Application of PK/PD principles to RTIs

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Examples of correlations between PK/PD predictions and outcome in human studies

- Otitis media
- Sinusitis
- AECB
- CAP

Evaluation of new antibiotics

- Quinolones
- Telithromycin

Development of PK/PD based MIC breakpoints
Outpatient Clinical Studies in Respiratory Tract Infections

- High rates of spontaneous resolution make it difficult to show differences in efficacy between agents.
- The BEST objective measure of the effectiveness of an antibiotic is eradication of the pathogen from the site of infection.
- Bacteriologic outcome studies are not often performed due to necessity for invasive procedures to obtain specimens.
- Most studies are therefore designed to show equivalent clinical outcomes between established and new agents.
- Inadequacies of agents studied are therefore often not apparent.

There is a need for

- Statistically valid clinical studies
- Accurate prediction of efficacy
- Revised susceptibility breakpoints
- Newer dosage regimens
- Newer antibacterials
Outcomes in Trials of Antibacterial Drugs for AOM

Measure of outcome

- **Clinical**: Symptomatic improvement, or symptomatic and otoscopic improvement, etc.
- **Bacteriologic**: Eradication of bacteria
- **Bacteriologic/Clinical**: Clinical improvement plus eradication of bacteria in clinical failures

Timing of outcome

- During therapy
- End of therapy
- After therapy
Clinical versus Bacteriological Outcomes

Differentiating Between Antibiotics in AOM

- Bacteriologic outcome during therapy and clinical outcome at end of therapy have been shown to be the most useful time points to assess therapy.

- Outcome by day 30 (Test-of-Cure) shows no relationship to treatment due to frequent new viral and bacterial infections.

- Outcome is worse in patients with risk factors:
  - <2 years old
  - Prior AOM
  - Prior antibiotics
  - Daycare
  - Siblings

The Pollyanna Phenomenon

Comparison of three strategies for evaluating efficacy of antibacterial drugs for the treatment of AOM. For each hypothetical level of bacteriologic efficacy, calculated clinical efficacy rates are connected by solid line.

Sample sizes required to detect differences between antibacterial drugs for acute otitis media

Comparison of bacteriologic versus clinical outcomes in trials of two drugs (half the patients would be in each arm of a study)

Bacteriologic efficacy of drug A compared with drug B

No. of patients required to detect 60 vs. 90% bacteriologic efficacy*:
- Clinical/clinical: 1934
- Bacterial/clinical: 780 bacteriologically evaluable
- Bacterial/bacterial: 100 bacteriologically evaluable

Comparison of bacteriologic vs clinical outcomes in AOM

# Theoretical Clinical Impact of Drug Efficacy in USA

<table>
<thead>
<tr>
<th>Bacteriologic efficacy</th>
<th>Number of children with persistent symptoms on day 3–6 per million prescriptions</th>
<th>Number of children with persistent symptoms on day 3–6 per 20 million prescriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>90%</td>
<td>20,000</td>
<td>400,000</td>
</tr>
<tr>
<td>70%</td>
<td>60,000</td>
<td>1,200,000</td>
</tr>
<tr>
<td>50%</td>
<td>100,000</td>
<td>2,000,000</td>
</tr>
<tr>
<td>30%</td>
<td>140,000</td>
<td>2,800,000</td>
</tr>
</tbody>
</table>

The correlation between antibacterial susceptibility and clinical outcome has been debated for decades. Many variables can affect clinical outcome:

- Severity of disease
- Severe medical co-morbidity
- Age of patient
- Virulence of infecting pathogen
- Bacterial load
- PK/PD of antibacterial at site(s) of infection
- Evolving new resistance mechanisms
- Patient compliance
Bacteriologic Failure of Macrolide Therapy

- Numerous case reports with bacteriologic evidence for macrolide failure in patients infected with macrolide-resistant pneumococci
- Treatment failure documented with erythromycin, azithromycin, clarithromycin and josamycin
- Macrolide-resistant pneumococci cultured from blood and other normally sterile sites (children and adults)
- Pneumococcus with erythromycin MIC $>8 \, \mu g/mL$ isolated from blood

