THE BASICS OF PK/PD WITH REGARDS TO BREAKPOINTS
WHAT WE HOPE TO GET FROM A BREAKPOINT

- Breakpoint Ideal
  - Predict clinical outcome
  - Detect resistance mechanisms
  - Separate mutant from wildtype population
  - Predict cross resistance with other drugs

- Clinical Breakpoints
  - Identify a patient, by MIC, for which there is a high probability of clinical response to a properly dosed antimicrobial.
WHY CAN’T WE JUST USE CLINICAL DATA (FROM TRIALS OR OTHER) TO SET BP?

Why?
Almost all clinical trials are designed assuming everybody has the same PK
PK typically determined in healthy volunteers
In trial, everyone gets the same dose, from volunteer PK
WHAT IS PK AND PD?

- Pharmacokinetics (PK)
  - The process by which a drug is absorbed, distributed, metabolized and eliminated by the body. Relates to drug concentration over time in vivo.

- Pharmacodynamics (PD)
  - The relationship between drug concentration and its antimicrobial effects over time in vivo.

- Tells us about the relationship between the amount of drug available at the site of the infection and the ability of the drug to inhibit/kill the bacteria at that site.
PK/PD - ANTIMICROBIAL AGENTS

Pharmacokinetics

- Absorption
- Distribution
- Elimination

Pharmacodynamics

- Varying concentration in serum over time
- Concentration in non-infected tissue and body fluids over time
- Concentration at site of infection over time
- Toxicologic effect
- Microbial killing or inhibition over time

Dosage Regimen

Adapted from Craig WA. 1998. CID. 26:1-10.
There is a relationship between antimicrobial drug concentration and bacterial killing

PK-PD indices for the drug are known

By raising the MIC, all resistance mechanisms are equal
Example: ESBLs are no different than AmpCs
PK/PD Indices

Depending on the antimicrobial, target might be:

- Time above MIC (e.g., β lactams)
- Area under the curve : MIC ratio (e.g., vancomycin)
- Ratio of Cmax to MIC (e.g., Aminoglycosides)
EXAMPLE: CEFTAZIDIME AND KLEBSIELLA PNEUMONIAE

- Murine data (log CFU/lung 24 hr after antimicrobial administration) plotted by three PK/PD Indices:

- Cmax / MIC ratio
- AUC / MIC ratio
- % Time above MIC

Craig WA: Pharmacodynamics of antimicrobials, In Antimicrobial Pharmacodynamics in Theory and Clinical Practice 2002
Don’t forget...

There is a wide range of PK among different patients!

Data from 252 patients given a 500 mg dose of levofloxacin

Depends on:
- creatinine clearance
- weight
- sickness
- genetics (metabolism)
- age
- organ function
- drug-drug interactions
To help address variability, use “population” PK

Old way: measure a bunch of patients / volunteers and obtain mean/median and standard deviation

New way: fancy mathematical models (allows partitioning of variables / use of ‘inflated variance’ for critically ill patients)
MONTE CARLO SIMULATION

- PK/PD application
  - Generate random PK and MIC values from data set
  - Calculate PK-PD exposure measure
  - Plot results in a probability chart
HOW LONG T>MIC IS ENOUGH?

- Experience tells us:
  - SSTI, just need stasis
  - HAP/VAP, need 2-3 log killing
  - Depends on bacterial burden

1. Craig 1998 CID 26:1-12
HOW LONG >MIC IS ENOUGH?

- **Antibiotic class**
  - Example: less T>MIC for is required for carbapenems vs. cephems, because they have faster killing

- **Organism**
  - Example: less T>MIC is required for killing of *Pseudomonas aeruginosa* vs. *Enterobacteriaceae*
**What PK/PD Target Value is Desired for B-Lactams (E.G., “Target Attainment”)?**

<table>
<thead>
<tr>
<th>Antimicrobials</th>
<th>Free Drug % Time &gt; MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bacteriostatic (%)</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>35-40</td>
</tr>
<tr>
<td>Penicillins</td>
<td>30</td>
</tr>
<tr>
<td>Carbapenemems</td>
<td>20-30</td>
</tr>
</tbody>
</table>

