Antibiotic Pharmacokinetics and Pharmacodynamics for Laboratory Professionals

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Objectives

• Describe the pharmacokinetics and pharmacodynamics of commonly used antibiotics
• Summarize contemporary application of antibiotic pharmacokinetics and pharmacodynamics
• Discuss situations in which clinicians may ask for additional antibiotic susceptibility testing
The Importance of PK/PD

• “Newer” concept in antibiotic therapy
• Preserve/increase efficacy of existent antibiotics
• Involves use of pharmacology, clinical outcomes and microbiology to optimize antimicrobial use
  – Improve outcomes
  – Minimize toxicity and resistance
Objectives

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Pharmacokinetics ("ADME")

- **Absorption**: The process by which a drug proceeds from the site of administration to the site of measurement; most often the blood.
- **Distribution**: The process of reversible transfer of drug to and from the site of measurement.
- **Metabolism**: The process of conversion of one chemical species to another chemical species.
- **Elimination**: The irreversible loss of drug from the site of measurement. By metabolism or excretion.

**Antimicrobial PK/PD**

**Pharmacokinetics (PK):**
the action of the body on the administered agent, absorption, distribution, metabolism & excretion, that define drug exposure.

**Pharmacodynamics (PD):**
the biochemical & physiologic response of a drug and its mechanism of action.

- The relationship between drug potency, drug concentration and effect.
- Antimicrobials are unique in that the target is the pathogen – not the host.
- Relationship between PK and drug effect on pathogen based on potency / activity of the drug vs the organism.
- **In vitro**: microbial death, growth inhibition, emergence of resistance.
- **In vivo**: clinical response.


Antimicrobial PK/PD

Pharmacokinetics (PK) & Pharmacodynamics (PD) of Antimicrobial Therapy

- **PK**: Quantified exposure
- **PD**: Antimicrobial effect. Host toxicity. Resistance.
  - The relationship between drug potency, drug concentration and effect.

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Minimum Inhibitory Concentration (MIC)

MIC: Surrogate of potency at the site of infection.

Known quantity of bacteria in each tube

Increasing antibiotic concentrations

MIC: Lowest concentration of an antimicrobial that results in inhibition of visible growth of a microorganism
Automated Susceptibility Testing – Clinical Caveats

- ± one doubling dilution
  - Multiple isolates, different MICs
- Specific issues:
  - *P. aeruginosa* and Vitek II
  - Pip/tazo issues on Vitek II
  - *S. aureus* vancomycin MIC
- Lack of testing for newer agents
Pharmacodynamic Parameters Relating to Efficacy

**Time Dependent Antibiotics:**
Beta-lactams, Linezolid, Tetracycline, TMP/SMX
Time > MIC

**Concentration Dependent Antibiotics:**
Peak/MIC: Aminoglycosides
AUC/MIC: Fluoroquinolones, vancomycin, azithromycin
Fractionating a total daily dose into once-, twice-, four-times-, and eight-times-daily fractions (same total daily dose)

- AUC will remain ~ unchanged. Cmax progressively declines.
- Time > MIC progressively increases.

<table>
<thead>
<tr>
<th>Total dose (mg/kg/24 h)</th>
<th>Interval</th>
<th>Dose (mg/kg) administered</th>
<th>AUC/MIC</th>
<th>Cmax/MIC</th>
<th>% T &gt; MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1600</td>
<td>q24h</td>
<td>1600 × 1</td>
<td>No change</td>
<td>↑↑↑</td>
<td>-</td>
</tr>
<tr>
<td>1600</td>
<td>q12h</td>
<td>800 × 2</td>
<td>No change</td>
<td>↑↑</td>
<td>↑</td>
</tr>
<tr>
<td>1600</td>
<td>q6h</td>
<td>400 × 4</td>
<td>No change</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>1600</td>
<td>q3h</td>
<td>200 × 8</td>
<td>No change</td>
<td>-</td>
<td>↑↑↑</td>
</tr>
</tbody>
</table>