# 24 Case Reports of Bacteriologic Failure of Macrolide Therapy of RTIs Caused By Drug-resistant Pneumococci

<table>
<thead>
<tr>
<th>Agent</th>
<th>Site</th>
<th>MIC (µg/mL)</th>
<th>Agent</th>
<th>Site</th>
<th>MIC (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythromycin</td>
<td>Blood</td>
<td>&gt;8</td>
<td>Azithromycin</td>
<td>Blood</td>
<td>16</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Lung puncture</td>
<td>&gt;8</td>
<td>Azithromycin</td>
<td>Blood</td>
<td>8</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Lung puncture</td>
<td>&gt;8</td>
<td>Azithromycin</td>
<td>Blood</td>
<td>8</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Blood</td>
<td>&gt;8</td>
<td>Azithromycin</td>
<td>Blood</td>
<td>&gt;128</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Blood</td>
<td>&gt;8</td>
<td>Azithromycin</td>
<td>Blood</td>
<td>8</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Blood</td>
<td>&gt;8</td>
<td>Azithromycin</td>
<td>Blood</td>
<td>16</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Blood</td>
<td>8</td>
<td>Azithromycin</td>
<td>Blood</td>
<td>16</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Blood</td>
<td>&gt;8</td>
<td>Azithromycin</td>
<td>Blood</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Blood</td>
<td>&gt;8</td>
<td>Azithromycin</td>
<td>Blood</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Blood</td>
<td>&gt;8</td>
<td>Azithromycin</td>
<td>Blood</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Josamycin</td>
<td>Blood</td>
<td>&gt;8</td>
<td>Azithromycin</td>
<td>Blood</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Josamycin</td>
<td>Blood</td>
<td>&gt;8</td>
<td>Azithromycin</td>
<td>Blood</td>
<td>&gt;8</td>
</tr>
</tbody>
</table>

# Case Reports of Macrolide-Resistant *S. pneumoniae* Bacteremia

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation:</td>
<td>Pneumonia</td>
<td>Bronchitis</td>
<td>Pneumonia</td>
<td>AOM</td>
</tr>
<tr>
<td>Initial Therapy:</td>
<td>Azithromycin</td>
<td>Azithromycin</td>
<td>Clarithromycin</td>
<td>Azithromycin</td>
</tr>
<tr>
<td>Penicillin</td>
<td>MIC µg/mL</td>
<td>0.03 (S)</td>
<td>0.4 (I)</td>
<td>0.25 (I)</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0.12 (S)</td>
<td>0.2 (S)</td>
<td>0.12 (S)</td>
<td>0.12 (S)</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>0.25 (S)</td>
<td>0.25 (S)</td>
<td>0.125 (S)</td>
<td>0.125 (S)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td><strong>8 (R)</strong></td>
<td><strong>16 (R)</strong></td>
<td><strong>8 (R)</strong></td>
<td><strong>16 (R)</strong></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>0.06 (S)</td>
<td>0.06 (S)</td>
<td>&lt;0.016 (S)</td>
<td>0.06 (S)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1.0 (S)</td>
<td>0.5 (S)</td>
<td>1.0 (S)</td>
<td>0.5 (S)</td>
</tr>
<tr>
<td>Outcome:</td>
<td>Bacteremia</td>
<td>Bacteremia</td>
<td>Bacteremia</td>
<td>Bacteremia</td>
</tr>
<tr>
<td>Effective therapy:</td>
<td>Ceftriaxone + vancomycin; D/C pen V</td>
<td>Cefotaxime + azithromycin; D/C levofloxacin</td>
<td>Vancomycin</td>
<td>Ceftriaxone</td>
</tr>
</tbody>
</table>

Adapted from Kelley MA. *Clin Infect Dis.* 2000;31:1008-1011.
# Case Reports of Macrolide-Resistant *S. pneumoniae* Bacteremia

