</th>
<th>Adult dose</th>
<th>Maximum daily dose (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefepime</td>
<td>EI</td>
<td>NR</td>
<td>1-4 g over 4 hr every 8-12 hr</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>CI</td>
<td>150 mg/kg/day over 24 hr</td>
<td>NR</td>
<td>6</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>EI</td>
<td>300-400 mg/kg/day over 3-4 hr every 6-12 hr</td>
<td>2-4 g over 3-4 hr every 6-8 hr</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>CI</td>
<td>NR</td>
<td>NR</td>
<td>8</td>
</tr>
<tr>
<td>Meropenem</td>
<td>EI</td>
<td>NR</td>
<td>2 g over 2-4 hr every 8-12 hr</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>CI</td>
<td>NR</td>
<td>2 g over 8 hr every 8 hr</td>
<td>6</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>EI</td>
<td>150-400 mg/kg/day over 4 hr every 6-8 hr</td>
<td>4.5 g over 4 hr every 6-8 hr</td>
<td>12-16</td>
</tr>
</tbody>
</table>

Fischer et al., Pediatr Pulmonol. 2015.

**Antibiotic Strategies**

- Combination therapy (Beta lactam + aminoglycoside) that targets *P. aeruginosa* is recommended for empiric treatment of pulmonary exacerbations
  - Enhance activity
  - Reduce selection of resistance
- Combination ≠ Single agent in treatment of exacerbations

What are the anti-pseudomonal aminoglycosides?

- Amikacin
- Gentamicin
- Tobramycin

Anti-Pseudomonal Antibiotic Mechanisms of Action
Pharmacodynamics (PD) of Anti-pseudomonal Antibiotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Class</th>
<th>Dose (mg/kg/day)</th>
<th>Dose Interval (hrs)</th>
<th>Adult Maximum Dose (gm/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Aminoglycoside</td>
<td>15</td>
<td>8-12</td>
<td>1.5</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Aminoglycoside</td>
<td>3-7.5</td>
<td>8-12</td>
<td>NA</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Aminoglycoside</td>
<td>10</td>
<td>6</td>
<td>NA</td>
</tr>
</tbody>
</table>
Anti-Pseudomonal Aminoglycoside Utilization in CF

- 61-94.3% of CFF-accredited centers reported to use aminoglycosides in all patients
- 95.5% reported to use aminoglycosides in combination with beta-lactams

Anti-Pseudomonal Aminoglycoside Utilization in CF

- 61-98.5% of respondents utilize “once-daily” dosing of tobramycin (10 mg/kg/day)
- 34.4-42.4% utilize once daily amikacin (30 mg/kg/day)
- 20.3-25.8% utilize once daily gentamicin (10 mg/kg/day)
Cystic Fibrosis Module #3: Management of Acute Pulmonary Exacerbations: Pseudomonas and Beyond

CF Pulmonary Exacerbation Guidelines

TABLE 2. EVALUATION OF THE EVIDENCE

<table>
<thead>
<tr>
<th>Question</th>
<th>Studies</th>
<th>N</th>
<th>Categorization</th>
<th>Magnitude of Benefit</th>
<th>Grade of Recommendation</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of treatment*</td>
<td>1 RCT(7)</td>
<td>17</td>
<td>Low</td>
<td>Insufficient evidence that hospital and home treatment are equivalent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic therapies simultaneous use of inhaled and IV antibiotics</td>
<td>9</td>
<td>0</td>
<td>Low</td>
<td>Insufficient evidence to recommend for or against simultaneous use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Airway clearance therapies</td>
<td>17 RCT(13-41)</td>
<td>768</td>
<td>Low</td>
<td>Continue current practices</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminoglycoside dosing*</td>
<td>4 RCT(21, 31-33)</td>
<td>349</td>
<td>Moderate</td>
<td>Small</td>
<td>Once-daily dosing is acceptable for treatment of Pseudomonas</td>
<td></td>
</tr>
<tr>
<td>Continuous infusions</td>
<td>1 RCT(1)</td>
<td>5</td>
<td>Low</td>
<td>Insufficient evidence to recommend for daily versus three times a day dosing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of antibiotics*</td>
<td>1 RCT(10)</td>
<td>34</td>
<td>Low</td>
<td>Insufficient evidence to define optimal duration of antibiotics</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Moore et al., J Infect Dis. 1987

