Importance of Time Above MIC for In-Vivo Activity of Augmentin and Other Beta-Lactams in Acute Otitis Media

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Pharmacology of Antimicrobial Therapy

Dosage Regimen → Time Course of Serum Levels

Absorption → Time Course of Levels at Site of Infection

Distribution → Time Course of Levels in Tissues and Body Fluids

Elimination → Time Course of the Pharmacologic and Toxicologic Effect

Pharmacokinetics

Pharmacodynamics
Parameters of Antimicrobial Activity

- **Potency:**
  1. MIC
  2. MBC

- **Time Course of Activity:**
  1. Rate of killing and effect of increasing concentrations
  2. Persistent effects (postantibiotic effect, postantibiotic sub-MIC effects, postantibiotic leukocyte enhancement)
Pattern of Antimicrobial Activity for Amoxicillin and Other β-Lactams

- Time-dependent killing and minimal to moderate persistent effects
- Goal of dosing regimen: optimize duration of exposure
- Time Above MIC major parameter correlating with efficacy
Relationship Between Peak/MIC Ratio and Efficacy for Cefotaxime against *Klebsiella pneumoniae* in a Murine Pneumonia Model

Craig CID, 1998
Relationship Between 24-Hr AUC/MIC and Efficacy for Cefotaxime against *Klebsiella pneumoniae* in a Murine Pneumonia Model
Relationship Between Time Above MIC and Efficacy for Cefotaxime against *Klebsiella pneumoniae* in a Murine Pneumonia Model
Relationship Between Time Above MIC and Efficacy for Amoxicillin against *Streptococcus pneumoniae* in a Murine Thigh-Infection Model

![Graph showing the relationship between time above minimum inhibitory concentration (MIC) and efficacy for amoxicillin against *Streptococcus pneumoniae* with a regression line and R² value of 93%.]
Time Above MIC for β-Lactams

• Is the magnitude of the parameter required for efficacy the same in different animal species including humans?  **YES**

• Does the magnitude of the parameter vary with:
  1. the dosing regimen?  **NO**
  2. different sites of infection (e.g. blood, lung, peritoneum, soft tissue)?  **NO**
  3. different drugs within the same class?  **Penicillins less than cephalosporins; no difference within groups providing free, unbound drug levels are used**
  4. different organisms including resistant strains?  **FOR SOME; no difference for penicillin-resistant pneumococci**
Relationship Between MIC and T>MIC for Amoxicillin & Cefpodoxime with strains of S. pneumoniae
Time Above MIC: β-Lactams

• T>MIC (% of dosing interval) required for the static dose against most organisms in neutropenic mice vary from 25-35% for penicillins and from 30-45% for cephalosporins

• The presence of neutrophils reduces the T>MIC required for efficacy by 5-10%

• Free drug levels of penicillins and cephalosporins need to exceed the MIC for 35-50% of the dosing interval to produce maximum survival
Relationship Between T>MIC and Efficacy for Amoxicillin against *Streptococcus pneumoniae* in Murine Pneumonia and Thigh-Infection Models

Craig CID, 2001
Relationship Between Time Above MIC and Efficacy in Animal Infection Models for *S. pneumoniae*

Cephalosporins
Penicillins

Craig CID, 1998
Nickolau AAC 2000
Time Above MIC vs Efficacy in Acute Otitis Media and Acute Sinusitis

- Bacteriologic cure for different beta-lactams against *S. pneumoniae* and *H. influenzae* from double tap studies in acute otitis media and acute maxillary sinusitis

- Time above MIC calculated from serum levels and MICs for different organisms

Craig & Andes, Pediatr Infect Dis J, 1996
Dagan et al studies
Gwaltney & Scheld studies
Relationship Between $T_{\text{MIC}}$ and Bacterial Eradication with Beta-Lactams in Otitis Media (Circles) and Maxillary Sinusitis (Squares)
General Conclusions

Time above MIC is the important determinant of activity for β-Lactams against major respiratory pathogens, including penicillin-resistant pneumococci.

Studies in acute otitis media and sinusitis demonstrate a good correlation between the time above MIC required for bacteriologic cure of pneumococci and the time above MIC required for a 2 log kill or 90-100% survival in animal infection models.
What Does Theory Predict for the 90/6.4/day Formulation of Augmentin?

Animal Data:

- Pneumonia study in rats with simulation of human pharmacokinetics

Pharmacokinetic Data:

- Extrapolated data from 5 children that received 45/6.4 mg/Kg/day
- Recent study in 18 children that received 90/6.4 mg/Kg/day (mean age 5 years and range in age from 0.3-11 years)
Efficacy of Simulated Human Concentrations of Amoxicillin/Clavulanate in Pneumococcal Respiratory Tract Infections in Rats

Woodnut et al. AAC, 2000
**DAILY 45 MG/KG Q12 VS 90 MG/KG Q12**

- **45mg/kg/d**
  - * in 5 children
- **90mg/kg/d (extrapolated)**
  - ** derived by doubling the dose of 45 mg/kg/d**
  - ** in 19 children

**Plasma Concentration [ug/mL]**

- **T>MIC=28%**
- **T>MIC=41%**
- **T>MIC=50%**

**Time [h]**

- 0 1 2 3 4 5 6 7 8 9 10 11 12
Mean amoxicillin plasma-concentration profile following administration of Augmentin 600 suspension (45/3.2 mg/kg) to paediatric patients (n=18)

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<tr>
<th>Plasma conc (mcg/mL)</th>
<th>Time (hours)</th>
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<tr>
<td>T&gt;MIC 4 mcg/mL = 57%</td>
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<tr>
<td>T&gt;MIC 8 mcg/mL = 28%</td>
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Plasma conc (mcg/mL)