<table>
<thead>
<tr>
<th>Patient age</th>
<th>Presentation</th>
<th>Initial therapy</th>
<th>Site of isolation</th>
<th>Outcome</th>
<th>MICs (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 mo</td>
<td>AOM</td>
<td>TMP/SMX, cefixime, clarithromycin</td>
<td>CSF, blood</td>
<td>Meningitis</td>
<td>Survived</td>
</tr>
<tr>
<td>10 mo</td>
<td>AOM</td>
<td>Azithromycin</td>
<td>CSF, blood</td>
<td>Meningitis</td>
<td>Survived</td>
</tr>
<tr>
<td>44 yo</td>
<td>Cough, fever</td>
<td>Azithromycin</td>
<td>Blood, BAL</td>
<td>Bacteremia</td>
<td>Survived</td>
</tr>
<tr>
<td>65 yo</td>
<td>Cough</td>
<td>Cephalexin, azithromycin, Clindamycin</td>
<td>Blood, BAL</td>
<td>Pneumonia</td>
<td>Survived</td>
</tr>
<tr>
<td>52 yo</td>
<td>Sinusitis, cough</td>
<td>Azithromycin</td>
<td>Blood</td>
<td>Pneumonia</td>
<td>Survived</td>
</tr>
</tbody>
</table>

- **Penicillin**: 0.06 (S) 0.12 (I) 2 (R) 1 (I) 2 (R)
- **Cefotaxime/ceftiraxone**: 0.12 (S) 0.06 (S) 1 (I) 0.5 (S) 0.5 (S)
- **TMP/SMX**: 4/80 (R) - 8/152 (R) - 4/76 (R)
- **Erythromycin**: 2 (I) >256 (R) - -
- **Azithromycin**: 4 (R) - 8 (R) 8 (R) >128 (R)
- **Clarithromycin**: 1 (I) - - -
- **Clindamycin**: ≤0.12 (S) - 0.25 (S) - >256 (R)
- **Cefixime**: 1 - - -
- **Levofoxacin**: - - 0.5 (S) 1 (S) 0.5 (S)

Resistance Mechanisms of
*S. pneumoniae*: Macrolides

- **Active efflux—M phenotype** (*mef*)
  - Efflux pump associated with *mefE* gene
  - MICs in range of 1-32 µg/mL
  - Usually susceptible to clindamycin

- **Target modification—MLS$_B$ phenotype** (*erm*)
  - Methylation of 23S ribosomal RNA blocks binding of macrolides/azalides
  - Ribosomal methylase encoded by *ermAM* gene
  - MICs >64 µg/mL
  - Resistant to Macrolides, Lincomycins (e.g., clindamycin) and Streptogramin B

Bacteriologic Failure of Macrolide Therapy for *S. pneumoniae*

- Analysis of treatment failures documents a threshold for bacteriologic failure at an MIC of \( \sim 8 \) µg/mL.
- Level unachievable for 50% of the dosing interval in patients treated with IV erythromycin.
- Bacteriologically documented failures in patients infected with pneumococci expressing *mefE* resistance with MIC \( \geq 8 \) µg/mL.
- Level of MIC is more important predictor of clinical relevance of macrolide resistance than presence of *mefA* gene.

Klugman KP. *Eur Respir J.* 2002;20:(suppl 36)S1-S6.
Emergence of Macrolide-R During Therapy of Pneumococcal Pneumonia

- Case Report: 28-year old male (previously healthy)
  - 5-day history of cough/dyspnea; hypotension; hypothermia; rales; WBC 14,000 mm$^3$ (28% bands); RUL and RML infiltrates
  - *S. pneumoniae* cultured from sputum; negative blood culture

- Empirical therapy with 500 mg azithromycin IV
  - Condition improved rapidly; 4th day of treatment sudden deterioration; pneumococci isolated from BAL and pleural fluid
  - Ceftriaxone+vancomycin given but patient died (multi-organ failure)