Time kill curves for *P. aeruginosa* following exposure at one-quarter to 64x MIC

Concentration Dependent Agents

Classic example – Aminoglycosides, but also Fluoroquinolones, Daptomycin. Dosed-related increase in magnitude of kill & suppression of resistance

**PAE:** Persistent suppression of bacterial growth at concentrations below the MIC.

Growth curves of *P. aeruginosa* in neutropenic mice following single doses of tobramycin 4, 12, 20mg/kg

Growth curves of *P. aeruginosa* in neutropenic mice following imipenem 200mg/kg and tobramycin 8mg/kg, alone and in combination.
PK/PD
From Mice to Men

Septic shock, *P. aeruginosa* pneumonia, Severe ARDS on ECMO

**Index: BAL Pseudomonas**

7 days later: BAL Pseudomonas
Day 5 Meropenem 2 Q8hours over 3 hours

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Sensitivity</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>AZTREONAM</td>
<td>Sensitive</td>
<td>4</td>
</tr>
<tr>
<td>CEFEPIME</td>
<td>Sensitive</td>
<td>&lt;=2</td>
</tr>
<tr>
<td>CEFTAZIDIME</td>
<td>Sensitive</td>
<td>&lt;=2</td>
</tr>
<tr>
<td>CIPROFLOXACIN</td>
<td>Sensitive</td>
<td>&lt;=0.5</td>
</tr>
<tr>
<td>GENTAMICIN</td>
<td>Sensitive</td>
<td>4</td>
</tr>
<tr>
<td>IMIPENEM</td>
<td>Sensitive</td>
<td>&lt;=1</td>
</tr>
<tr>
<td>LEVOFLOXACIN</td>
<td>Sensitive</td>
<td>&lt;=0.5</td>
</tr>
<tr>
<td>MEROPENEM</td>
<td>Sensitive</td>
<td>&lt;=1</td>
</tr>
<tr>
<td>PIPERACillin/TAZOBAC</td>
<td>Sensitive</td>
<td>&lt;=8</td>
</tr>
<tr>
<td>TOBRAMYCIN</td>
<td>Sensitive</td>
<td>2</td>
</tr>
</tbody>
</table>

**Comments:** PSEUDOMONAS AERUGINOSA (MIC) MANY PSEUDOMONAS AERUGINOSA
Time Dependent Agents

Beta-Lactams: Time above MIC Matters
Plateau of bactericidal effect at concentrations >4x MIC
AHC Extended Infusion Protocols: Meropenem, Pip/Tazobactam, Cefepime

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Fraction of Dosing Interval Required for Free Drug Concentrations to Exceed the MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td><strong>30%</strong></td>
</tr>
<tr>
<td>Cephalosporins</td>
<td><strong>35-40%</strong></td>
</tr>
<tr>
<td>Carbapenems</td>
<td><strong>20%</strong></td>
</tr>
</tbody>
</table>

**Impact of Time above the MIC for Enterobacteriaceae**
Percent of dosing interval in which free-drug concentrations exceed the MIC (T > MIC) required for 3rd/4th gen cephalosporins vs. *E.coli, Klebsiella, Enterobacter & Serratia* spp producing varying β-lactamases in a murine thigh infection model.

CLSI 2014: Clinical Failures with cefepime MICs of 4-8mcg/mL, especially when lower (FDA approved) doses were used.
Dose optimization as a barrier to resistance.