Clinical response to Aminoglycosides

Response rate (%) vs. Maximum Peak/ MIC ratio

Moore et al. J Infect Dis. 1987
Cystic Fibrosis Module #3: Management of Acute Pulmonary Exacerbations: Pseudomonas and Beyond

Pharmacodynamics of Aminoglycosides in CF


Pharmacodynamics of Aminoglycosides in CF

Literature for Once Daily Aminoglycosides in CF

• Tobramycin
  – 10 PK studies (7-15 mg/kg/day)
  – 7 PD studies (7-15 mg/kg/day)
  – 5 efficacy studies (9-10 mg/kg/day)
  – Cochrane Review (Smyth et al. updated in 2014)

• Amikacin
  – 4 PK studies (30-35 mg/kg/day)
  – 1 PD study (35 mg/kg/day)
  – 1 efficacy/tolerability study (35 mg/kg/day)

• Gentamicin
  – None
Smyth et al.

- Multi-centered, double-blind, randomized, control study
  - Comparing once versus three-times daily tobramycin treatment for pulmonary exacerbations of CF
- 244 patients (≥ 5 years of age, +PA at least once that was sensitive to tobramycin, ceftazidime, or both)

Smyth et al.

[Graph showing % Δ FEV1 for different groups and dosage frequencies]

Smyth et al. Lancet. 2005
Smyth et al.

- Conclusion: IV tobramycin has equal efficacy if given once or three-times daily (with ceftazidime) for pulmonary exacerbations of CF. The once daily might be less nephrotoxic in children.
Evidence-Based Dosing Summary

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Class</th>
<th>Dose (mg/kg/day)</th>
<th>Dose Interval (hrs)</th>
<th>Adult Maximum Dose (gm/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Aminoglycoside</td>
<td>30-35</td>
<td>24</td>
<td>Peak range: 80-120 mg/L Trough &lt; 1 mg/L</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Aminoglycoside</td>
<td>Not recommended for routine use</td>
<td>Not recommended for routine use</td>
<td>Not recommended for routine use</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Aminoglycoside</td>
<td>10</td>
<td>24</td>
<td>Peak range: 20-40 mg/L Trough: &lt; 1 mg/L</td>
</tr>
</tbody>
</table>


Fluoroquinolones & Colistimethate

Ciprofloxacin

Levofloxacin

Colistimethate sodium

FDA-approved package inserts
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Anti-Pseudomonal Antibiotic Mechanisms of Action

Pharmacodynamics (PD) of Anti-pseudomonal Antibiotics
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FDA-approved Dosing

<table>
<thead>
<tr>
<th>Drug</th>
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<th>Dose (mg/kg/day)</th>
<th>Dose Interval (hrs)</th>
<th>Adult Maximum Dose (gm/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>Fluoroquinolone</td>
<td>30</td>
<td>8-12</td>
<td>1.2</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Fluoroquinolone</td>
<td>750 mg</td>
<td>24</td>
<td>750 mg</td>
</tr>
<tr>
<td>Colistimethate sodium</td>
<td>Polymixin</td>
<td>2.5-5</td>
<td>6-12</td>
<td>300 mg/day (colistin base)</td>
</tr>
</tbody>
</table>

Anti-Pseudomonal Fluoroquinolone & Colistimethate Utilization in CF

- 1.5% of respondents to survey by Prescott utilize ciprofloxacin in combination with aminoglycoside
- No utilization rates for colistimethate sodium
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Evidence-Based Dosing Summary