- Initial isolate fully susceptible to all antibiotics tested including penicillin (MIC <0.016 µg/mL), clindamycin (MIC 0.008 µg/mL), azithromycin (MIC 0.008 µg/mL)

- Later isolate, although still susceptible to penicillin and clindamycin, resistant to azithromycin and quinupristin-dalfopristin (MICs 2 to 4 µg/mL)

- Not *erm* or *mef*; insertion in gene of ribosomal protein L22

Case Reports: Clinical Failure of Levofloxacin in Patients with Quinolone-resistant *S. pneumoniae*

- Levofloxacin treatment failure in pneumococcal pneumonia¹
  - 63-year-old male with community-acquired pneumonia (CAP); received levofloxacin for bronchitis days earlier
  - Levofloxacin started in hospital; persistent disease
  - *S. pneumoniae* (sputum) levofloxacin MIC >32 µg/mL; improved with ceftriaxone

- Three levofloxacin treatment failures of pneumococcal RTI²
  - Three cases of *S. pneumoniae* infection (CAP, chronic sinusitis, hospital-acquired pneumonia)
  - Baseline isolates from two patients were levofloxacin-R (MICs >4 to >32 µg/mL)
  - Two patients had significant history of prior fluoroquinolone use

- Levofloxacin failure in a patient with pneumococcal pneumonia³
  - 53-year-old male with pneumococcal pneumonia and underlying comorbidities
  - Pen-S MIC 0.0023 µg/mL, but treated with levofloxacin due to local penicillin shortage
  - Levofloxacin-R MIC 6 µg/mL resulted in clinical failure

---

### Characteristics of *S. pneumoniae* Isolated Before (b), During (d), or After (a) Therapy with Levofloxacin from Four Patients with CAP

<table>
<thead>
<tr>
<th>Patient</th>
<th>Source and time</th>
<th>Serotype</th>
<th>MIC (µg/mL)</th>
<th>Amino acid substitution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>LEVO</td>
<td>MOXI</td>
</tr>
<tr>
<td>1</td>
<td>Sputum-b</td>
<td>23F</td>
<td>1(S)</td>
<td>0.12(S)</td>
</tr>
<tr>
<td></td>
<td>Sputum-a</td>
<td>23F</td>
<td>8(R)</td>
<td>1(S)</td>
</tr>
<tr>
<td>2</td>
<td>Sputum-b</td>
<td>6A</td>
<td>4(I)</td>
<td>0.25(S)</td>
</tr>
<tr>
<td></td>
<td>Sputum-d</td>
<td>6A</td>
<td>16(R)</td>
<td>4(R)</td>
</tr>
<tr>
<td>3*</td>
<td>Blood-b</td>
<td>14</td>
<td>16(R)</td>
<td>4(R)</td>
</tr>
<tr>
<td></td>
<td>Pleural fluid-d</td>
<td>14</td>
<td>16(R)</td>
<td>4(R)</td>
</tr>
<tr>
<td>4*</td>
<td>Sputum-d</td>
<td>ND</td>
<td>16(R)</td>
<td>4(R)</td>
</tr>
</tbody>
</table>

* Prior fluoroquinolone exposure

Understanding Bacteriologic Failure Due to Penicillin Resistance in Invasive Pneumococcal Pneumonia

- **Azoulay-Dupuis**
  - Primary determinant of decreased virulence might be the serotype, rather than acquired penicillin resistance (animal model)

- **Quach**
  - Invasive infections caused by PRSP and PSSP do not differ in clinical presentation, morbidity or mortality in a pediatric population
  - PRSP associated with increased length of ICU stay

- **Moroney**
  - Factors other than resistance, such as severity of illness at presentation have a stronger influence on pneumococcal pneumonia outcomes

- **Bedos**
  - 465 patients with pneumococcal pneumonia (29% Pen-I and 10.5% Pen-R), majority treated with β-lactams. No significant difference in mortality between Pen-S (18%) and Pen-I and Pen-R (14%) groups