- Exposed sensitive isolates to vancomycin to target an AUC/MIC 31-510.
- AUC/MIC <250: selection for resistant mutants with elevated MICs detected at 72hrs.
- Low level exposure: Similar data with quinolones vs *Pseudomonas* and Pneumococcus

**Table 2** Accessory gene regulator group II *Staphylococcus aureus* post-vancomycin exposure

| Dose (mg) | AUC/MIC (mg/L per hr) | Peak (mg/L) | Targeted Trough (mg/L) | MIC
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0 hr</td>
</tr>
<tr>
<td>62.5 q 12 hr</td>
<td>31</td>
<td>2.5</td>
<td>0.6</td>
<td>1</td>
</tr>
<tr>
<td>125 q 12 hr</td>
<td>62</td>
<td>5</td>
<td>1.2</td>
<td>1</td>
</tr>
<tr>
<td>250 q 12 hr</td>
<td>123</td>
<td>10</td>
<td>2.5</td>
<td>1</td>
</tr>
<tr>
<td>500 q 12 hr</td>
<td>264</td>
<td>20</td>
<td>5.0</td>
<td>1</td>
</tr>
<tr>
<td>750 q 12 hr</td>
<td>382</td>
<td>30</td>
<td>7.5</td>
<td>1</td>
</tr>
<tr>
<td>1,000 q 12 hr</td>
<td>510</td>
<td>40</td>
<td>10.0</td>
<td>1</td>
</tr>
</tbody>
</table>

AUC = area under the concentration–time curve; MIC = minimum inhibitory concentration.
Antifungal PK/PD

PK/PD relationship of antifungal dose over time relative to organism MIC.

- Cmax/MIC
- AUC/MIC
- T>MIC

Antimicrobial Optimization: PK/PD Summary

PK/PD essential to leverage efficacy, minimize toxicity and optimize response

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- **Summarize contemporary application of antibiotic pharmacokinetics and pharmacodynamics**
- Discuss situations in which clinicians may ask for additional antibiotic susceptibility testing
β-Lactams: Extended or Continuous Infusion

- Increase time above MIC
  - ICU patients
- Potential for lower total daily doses
  - Cost containment
  - Minimize toxicity
- IV access poses problems
- Common antibiotics include:
  - Pip/tazo, cefepime, ceftazidime, ceftaz/avibactam, aztreonam, oxacillin, nafcillin, vancomycin*, ?ceftolozane/tazo
Cefepime Target Attainment

Conventional Dose Methods & Target Attainment (30min infusions)

<table>
<thead>
<tr>
<th>Dose (All over 30min)</th>
<th>E.coli</th>
<th>Klebsiella</th>
<th>Pseudomonas</th>
<th>Acinetobacter</th>
</tr>
</thead>
<tbody>
<tr>
<td>1g q4h</td>
<td>95.3</td>
<td>95.3</td>
<td>82.6</td>
<td>57.9</td>
</tr>
<tr>
<td>1g q8h</td>
<td>93</td>
<td>93</td>
<td>45-71</td>
<td>--</td>
</tr>
<tr>
<td>2g q8h</td>
<td>95.8</td>
<td>95.8</td>
<td>84.9</td>
<td>61.1</td>
</tr>
<tr>
<td>1g q6h</td>
<td>91.9</td>
<td>91.9</td>
<td>69.5</td>
<td>41.5</td>
</tr>
<tr>
<td>2g q12h</td>
<td>78.9</td>
<td>78.9</td>
<td>53.6</td>
<td>28.2</td>
</tr>
<tr>
<td>1g q12h</td>
<td>66.1</td>
<td>66.1</td>
<td>35.5</td>
<td>11.6</td>
</tr>
</tbody>
</table>

Probability of Target Attainment at 60% $fT>MIC$ for Prolonged Infusion Regimens

Dotted line represents the intended target for 6 doses listed, each infused over 4hours.