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<tr>
<th>Drug</th>
<th>Drug Class</th>
<th>Dose (mg/kg/day)</th>
<th>Dose Interval (hrs)</th>
<th>Adult Maximum Dose (gm/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin oral</td>
<td>Fluoroquinolone</td>
<td>40</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Ciprofloxacin IV</td>
<td>Fluoroquinolone</td>
<td>30</td>
<td>8</td>
<td>1.2</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Fluoroquinolone</td>
<td>Insufficient evidence for recommendations</td>
<td>Insufficient evidence for recommendations</td>
<td></td>
</tr>
<tr>
<td>Colistimethate sodium (CMS)</td>
<td>Polymixin</td>
<td>8</td>
<td>8</td>
<td>480 mg/day (CMS)</td>
</tr>
</tbody>
</table>

Outpatient Management

- Oral anti-pseudomonal antibiotics
  - Fluoroquinolones (Ciprofloxacin and Levofloxacin)
- Inhaled antibiotics
  - Tobramycin
  - Aztreonam
**Staphylococcus aureus**

- Gram positive cocci in clusters
- Two species
- Methicillin-susceptible *S. aureus* (MSSA)
- Methicillin-resistant *S. aureus* (MRSA)

Cystic Fibrosis Foundation Patient Registry, 2014 Annual Data Report
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MRSA vs. MSSA in CF

- Associated with worse lung function
- Rapid lung function decline
- Increased risk of not recovering baseline lung function after an exacerbation
- Worse survival

MRSA in CF

- High rate of *P. aeruginosa* co-infection
- Increased visits to outpatient clinic
- More pulmonary exacerbations requiring antibiotics (IV/inhaled)


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Treatment Strategies

• Vary based on MSSA vs. MRSA
• Limited dosing information from literature for anti-staphylococcal antibiotics
• Guidelines from UK CF Trust
• No CFF guidelines exist

MSSA: Outpatient

• Amoxicillin/clavulanate:
  – 80-100 mg/kg/day div BID; max 4 grams/day
• Cefuroxime:
  – 30 mg/kg/day div BID; max 1 g/day
• Sulfamethoxazole/trimethoprim:
  – 8-12 mg/kg/day div TID; max 480 mg/day
• Clindamycin:
  – 40 mg/kg/day div every 8 hrs, max 1.8 gram/day
• Cephalexin:
  – 100 mg/kg/day div every 6-8 hrs, max 4 gram/day
MSSA Inpatient

- No standard guidelines exist
- All anti-pseudomonal beta-lactams have some degree of activity vs. MSSA
  - Piperacillin-tazobactam, Cefepime, Meropenem > Ceftazidime
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### MRSA Antibiotic Dosing-oral

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Pediatric utilization (%)</th>
<th>Adult utilization (%)</th>
<th>Reported pediatric dose&lt;sup&gt;a&lt;/sup&gt; (mg/kg/day)</th>
<th>Reported adult dose&lt;sup&gt;a&lt;/sup&gt; (mg)</th>
<th>Reported max dose&lt;sup&gt;a&lt;/sup&gt; (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfasulfadiazine</td>
<td>80 (31)</td>
<td>80 (38.7)</td>
<td>5-10 divided every 8-12 hr</td>
<td>160-330 every 8-24 hr</td>
<td>960</td>
</tr>
<tr>
<td>Linezolid</td>
<td>77 (28)</td>
<td>83 (28.1)</td>
<td>5-10 divided every 8-12 hr</td>
<td>600 every 8-12 hr</td>
<td>1800</td>
</tr>
<tr>
<td>Doca/ TMP</td>
<td>77 (11)</td>
<td>78 (16.8)</td>
<td>2-5 divided every 12-24 hr</td>
<td>100-200 every 12-24 hr</td>
<td>400</td>
</tr>
<tr>
<td>Minocycline</td>
<td>5 (5)</td>
<td>17 (5.1)</td>
<td>4 divided every 12-24 hr</td>
<td>10-40 divided every 12 hr</td>
<td>240</td>
</tr>
<tr>
<td>Sulfasulfadiazine</td>
<td>7 (10)</td>
<td>17 (3.7)</td>
<td>4 divided every 12 hr</td>
<td>10-40 divided every 12 hr</td>
<td>240</td>
</tr>
<tr>
<td>Rifampin</td>
<td>12 (41)</td>
<td>17 (5.7)</td>
<td>30-50 divided every 12 hr</td>
<td>500-1000 every 12 hr</td>
<td>2250</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>10 (33)</td>
<td>15 (5.1)</td>
<td>10-30 divided every 12-24 hr</td>
<td>500-750 every 12-24 hr</td>
<td>1500</td>
</tr>
<tr>
<td>Doca/TMP</td>
<td>4 (14)</td>
<td>7 (2.5)</td>
<td>2-4 divided every 12 hr</td>
<td>10-100 divided every 12 hr</td>
<td>750</td>
</tr>
<tr>
<td>Doca/TMP</td>
<td>15 (5)</td>
<td>30 (1.3)</td>
<td>2-4 divided every 12 hr</td>
<td>10-100 divided every 12 hr</td>
<td>750</td>
</tr>
</tbody>
</table>