- **Klugman**
  - Recent review of the available evidence suggests that penicillin and amoxicillin are not associated with bacteriologic failure in penicillin resistant pneumococcal pneumonia

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Levofloxacin pharmacodynamic study

• 134 hospitalized patients with culture-proven respiratory tract (N=100), skin/soft tissue (N=25) or complicated urinary tract (N=9) infections

• Commonest pathogens:
  • Streptococcus pneumoniae (N=21)
  • Staphylococcus aureus (N=15)

• Treated with IV levofloxacin 500 mg qd for 5-14 days

• Clinical (N=134) and bacteriological (N=116) outcomes followed

Levofloxacin AUCs
134 patients with resp, skin or urinary infections

Adapted from Preston et al., JAMA 1998, 279:125-129
Levofloxacin Peak Serum Concs.
134 patients with resp, skin or urinary infections

Adapted from Preston et al., JAMA 1998, 279:125-129
Levofloxacin MICs
134 patients with resp, skin or urinary infections

Adapted from Preston et al., JAMA 1998, 279:125-129
Levofloxacin PK/PD vs. clinical outcome
134 patients with resp, skin or urinary infections

AUC:MIC vs Peak:MIC ratios
\[ y = 7.873x^{0.9709} \]
\[ R^2 = 0.9435 \]

Adapted from Preston et al., JAMA 1998, 279:125-129
Levofloxacin MICs vs. clinical outcome
134 patients with resp, skin or urinary infections

AUC:MIC vs Peak:MIC ratios

$y = 7.873x^{0.9709}$

$R^2 = 0.9435$

AUC:MIC and Peak:MIC ratios very similar at low values

Levofloxacin MICs vs. clinical outcome
134 patients with resp, skin or urinary infections

AUC:MIC and Peak:MIC ratios: more scatter at high values

AUC:MIC vs Peak:MIC ratios

y = 7.873x^{0.9709}

R^2 = 0.9435

Levofloxacin PK/PD correlations with clinical outcome

134 hospitalized patients with respiratory tract, skin or complicated urinary tract infections treated with 500 mg qd for 5-14 days

Clinical outcome

- **AUC:MIC <25**
  - Peak:MIC <3
  - **Success**: 4 patients
  - **Failure**: 3 patients
  - **Clinical failure rate**: 43%

- **AUC:MIC 25-100**
  - Peak:MIC 3-12
  - **Success**: 23 patients
  - **Failure**: 3 patients
  - **Clinical failure rate**: 11.5%

- **AUC:MIC >100**
  - Peak:MIC >12
  - **Success**: 100 patients
  - **Failure**: 1 patient
  - **Clinical failure rate**: 1%

For AUC:MIC ratios <25 vs. >25, P=.003; for ratios <100 vs. >100, P=.001 (Fisher)

Levofloxacin PK/PD correlations with clinical outcome

134 hospitalized patients with respiratory tract, skin or complicated urinary tract infections treated with 500 mg qd for 5-14 days

Optimizing PK/PD parameters
Amoxicillin: “Time above MIC”

Goal: Antibiotic level above MIC for 40% of dosing interval

Example: Amoxicillin dosed at 12 h at 45 mg/kg/d and at 8 h at 40 mg/kg/d

Amoxicillin: “Time above MIC”

Goal: Antibiotic level above MIC for 40% of dosing interval

Example: Amoxicillin dosed every 12 hours at 45 and 90 mg/kg/d

Amoxicillin: “Time above MIC”

Goal: Antibiotic level above MIC for 40% of dosing interval

Example: Amoxicillin dosed at 12 h at 875 mg and at 8 h at 500 mg

Amoxicillin: “Time above MIC”

Goal: Antibiotic level above MIC for 40% of dosing interval

Example: Amoxicillin dosed at 12 h at 875 mg and 2000 mg

Extended-release amoxicillin-clavulanate (2000 mg amoxicillin per dose) vs. immediate release amoxicillin-clavulanate (875 and 2000 mg amoxicillin per dose)

Extended release formulation cannot be duplicated by using immediate release amoxicillin/clavulanate plus extra amoxicillin.