**Goal:** 90% probability of free drug concentration above the MIC for 60% of the dose interval.

Meropenem Target Attainment

- Extended infusion is “gold standard” in ICU patient
  - Can use if MIC ≥ 2
- Product stability at room temperature prohibits continuous infusion

Vancomycin

- Glycopeptide antibiotic, 60 years + clinical use
- Concentration-independent kill, post-abx effect
  - Slowly cidal vs. *Staphylococcus* spp.
  - Static vs. *Enterococcus* spp.
- Narrow therapeutic index, potential for toxicity → therapeutic drug monitoring
- $\text{AUC}_{24\text{-hour}} / \text{MIC} > 400 \text{mg/L}^* \text{hr}$ predicts efficacy against *S. aureus*

2009 Vanco Consensus Guidelines

• Maintain troughs > 10mg/L to prevent resistance

• Trough of 15-20mg/L surrogate for AUC$_{24\text{-hour}}$ of ≥ 400mg/L*hr
  – Based on practicality and presumed relationships to AUC$_{24\text{-hour}}$ target attainment
  – Limited human data

• Abandon when vancomycin MIC > 1mg/L

Troughs of 15-20mg/L?

- Troughs of 15-20mg/L may yield $\text{AUC}_{24\text{-hour}} > 400\text{mg/L*hr}$ for many patients.\(^1\)
- *Direct relationship* between vancomycin exposure and nephrotoxicity.\(^2\)
- Two-level AUC monitoring decreased median vanco trough level and rate of nephrotoxicity compared to historical trough-based monitoring.\(^3\)
- Prospective observational, multicenter study found elevated AUCs did not correlate with clinical efficacy but rather with nephrotoxicity.\(^4\)

AUC vs. Trough (n=34) [Unpublished Aurora Data]

*91.2% ICU; 85.3% of patients had bacteremia, endocarditis or pneumonia
High Dose Aminoglycosides for Gram-Negative Infections

• Hartford Nomogram vs. 2-level approach
• **Hartford**: simple, fine for MICs ≤ 1mg/L
• **2-level approach**: patient-specific, better for MICs of 2mg/L

\[ Ke = \frac{\ln(C_1/C_2)}{(T_2-T_1)} \]
\[ t^{\frac{1}{2}} = 0.693 / Ke \]

![Graph showing concentration over time for different dosing times.](image)
Fluoroquinolones (FQs)

- **Breakpoints matter**, especially for gram-negatives
- **FDA’s FQ breakpoints are controversial**

> Table 1. USCAST MIC breakpoints compared to three other antimicrobial agent breakpoint organizations when testing the fluoroquinolone class compounds (modified from the Quinolone Report, 2017; V.1.2).

<table>
<thead>
<tr>
<th>Organism/Antimicrobial</th>
<th>CLSI&lt;sup&gt;a&lt;/sup&gt;</th>
<th>USA-FDA</th>
<th>EUCAST&lt;sup&gt;b&lt;/sup&gt;</th>
<th>USCAST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entrobactriaceae</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≤1 / ≥4</td>
<td>≤1 / ≥4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>≤0.25 / &gt;0.5&lt;sup&gt;d&lt;/sup&gt;</td>
<td>≤0.25 / ≥1</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>≤2 / ≥8</td>
<td>≤2 / ≥8&lt;sup&gt;d&lt;/sup&gt;</td>
<td>≤0.5 / &gt;1</td>
<td>≤0.5 / ≥2</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>--</td>
<td>≤2 / ≥8&lt;sup&gt;e&lt;/sup&gt;</td>
<td>≤0.25 / &gt;0.25</td>
<td>≤0.25 / ≥0.5&lt;sup&gt;f&lt;/sup&gt; (valid for E. coli,</td>
</tr>
</tbody>
</table>
Ciprofloxacin and *P. aeruginosa*

- Cipro 400mg IV Q12h is standard dose
- 400 mg IV Q8h for *P. aeruginosa* improves PD target attainment and clinical cure.

**Ineffective** if MIC is 1mg/L, warranting consideration of a lower MIC breakpoint.

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Reasons Clinicians Request Additional Susceptibility Testing

- Drug interactions
- Allergies
- Outpatient “convenience”
- Synergy
- MIC at the “breakpoint”
Antibiotic Allergies

• B-lactam “allergy” is common
  – Up to 20% of hospitalized patients
    • Mostly “penicillins”
  – Up to 90% able to tolerate penicillin

• Poor history + clinician hesitancy = alternative therapy

• Alternative therapy associated with worse outcomes and adverse events

Allergy Example

- 60 year old Female with chronic kidney disease and catheter-associated urinary tract infection.

