MONTE CARLO SIMULATION & PK-PD TARGET ATTAINMENT ANALYSIS:

Application to Oral Time-Dependent Antimicrobial Regimens

Paul G. Ambrose, Pharm.D.
Director, Division of Infectious Diseases, Cognigen Corporation;
Adjunct Professor, University of the Pacific, School of Health Sciences
ACKNOWLEDGEMENTS

Co-Authors:

SUJATA M. BHAVNANI, PHARM.D.
Cognigen Corp., Buffalo, N.Y.

CHRIS M. RUBINO, PHARM.D.
Cognigen Corp., Buffalo, N.Y.

LUANN PHILLIPS, MBMA
Cognigen Corp., Buffalo, N.Y.

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BACKGROUND

Monte Carlo Simulation

- Introduced to the PK-PD community of practice in 1998 by Drusano (FDA Subcommittee on Anti-infective Drug Products).

- Has been used for evaluating antibiotic regimens for which outcome is best described by either AUC:MIC Ratio (PO or IV) and T>MIC (IV)

- We utilized an approach that may be useful to estimate the probability of attaining a given T>MIC for oral, time-dependent antibiotics
  - Amoxicillin-clavulanate
  - 500mg every 8 hrs versus 875mg every 12 hrs
AMOXICILLIN-CLAVULANATE

Why Should Anyone Care?

- Few drugs are available for clinical use in the community setting with reliable activity against *Streptococcus pneumoniae*.

- 500mg Q8hrs vs. 875mg Q12hrs is a relevant comparison because patients are markedly more compliant on twice-daily regimens.

- Given the limited therapeutic alternatives and the prevalence of multi-drug resistant pneumococci, it is important to demonstrate similar probabilities of PK-PD target attainment.
METHODS

Monte Carlo Simulations

- Simulations considered *Streptococcus pneumoniae* and *Haemophilus influenzae* collected in the U.S. and Europe

- Simulations also considered potential MIC breakpoints

- 10,000 patient simulation for each drug-organism or fixed MIC value combination

- In order to account for clavulanate exposure, important for efficacy against beta-lactamase producing strains of *H. influenzae*, a 2-step algorithm was used

- $T>MIC$ was computed numerically using the bisection method for finding roots of equations
METHODS

Simulation Assumptions

- One-compartment pharmacokinetic data for amoxicillin/amoxicillin-clavulanate was obtained from the medical literature and utilized for the purpose of simulation.

<table>
<thead>
<tr>
<th></th>
<th>Amoxicillin [Mean (%CV)]</th>
<th>Clavulanate [Mean (%CV)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>500 mg</td>
<td>875 mg</td>
</tr>
<tr>
<td>K_a (1/hr)</td>
<td>1.48 (14.2)</td>
<td>1.49 (28.7)</td>
</tr>
<tr>
<td>K_e (1/hr)</td>
<td>0.762 (15.5)</td>
<td>0.791 (23.3)</td>
</tr>
<tr>
<td>CL (L/hr)</td>
<td>24.5 (12.2)</td>
<td>24.7 (19.5)</td>
</tr>
<tr>
<td>fu</td>
<td>0.82</td>
<td>0.82</td>
</tr>
</tbody>
</table>

METHODS

Amoxicillin-Clavulanate MIC Distribution

- 4,725 isolates of *S. pneumoniae* & 2,505 isolates of *H. influenzae* collected in the United States (1999-2000)

AMOXICILLIN-CLAVULANATE PK-PD Goal of Therapy for *S. pneumoniae*

- Mice rendered neutropenic & infection induced by IM injection of 0.1mL of 10^5 to 10^6 CFU *S. pneumoniae*
- Animals received 7 mg/kg alone or in combination with clavulanate (ratio 4:1) every 8 hrs.
- Each data point represents the mean of two thighs.

SIMULATION RESULTS: *S. pneumoniae*

**Amoxicillin-Clavulanate (500-125mg Q8hr Regimen)**

<table>
<thead>
<tr>
<th>MIC</th>
<th>25%</th>
<th>30%</th>
<th>35%</th>
<th>40%</th>
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</thead>
<tbody>
<tr>
<td>0.12</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>0.25</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>0.5</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>1.0</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>2.0</td>
<td>100</td>
<td>100</td>
<td>99.9</td>
<td>98.7</td>
</tr>
<tr>
<td>4.0</td>
<td>99.7</td>
<td>95.4</td>
<td>63.2</td>
<td>17.4</td>
</tr>
<tr>
<td>8.0</td>
<td>10.0</td>
<td>0.7</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Entire MIC Distribution</td>
<td>99.1</td>
<td>98.7</td>
<td>97.2</td>
<td>95.7</td>
</tr>
</tbody>
</table>