Mean amoxicillin concentration (µg/mL)

Time (hours)

Immediate release Amox/Clav (2000 mg amoxicillin)
Extended release Amox/Clav (2000 mg amoxicillin)
Amox/Clav (875mg amoxicillin)

Amoxicillin MIC = 4 µg/mL
Amoxicillin MIC = 2 µg/mL

40% of 12-h dosing interval (4.8 h)

Extended release amoxicillin-clavulanate: Clinical Trials Design

- Clinical program developed according to FDA *Guidance for Industry: Developing Antimicrobial Drugs—General Considerations for Clinical Trials* (Center for Drug Evaluation and Research and Research, July 1998)

- Because large number of patients required to show clinical superiority, most comparative studies are designed to show noninferiority

- Most patients were therefore studied in noncomparative studies
Clinical Success and Bacteriologic Eradication at TOC for *S. pneumoniae* by Amox/Clav

MIC: All Indications Combined (RTI)

Clinical and bacteriological success (bacteriology PP population at TOC)
Clinical or bacteriological failure (bacteriology PP population at TOC)

GlaxoSmithKline, data on file.
Antimicrobial Recommendations for AOM

Prior Antibiotic Therapy

Day 0

Amoxicillin

Clinical failure on Day 3

Amoxicillin
Amox/clav
Cefuroxime

IM Ceftriaxone*

Tympanocentesis

Clinical failure on Day 10–28

Amox/clav
Cefuroxime
IM Ceftriaxone*

Same as Day 3

IM Ceftriaxone*
Clindamycin**
Tympanocentesis

Amoxicillin

*Three doses on consecutive days.

**Not effective against *H. influenzae* or *M. catarrhalis*.

## Antimicrobial Recommendations for AECB

<table>
<thead>
<tr>
<th>Category</th>
<th>Probable Pathogen</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Viral</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>Group 2</td>
<td><em>H. influenzae, S. pneumoniae, M. catarrhalis</em></td>
<td>Doxycycline, newer macrolide</td>
</tr>
<tr>
<td></td>
<td>possibly atypical organisms</td>
<td>newer cephalosporins</td>
</tr>
<tr>
<td>Group 3 &amp; 4</td>
<td>As above with the possible addition of <em>Pseudomonas</em> spp</td>
<td>Amoxicillin/clavulanate, fluoroquinolones*</td>
</tr>
<tr>
<td></td>
<td>Enterobacteriaceae, and other gram-negative pathogens</td>
<td></td>
</tr>
</tbody>
</table>

Bacteriologic outcome studies

- AOM
- AECB
Relationship between Time above MIC and bacterial eradication with β-lactams in otitis media

Craig & Andes, Pediatr Infect Dis J, 1996
Dagan et al studies
Relationship between Time above MIC and bacterial eradication with $\beta$-lactams in maxillary sinusitis

- Craig & Andes, Pediatr Infect Dis J, 1996
- Gwaltney & Scheld studies
Haemophilus influenzae: Bacteriological Failure Rates in AOM Studies (excl amox and SXT)

2nd Tympanocentesis Performed on Day 2-6 of treatment

**Haemophilus influenzae:** Bacteriological Failure Rates in AOM Studies with Amoxicillin and SXT

2nd Tympanocentesis Performed on Day 2-6 of treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Susceptible</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0</td>
<td>52</td>
</tr>
<tr>
<td>Amoxicillin 45</td>
<td>23</td>
<td>63</td>
</tr>
<tr>
<td>SXT</td>
<td>0</td>
<td>50</td>
</tr>
</tbody>
</table>

Streptococcus pneumoniae: Bacteriological Failure Rates in AOM Studies (excl. azithromycin and SXT)