### MRSA Antibiotic Dosing-IV

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Pediatric utilization (%)</th>
<th>Adult utilization (%)</th>
<th>Reported pediatric dose&lt;sup&gt;a&lt;/sup&gt; (mg/kg/day)</th>
<th>Reported adult dose&lt;sup&gt;a&lt;/sup&gt; (mg)</th>
<th>Reported max dose&lt;sup&gt;a&lt;/sup&gt; (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linezolid IV</td>
<td>35 (16)</td>
<td>44 (19)</td>
<td>5-30 divided every 8-12 hr</td>
<td>300-600 every 4-12 hr</td>
<td>1800</td>
</tr>
<tr>
<td>Vancomycin IV</td>
<td>30 (13)</td>
<td>31 (13)</td>
<td>5-20 divided every 6-12 hr</td>
<td>500-2000 every 6-12 hr</td>
<td>6000</td>
</tr>
<tr>
<td>Sulfasulfadiazine</td>
<td>28 (13)</td>
<td>33 (14)</td>
<td>6-20 divided every 8-12 hr</td>
<td>100-320 every 8-12 hr</td>
<td>960</td>
</tr>
<tr>
<td>Minocycline</td>
<td>9 (40)</td>
<td>9 (3.7)</td>
<td>10-20 divided every 12 hr</td>
<td>500-1200 every 12-24 hr</td>
<td>1200</td>
</tr>
<tr>
<td>Clindamycin IV</td>
<td>9 (44)</td>
<td>9 (3.7)</td>
<td>10-20 divided every 12 hr</td>
<td>500-1200 every 12-24 hr</td>
<td>1200</td>
</tr>
<tr>
<td>Doca/IV</td>
<td>1 (2.5)</td>
<td>1 (0.5)</td>
<td>2-5 divided every 12 hr</td>
<td>100 every 12 hr</td>
<td>200</td>
</tr>
<tr>
<td>Levofloxacin IV</td>
<td>7 (29)</td>
<td>5 (2)</td>
<td>10-20 divided every 12 hr</td>
<td>500-750 every 12-24 hr</td>
<td>1500</td>
</tr>
<tr>
<td>Ciprofloxacin IV</td>
<td>3 (1.3)</td>
<td>4 (1.7)</td>
<td>5-20 divided every 12 hr</td>
<td>1000 every 12 hr</td>
<td>3000</td>
</tr>
<tr>
<td>Rifampin IV</td>
<td>4 (1.8)</td>
<td>3 (1.3)</td>
<td>2 divided every 12 hr</td>
<td>100 every 12 hr</td>
<td>400</td>
</tr>
<tr>
<td>Doca/IV</td>
<td>2 (0.9)</td>
<td>5 (2)</td>
<td>17 divided every 12 hr</td>
<td>100 every 12 hr</td>
<td>200</td>
</tr>
<tr>
<td>Clindamycin IV</td>
<td>5 (2.3)</td>
<td>1 (0.4)</td>
<td>2-5 divided every 6 hr</td>
<td>100-600 every 12 hr</td>
<td>1200</td>
</tr>
<tr>
<td>Doca/IV</td>
<td>4 (1.8)</td>
<td>2 (0.8)</td>
<td>3-10 divided every 12 hr</td>
<td>300 every 12 hr</td>
<td>900</td>
</tr>
<tr>
<td>Levofloxacin IV</td>
<td>7 (29)</td>
<td>2 (0.8)</td>
<td>10-20 divided every 12 hr</td>
<td>500-1200 every 12 hr</td>
<td>1200</td>
</tr>
<tr>
<td>Ciprofloxacin IV</td>
<td>2 (0.9)</td>
<td>1 (0.4)</td>
<td>2-5 divided every 12 hr</td>
<td>100-600 every 12 hr</td>
<td>1200</td>
</tr>
<tr>
<td>Telavancin IV</td>
<td>0 (0)</td>
<td>1 (0.4)</td>
<td>20mg/kg/day divided every 12 hr</td>
<td>20mg/kg/day divided every 12 hr</td>
<td>200</td>
</tr>
</tbody>
</table>