*3 log reduction in colony-forming units

Bacteriostatic and bactericidal activity of β-lactams depends on duration of time that free (unbound) drug levels exceed MIC (% T > MIC)

## EXAMPLE: CEFTRIAXONE 1G Q24H S. PNEUMONIAE (NON-MENINGITIS)

<table>
<thead>
<tr>
<th>MIC</th>
<th>30%</th>
<th>40%</th>
<th>50%</th>
<th>60%</th>
</tr>
</thead>
<tbody>
<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>99.4</td>
<td>92.9</td>
</tr>
<tr>
<td>2.0</td>
<td>99.0</td>
<td>87.1</td>
<td>58.0</td>
<td>25.0</td>
</tr>
<tr>
<td>4.0</td>
<td>65.6</td>
<td>8.4</td>
<td>0.8</td>
<td>0.1</td>
</tr>
</tbody>
</table>

What MIC is considered S vs. I vs. depends on what is determined to be an appropriate target time above the MIC!
### EXAMPLE: CEFTRIAXONE 1G Q24H S. PNEUMONIAE (NON-MENINGITIS)

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<td>0.8</td>
<td>0.1</td>
</tr>
</tbody>
</table>

For *S. pneumoniae* and the beta-lactams, 40% T>MIC is considered appropriate\(^1\) (Based on animal data and/or clinical data, as available)

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1. Craig 1998 CID 26:1-12
## EXAMPLE: DOSING DIFFERENCES S. PNEUMONIAE (NON-MENINGITIS)

<table>
<thead>
<tr>
<th>MIC</th>
<th>Probability of obtaining a 40% T&gt; MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ceftriaxone 1g Q24</td>
</tr>
<tr>
<td>0.25</td>
<td>100</td>
</tr>
<tr>
<td>0.5</td>
<td>100</td>
</tr>
<tr>
<td>1.0</td>
<td>S</td>
</tr>
<tr>
<td>2.0</td>
<td>I</td>
</tr>
<tr>
<td>4.0</td>
<td>R</td>
</tr>
</tbody>
</table>

Dose plays a big role in the time above the MIC!!

“Breakpoint established with the understanding that a dosage of at least 1 g every 8 hours would be administered for cefotaxime”
Pharmacodynamics of Vancomycin and Other Antimicrobials in Patients with \textit{Staphylococcus aureus} Lower Respiratory Tract Infections

Pamela A. Moise-Broder,\textsuperscript{1} Alan Forrest,\textsuperscript{1,2} Mary C. Birmingham\textsuperscript{1} and Jerome J. Schentag\textsuperscript{1,2}

1 CPL Associates, LLC, Amherst, New York, USA
2 University at Buffalo School of Pharmacy and Pharmaceutical Sciences, Buffalo, New York, USA
OUTCOMES ASSOCIATED WITH PK/PD TARGET

Clinical Response

<table>
<thead>
<tr>
<th>24-hour AUC/MIC</th>
<th>Cure</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>655 ± 374</td>
<td>378 ± 225</td>
</tr>
</tbody>
</table>

p = .0029

Bacteriological Response

<table>
<thead>
<tr>
<th>24-hour AUC/MIC</th>
<th>Eradicate</th>
<th>Persist</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>951 ± 1342</td>
<td>405 ± 224</td>
</tr>
</tbody>
</table>

p = .0046

DRUG ADMINISTRATION ALSO MAKES A DIFFERENCE

Example: Probability of cefepime target attainment

Intermittent dosing
1g Q12 → 2g Q8

Continuous infusion
2g/d → 6g/d

Allows one to use cefepime for isolates with high MICs
### Site and Type of Infection

<table>
<thead>
<tr>
<th>Site and Type of Infection</th>
<th>Dose</th>
<th>Frequency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate to severe pneumonia</td>
<td>1-2 g IV</td>
<td>Every 12 hours</td>
<td>10 days</td>
</tr>
<tr>
<td>Empiric therapy for febrile neutropenic patients</td>
<td>2 g IV</td>
<td>Every 8 hours</td>
<td>7 days</td>
</tr>
<tr>
<td>Mild to moderate uncomplicated UTI</td>
<td>0.5 – 1 g IV</td>
<td>Every 12 hours</td>
<td>7-10 days</td>
</tr>
<tr>
<td>Severe uncomplicated UTIs (incl pyelonephritis)</td>
<td>2 g IV</td>
<td>Every 12 hours</td>
<td>10</td>
</tr>
<tr>
<td>Complicated intra-abdominal infections</td>
<td>2 g IV</td>
<td>Every 12 hours</td>
<td>7-10 days</td>
</tr>
</tbody>
</table>

SPEAKING OF DOSING...