2nd Tympanocentesis Performed on Day 2-6 of treatment

Streptococcus pneumoniae: Bacteriological Failure Rates in AOM Studies with Azithromycin and SXT

2\textsuperscript{nd} Tympanocentesis Performed on Day 2-6 of treatment

Pre-therapy pathogens:  
- *H. influenzae*  
  - Amox/clav (N=96): 16%  
  - Azithromycin (N=79): 33%  
- *S. pneumoniae*  
  - Amox/clav (N=96): 35%  
  - Azithromycin (N=79): 34%  

Azithromycin failures:  
- *S. pneumoniae*: 8/27  
- *H. influenzae*: 13/26

Bacterial Eradication and Clinical Efficacy in AECB (EOT)

Pre-therapy pathogens:

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Cipro (N=118)</th>
<th>Clarithro (N=103)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. influenzae</em></td>
<td>38%</td>
<td>27%</td>
</tr>
<tr>
<td><em>M. catarrhalis</em></td>
<td>20%</td>
<td>23%</td>
</tr>
<tr>
<td><em>S. pneumoniae</em></td>
<td>14%</td>
<td>15%</td>
</tr>
</tbody>
</table>

MIC distributions of RTI pathogens

- MIC distributions can provide a basis for comparing susceptibilities of different bacterial species causing infections at the same sites.

- MIC distributions can show if discrimination between isolates with different MICs is likely to be possible in clinical studies.

- MIC distributions can be applied to clinically determined breakpoints to determine susceptibility of isolates.
Amoxicillin

Bacteriologic failure rate in AOM:

45 mg/kg/d
- **S. pneumoniae**: 10% penS, 20% penNS
- **H. Influenzae**: 23% BLneg, 63% Blpos

90 mg/kg/d
- Not done

Alexander Project USA 2000: S. pneumoniae (n=1362), H. influenzae (n=634), M. catarrhalis 2000 (n=206)
Alexander Project USA 2000: S. pneumoniae (n=1362), H. influenzae (n=634), AugSR M. catarrhalis (n=972)
Eradication of \textit{S. pneumoniae} in AOM According to Amoxicillin-clavulanate MIC (N=149)

### Alexander Project USA 2000:

- **S. pneumoniae** (n=1362), **H. influenzae** (n=634), **M. catarrhalis** 2000 (n=206)

<table>
<thead>
<tr>
<th>Strain</th>
<th>MIC in ug/mL</th>
<th>penS (%)</th>
<th>penNS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae</td>
<td></td>
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<tr>
<td>H. influenzae</td>
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<tr>
<td>M. catarrhalis</td>
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</tr>
</tbody>
</table>

Bacteriologic failure rate in AOM:

- **S. pneumoniae**: 10% penS, 62% penNS
- **H. influenzae**: 37%
Ceftriaxone

Bacteriologic failure rate in AOM:

One dose:
- **S. pneumoniae**: 0% penS, 53% penNS
- **H. Influenzae**: 0%

Three daily doses:
- **S. pneumoniae**: 0% penS, 9% penNS
- **H. Influenzae**: 0%

Adapted from Alexander Project 2000; GlaxoSmithKline, data on file.
Alexander Project USA 2000:  
S. pneumoniae (n=1362), H. influenzae (n=634),  
M. catarrhalis 2000 (n=206)
Bacteriologic failure rate in AOM:
- **S. pneumoniae**: not studied
- **H. Influenzae**: not studied

Alexander Project USA 2000: S. pneumoniae (n=1362), H. influenzae (n=634), M. catarrhalis 2000 (n=206)
Cefprozil

Bacteriologic failure rate in AOM:
- **S. pneumoniae** 8% penS penR ND
- **H. Influenzae** 57%

Alexander Project USA 2000:  **S. pneumoniae** (n=1362), **H. influenzae** (n=634), **M. catarrhalis** 2000 (n=206)
Cefixime

Bacteriologic failure rate in AOM:

- S. pneumoniae 27% penS penR ND
- H. Influenzae 4%

Alexander Project USA 2000:  
S. pneumoniae (n=1362), H. influenzae (n=634), M. catarrhalis 2000 (n=206)
Cefditoren

Bacteriologic failure rate in AOM:
- S. pneumoniae: not studied
- H. Influenzae: not studied

Adapted from Jacobs ICAAC 1997 abstr E103, Kelly ICAAC 1999 abstr 2323, and Spectracef Prescribing Information 2002
Ceftibuten

Bacteriologic failure rate in AOM:
- **S. pneumoniae**: not studied
- **H. Influenzae**: not studied

Adapted from Jacobs ICAAC 1997 abstr E103, and Cedax Prescribing Information 2002
Azithromycin

Bacteriologic failure rate in AOM:

- **S. pneumoniae**
  - 5% aziS
  - 92% aziR

- **H. Influenzae**
  - 67%

Alexander Project USA 2000:  
**S. pneumoniae** (n=1362), **H. influenzae** (n=634),  
AugSR **M. catarrhalis** (n=969)
Clarithromycin

Bacteriologic failure rate in AOM:
- **S. pneumoniae**: 0% clarS clarR ND
- **H. Influenzae**: 80%

Alexander Project USA 2000:  **S. pneumoniae** (n=1362), **H. influenzae** (n=634), AugSR **M. catarrhalis** (n=969)
Clindamycin

Bacteriologic failure rate in AOM:

- S. pneumoniae: not studied
- H. Influenzae: not studied

Alexander Project USA 2000: S. pneumoniae (n=1362)
AugSR H. influenzae (n=3793) M. catarrhalis 2000 (n=970)
Telithromycin

Bacteriologic failure rate in AOM:
- S. pneumoniae: not studied
- H. Influenzae: not studied

Doxycycline

Bacteriologic failure rate in AOM:
- S. pneumoniae: not studied
- H. influenzae: not studied

Alexander Project USA 2000: S. pneumoniae (n=1362), H. influenzae (n=634), M. catarrhalis 2000 (n=206)
Alexander Project USA 2000:  
S. pneumoniae (n=1362), H. influenzae (n=634),  
M. catarrhalis AugSR (n=972)
Alexander Project USA 2000:  
S. pneumoniae (n=1362), H. influenzae (n=634), 
M. catarrhalis AugSR (n=972)
Levofloxacin

Bacteriologic failure rate in AOM:
- **S. pneumoniae** not studied
- **H. Influenzae** not studied

**S. pneumoniae** failures in CAP and sinusitis in levofloxacin resistant strains (MICs 4-16 ug/ml)

Alexander Project USA 2000:  **S. pneumoniae** (n=1362), **H. influenzae** (n=634), **M. catarrhalis** AugSR (n=972)
**Gatifloxacin**

**Bacteriologic failure rate in AOM***:
- *S. pneumoniae* 7%
- *H. Influenzae* 0%

*Augmentin XR surveillance data

*Dagan et al. ICAAC 2001, abstract G-1558a*
Bacteriologic failure rate in AOM:

- *S. pneumoniae*: not studied
- *H. Influenzae*: not studied

Augmentin XR surveillance data

**Moxifloxacin**

- **MIC in ug/mL**
  - 0
  - 0.01
  - 0.02
  - 0.03
  - 0.06
  - 0.12
  - 0.25
  - 0.5
  - 1
  - >1

- **% of strains**
  - 0
  - 10
  - 20
  - 30
  - 40
  - 50
  - 60
  - 70
  - 80
  - 90
  - 100

**Species**

- M. catarrhalis
- S. pneumoniae
- H. influenzae

**Microorganism**

- *M. catarrhalis*
- *S. pneumoniae*
- *H. influenzae*
Conclusions

*In vitro* resistance does correlate with outcome in humans provided appropriate studies are performed (adequately sized clinical outcome studies, bacteriologic outcome studies, PK/PD studies) AND appropriate PK/PD-based susceptibility breakpoints are used.