Haemophilus influenzae

- Gram negative coccobacillus
- 2 different categories:
  - Encapsulated
  - Unencapsulated
- Causes upper respiratory tract infections
H. flu in CF

- Can form biofilms—pathogenic?
- Most clinics regard as pathogen, so treat
- No trials exist showing benefit of eradication
- No trials exist of antibiotic regimen
- Guidelines from UK CF Trust
- No CFF guidelines exist

H. flu: Outpatient

- Amoxicillin/clavulanate:
  - 80-100 mg/kg/day div BID; max 4 grams/day
- Cefuroxime:
  - 30 mg/kg/day div BID; max 1 g/day
- Cefdinir
  - 14 mg/kg/day div daily-BID; max 600 mg/day
H. flu: Inpatient

- No standard guidelines exist
- All anti-pseudomonal beta-lactams have some degree of activity vs. H. flu

Burkholderia cepacia complex

- Non-lactose fermenting gram negative rod
- 18 different species for the complex
  - B. cenocepacia
  - B. multivorans
  - B. vietamensis
- Lives in soil and water & moist enviroments
- Infections seen in patients who are immunocompromised

Regan KH, et al., Cochrane Database of Systematic Reviews. 2014.
B. cepacia complex in CF

- Very virulent
- Associated with increased morbidity and mortality
- May be transmitted from one CF patient to another
- Can cause “cepacia syndrome”—rapid progressive pneumonia and sepsis
- Can lead to unpredictable decline in lung function (mild to rapid deterioration)
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**Treatment of *B. cepacia* complex**

- Intrinsic resistance to tobramycin
- Can develop resistance to beta-lactams quickly
- No studies have been shown to eradicate or prevent/delay onset of chronic *B. cepacia* complex infection
- Some antibiotics have activity—follow susceptibilities

Regan KH, et al., Cochrane Database of Systematic Reviews. 2014.

**Non-tuberculosis Mycobacteria (NTM)**

- Acid-fast rod bacteria (AFB)
- 2 sub-species in CF
  - M. avium complex (MAC)
  - M. abscessus
- Live in moist, wet environments

NTM in CF

- Acquisition increases with age of patient
- Increases morbidity and mortality
- More rapid decline in lung function

International NTM Guidelines for CF

US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis

Other bacterial pathogens

- **Stenotrophomonas maltophilia**
  - Non-lactose fermenting gram negative rod
  - Loves moist, humid environments
  - Resistant to most antibiotics

- **Achromobacter xylosoxidans**
  - Non-lactose fermenting gram negative rod
  - Moist environments
  - Resistant to many antibiotics
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Other bacteria in CF

- **Stenotrophomonas**
  - Resistance is a major issue in CF
  - Antibiotic use has been shown to increase rate of S. maltophilia in CF
  - Risk factor for pulmonary exacerbations, but not decreased lung function or mortality
  - No guidelines on how to treat

- **Achromobacter**
  - Antibiotic resistance is an issue
  - Decrease in lung function, increase hospitalization rate
  - No guidelines on how to treat

Conclusions

• Optimization of antibiotics are necessary in the treatment of APE due to various bacteria
• Very few guidelines exist to direct antibiotic dosing
• Further studies are needed to determine efficacy/safety of antibiotics against CF pathogens