- > 100,000 cfu/mL
- *P. aeruginosa*
- Blood cultures (2/2) NGTD
- Allergies:
  - TMP/SMX (rash)
  - Pip/tazo (rash)
  - Levofloxacin (rash, anxiety)

*patient tolerated cefepime

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>4</td>
<td>S</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>&gt;8</td>
<td>R</td>
</tr>
<tr>
<td>Cefepime</td>
<td>16</td>
<td>R</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>16</td>
<td>R</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1</td>
<td>S</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2</td>
<td>S</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>2</td>
<td>S</td>
</tr>
<tr>
<td>Meropenem</td>
<td>8</td>
<td>R</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>2</td>
<td>S</td>
</tr>
</tbody>
</table>
Allergy Example (continued)

• MD requesting ceftolozane/tazo Etest
  – doesn’t want AG due to MIC and kidney disease
  – doesn’t want FQ due to MIC and allergy history

• Empirically treated with ceftolozane/tazo and RUO Etest MIC comes back as 1mg/L (“Susceptible”)
Outpatient Convenience Example

• 55 year old male with MSSA bacteremia and MSSA recovered from knee joint s/p debridement. Treated with Nafcillin 2g every 4 hours in the hospital but this is not possible for him as an outpatient.
  – Insurance won’t cover home health
  – Patient also wants to return to work

• MD requests the daptomycin MIC which is hidden by your lab for MSSA isolates.
  – Will allow for once daily dosing at infusion clinic
Extenuating Circumstances Example

• 29yo male, injection drug user with MSSA bacteremia and native, right-sided (tricuspid valve) endocarditis.
• Receiving nafcillin and repeat blood cultures are negative.
• Patients attempting to leave AMA.
• ID MD calls and asks for levofloxacin MIC for the MSSA isolate.
Extenuating Circumstances Example

• Cipro and Levo MICs for MSSA?
• Both are “susceptible”

• MD writes prescriptions for oral ciprofloxacin and rifampin
  – Effective for native, right-sided MSSA endocarditis in small U.S. cohort

Drug Interaction Example

- VRE abdominal wall abscess responding to daptomycin (MIC 4mg/L) and now the MD hopes to finish therapy with an oral antibiotic.
- The linezolid MIC is 2mg/L but the patient is on sertraline (anti-depressant), trazodone (for sleep) and amitriptyline (for fibromyalgia).
Drug Interaction Example (continued)

• Linezolid is a reversible, nonselective inhibitor of monoamine oxidase and has the potential for interaction with adrenergic and serotonergic agents
  – Serotonin syndrome; severe side effect
• MD is asking for tedizolid MIC as this agent much less likely to interact with her other medications
• “Send out” susceptibility test
Hidden susceptibility Example

- 90 year old female with a vancomycin-resistant E. faecium UTI. MD would like oral therapy and the isolate is linezolid non-susceptible (4mg/L) and resistant to nitrofurantoin (64mg/L). The daptomycin MIC is 2mg/L.
- MD is asking for tetracycline MIC and a fosfomycin Etest MIC.
• Why tetracycline?

• Doxycycline can be used for VRE UTI
  – Cite data
  – Tetracycline susceptibility predicts doxycycline susceptibility (M100)

• Fosfomycin has a broad-spectrum of activity and is a good option for UTI.
  – NOT for pyelonephritis nor bacteremia
Conclusions

• PK/PD commonly used by clinicians to optimize anti-infective therapy while minimizing toxicity and resistance development
• PK/PD literature is dynamic
• Clinicians are often confronted with situations in which additional susceptibility data can be informative
Questions

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