**PCN-S**
- 100
- 100
- 100
- 100

**PCN-I**
- 100
- 100
- 99.6
- 98.5

**PCN-R**
- 98.5
- 87.7
- 76.5
- 62.1
**SIMULATION RESULTS: S. pneumoniae**

*Amoxicillin-Clavulanate (875-125mg Q12hr Regimen)*

<table>
<thead>
<tr>
<th>MIC</th>
<th>25%</th>
<th>30%</th>
<th>35%</th>
<th>40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.12</td>
<td>100</td>
<td>100</td>
<td>99.8</td>
<td>99.3</td>
</tr>
<tr>
<td>0.25</td>
<td>100</td>
<td>99.8</td>
<td>99.3</td>
<td>96.9</td>
</tr>
<tr>
<td>0.5</td>
<td>99.8</td>
<td>99.3</td>
<td>96.4</td>
<td>91.8</td>
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<tr>
<td>1.0</td>
<td>99.3</td>
<td>95.9</td>
<td>90.5</td>
<td>79.3</td>
</tr>
<tr>
<td>2.0</td>
<td>95.2</td>
<td>87.2</td>
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<td>50.6</td>
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<tr>
<td>4.0</td>
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<td>37.1</td>
<td>20.4</td>
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<tr>
<td>8.0</td>
<td>36.3</td>
<td>19.5</td>
<td>8.5</td>
<td>3.3</td>
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<tr>
<td>Entire MIC Distribution</td>
<td>99.7</td>
<td>96.1</td>
<td>93.3</td>
<td>90.4</td>
</tr>
</tbody>
</table>

- **S** for Sensitive
- **I** for Intermediate
- **R** for Resistant
SIMULATION RESULTS: *H. influenzae*
Amoxicillin-Clavulanate

<table>
<thead>
<tr>
<th>Dose</th>
<th>MIC Distribution</th>
<th>n</th>
<th>25%</th>
<th>30%</th>
<th>35%</th>
<th>40%</th>
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</thead>
<tbody>
<tr>
<td>500-125 mg</td>
<td>Entire</td>
<td>2505</td>
<td>99.9</td>
<td>99.9</td>
<td>99.8</td>
<td>98.7</td>
</tr>
<tr>
<td>Q8 hr</td>
<td>BL-</td>
<td>1645</td>
<td>100</td>
<td>100</td>
<td>99.9</td>
<td>98.3</td>
</tr>
<tr>
<td></td>
<td>BL+</td>
<td>860</td>
<td>99.9</td>
<td>99.8</td>
<td>99.5</td>
<td>99.5</td>
</tr>
<tr>
<td>875-125 mg</td>
<td>Entire</td>
<td>2505</td>
<td>98.2</td>
<td>97.5</td>
<td>95.9</td>
<td>93.5</td>
</tr>
<tr>
<td>Q12 hr</td>
<td>BL-</td>
<td>1645</td>
<td>99.7</td>
<td>98.9</td>
<td>97.7</td>
<td>94.9</td>
</tr>
<tr>
<td></td>
<td>BL+</td>
<td>860</td>
<td>95.2</td>
<td>94.8</td>
<td>92.3</td>
<td>90.8</td>
</tr>
</tbody>
</table>
CONCLUSIONS

- The bisection method is useful for PK-PD target analyses for oral, time-dependent antimicrobial agents.
- From PK-PD perspective, the 875 mg amoxicillin-clavulanate regimen Q12 hr is generally comparable to 500 mg Q8 hr amoxicillin-clavulanate regimen.
- These data suggest that the current NCCLS breakpoints for amoxicillin against *S. pneumoniae* of 2, 4 and 8 mg/L for susceptible, intermediate and resistant, respectively, are reasonable.
QUESTIONS, COMMENTS OR WISE REMARKS?
BACK-UP METHODS

2-Step Algorithm

Obs. MIC • 0.25 • 24 ≤ Clavulanate AUC$_{0-24}$?

No

We assume PK-PD target not attained

Yes

Calculate T>MIC (Amoxicillin)


Since the clavulanate component is critical to activity of amoxicillin-clavulanate against *H. influenzae*, we considered a 2-step algorithm:

- Susceptibility testing of *H. influenzae* uses a fixed ratio of 4:1 amoxicillin:clavulanate.
- Approximately 97% of *H. influenzae* strains had MIC values of ≤2 mg/L.
- A MIC value of 2 mg/mL may be thought of as a clavulanate AUC\textsubscript{24} of 12.
- Since the mean and std. dev. of clavulanate AUC\textsubscript{24} was 19.2 +/- 2.4, in >99% (3 Std. Dev.) of the instances the AUC\textsubscript{24} in subjects would be expected to be 12 or greater.
- Thus, in these simulations clavulanate exposure is sufficient in approximately at least 97% of all instances and the simulation largely simplifies to considering the amoxicillin component.
PK-PD Goal of Therapy β-Lactams
*S. pneumoniae & H. influenzae*

- Data from AOM or ABRS studies
- Pre-therapy and repeat sinus puncture or tympanocentesis
- 40% T>MIC or greater required to achieve 85-100% bacteriologic cure for both organisms