FDA Cefepime Package Insert for Cefepime = 4 unique doses!
AND THOSE WERE JUST THE APPROVED DOSES!

Cefepime regimens across 120 U.S. hospitals in 2012

Percent Daily Dose (grams)

- 0.5-1.5: 12%
- 2: 17%
- 3: 29%
- 4: 33%
- >6: 9%
THIS IS HOW WE WOUND UP WITH “S-DD” FOR CEFEPIME

<table>
<thead>
<tr>
<th>Test/Report Group</th>
<th>Antimicrobial Agent</th>
<th>Disk Content</th>
<th>Zone Diameter Interpretive Criteria (nearest whole mm)</th>
<th>MIC Interpretive Criteria (µg/mL)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Cefepime</td>
<td>30 µg</td>
<td>≥25</td>
<td>19–</td>
<td>–</td>
</tr>
</tbody>
</table>
### APPENDIX E, M100 S24

#### Table 2A. *Enterobacteriaceae*

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>Interpretive Criteria</th>
<th>SDD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC (µg/mL)</td>
<td>Dose</td>
</tr>
<tr>
<td>Cefepime</td>
<td>≤2</td>
<td>1 g every 12 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
RESISTANCE MECHANISM DOES NOT MATTER IN THIS!

Example: cephem exposure-response in vivo

Key message:

When adequate concentrations of drug are provided, ESBL and non-ESBL strains share same exposure-response curve

No “special mystery” behind ESBL-producing strains.

“All about the MIC”

T>MIC for Cefepime not influenced by ESBL production

Target T>MIC = 30%

Stasis

1 log killing

ESBL Expressing isolates
HOW IT FITS TOGETHER

Clinical Trials

Animal PK-PD

Target PK-PD Index (eg, %T>MIC 30%)

Human PK and PK-PD simulation (Monte Carlo)

MIC Breakpoint Recommendation
PK/PD Data

Microbiological Data

Clinical Data

MIC Breakpoints to Define S, I, R
CLINICAL BREAKPOINT $\leq 2 \, \mu G/ML$

P. AERUGINOSA (N=100) (DRUG X)

Most patients failed

Most patients responded

Some patients responded

Percent of Isolates

MIC ($\mu g/ml$)

S

I

R

$\leq 0.5$

1

2

4

8

$\geq 16$
Microbiological Breakpoint $\leq 4 \, \mu g/ml$

*P. aeruginosa (n=1000) (Hypothetical Drug X)*

<table>
<thead>
<tr>
<th>MIC, mcg/ml</th>
<th>Percent of Isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\leq 0.5$</td>
<td>15%</td>
</tr>
<tr>
<td>1</td>
<td>30%</td>
</tr>
<tr>
<td>2</td>
<td>20%</td>
</tr>
<tr>
<td>4</td>
<td>5%</td>
</tr>
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<td>8</td>
<td>10%</td>
</tr>
<tr>
<td>$\geq 16$</td>
<td>20%</td>
</tr>
</tbody>
</table>

- **Wild type isolates**
- **Isolates w/ acquired or mutational resistance**
1. **Pharmacokinetics** = absorption, distribution and elimination of drug. Combined with dose, determine the time course of drug concentration in serum (tissues / fluids).

2. **Pharmacodynamics** = relationship between serum concentration and the effect of the drug (i.e. bacterial killing).

3. Antimicrobial activity $\rightarrow$ relationship between PK and PD

4. Desired effect (killing or stasis) determines PK/PD target

When setting breakpoints, the probability of target attainment vs. MIC is taken into consideration, along with microbiological data and outcome studies.