Optimizing Antibiotic Use through Pharmacokinetic and Pharmacodynamic Principles

Natalie Williams-Bouyer, Ph.D.
Associate Professor
Department of Pathology
Division of Clinical Microbiology
UTMB Health
Galveston, Texas
Objectives

• Review the basic concepts of pharmacokinetics (PK) and pharmacodynamics (PD).

• Discuss the importance of understanding PK/PD properties of the major antibiotic classes.

• Discuss how optimal dosing of antibiotics through the use of PK/PD principles can be utilized to reduce the misuse/overuse of these agents and antibiotic resistance.
“The rational use of antibacterial drugs should be based upon two principles. First, the specific identity of the infecting organism must be determined. Second, a test must be devised which will provide an accurate estimate that the antibiotic will be effective in vivo.”

Petersdorf and Plorde
In the 1963 review article entitled “The Usefulness of In Vitro Sensitivity Test in Antibiotic Therapy”, Petersdorf and Plorde commented on the relatively new practice (25 years at the time) of utilization of antimicrobial agents to treat infectious agents. In this review, the authors commented on the tempered enthusiasm and usage of these drugs could exert both beneficial and harmful effects. Due to this it was noted that certain criteria were necessary for the rational use of these agents (Annu. Rev. Med. 14:41-56; 1963).

The authors noted that experimental infections in animals had been performed to assess antimicrobial activity. However, the response to drug activity had been found to be an unreliable guide to treatment in human disease. The method was also expensive and cumbersome. Therefore, efforts were made toward development of in vitro sensitivity tests and their application to clinical infections.
Basis of *In Vitro* Susceptibility Testing Development

- Earliest methods based on comparison of the infecting organism with a standard strain of known susceptibility.

- Later tests based on a comparison of antibiotic concentration in body fluids with the minimal inhibitory concentration of drug to inhibit growth *in vitro*.

  - Organism defined as sensitive based on conc. of antibiotic attainable in the body, which exceeds necessary conc. to inhibit its growth *in vitro*. 
In Vitro Susceptibility Testing

- Designed to determine the activity of antimicrobial agents in a standardized, static test environment:
  - Exposure of relatively small numbers of organisms ($10^5$ to $10^6$ CFU) to constant levels of antibiotics.
  - Relatively constant state of bacterial growth and fixed conditions of temperature, humidity and oxygen conc.
  - *In vitro* activity assessed by determining minimal inhibitory concentration (MIC)
    - Most important measure of antimicrobial potency.
Traditionally, antimicrobial selection by clinicians has been based on in vitro susceptibility data as well as clinical trials that enrolled patients infected with susceptible pathogens. These trials were largely powered to show equivalence or non-inferiority between agents (*Pharm Times*. 2007; 79-88).

The in vitro antimicrobial activity of antibiotics is usually assessed by determining the MIC after overnight aerobic incubation of a standardized inoculum of bacteria in low protein liquid medium at pH 7.2. *In vitro* conditions vary from those at the site of infection, where the environment is frequently anaerobic and acidic, and tissue protein may bind a variable amount of the drug.
Limitations of *In Vitro* Susceptibility Testing

- Does not address the clinical situation where large numbers of organisms ($\geq 10^9$) are exposed to fluctuating levels of antibiotic.

- Discrepancy between *in vitro* susceptibility test results and therapeutic effectiveness
  - Occurs from the many factors that affect influence on the interactions of the antibiotic and bacteria *in vivo*
Note:

- The *in vitro* antimicrobial activity of antibiotics is usually assessed by determining the MIC after overnight aerobic incubation of a standardized inoculum of bacteria in low protein liquid medium at pH 7.2. *In vivo* conditions vary from those at the site of infection, where the environment is frequently anaerobic and acidic, and tissue protein may bind a variable amount of the drug.

- MIC is determined at a fixed point in time after exposure to antibiotic concentrations that remain constant throughout an overnight incubation period. The MIC does not provide information on the time course of the antimicrobial effect of the fluctuating antibiotic levels, which are present in a treated patient.
How are *in vitro* susceptibility testing results utilized in the big picture of antibiotic treatment efficacy?
Factors Influencing Outcome of Antibiotic/Pathogen Interaction

- Pathogen
- Host Factors
- Antibiotic (Drug) Factors
Pathogen Factors

- Inoculum size
- Growth phase
- Virulence factors
  - Toxins
  - Extracellular enzymes
  - Metabolic products
Note:

- Factors that pertain to the pathogen may influence therapeutic effectiveness of an antibiotic:

- Virulence may result in enzyme elaboration and toxin production that are detrimental to the host, even in the presence of active antibiotics. Resultant tissue necrosis and abscess formation limit drug penetration and can impede antibiotic activity.

- Activity of certain classes of antibiotics (e.g. Beta-lactams) is subject to inoculum effect, where the activity of an antibiotic decreases as the concentration of the organism increases. Animal models have shown clinical correlation to the inoculum effect.
Host Factors: Pharmacokinetics (PK)

- Derived from the ancient Greek:
  - Pharmakon = Drug
  - Kinetikos = Motion

- The science of the rate of movement of drugs within biological systems, as affected by:
  - Absorption
  - Distribution
  - Protein Binding
  - Metabolism
  - Penetration
  - Intracellular Concentration
  - Elimination

- Collectively determine time course of drug conc. in serum.
- Affect time course of drug conc. in body tissues and fluids.
Note:

- Major PK factors include:
  - Adsorption: affected by MW, ionization and formulation of the antibiotic; associated patient factors include route of administration, acidity/alkalinity of stomach/intestine, rate of gastric emptying and presence of food in the stomach.
  - The rate and extent of adsorption is referred to as bioavailability; dependent on route of administration.
  - Distribution: dependent on membrane permeability, plasma protein binding, blood flow to tissues, lipophilicity of drug
  - Metabolism: body works to convert drugs to less active forms and increase water solubility; liver is primary site for drug metabolism.
  - Elimination: most antibiotics are excreted renally; some excretion from bile through feces
Antibiotic Factors: Pharmacodynamics (PD)

• The relationship between drug concentration and its effective activity

• Measures of PD specific to antibiotics include:
  • Minimal concentration of an antimicrobial needed to inhibit bacterial growth (MIC)

  • Measure of drug exposure

  • Persistent effects
Antibiotic Characteristics

• **Mode of Action**
  • Exploit biochemical differences between infecting organism and host
  • Operate by *impairing crucial life sustaining processes* in the microbe (i.e.- inhibition of components necessary for bacterial growth)

• **Target**
  • Component necessary for bacterial growth
  • Should be *selective* to microorganism to minimize toxicity

• **Route of Administration (Oral vs. Parenteral vs. Topical)**
  • Large determinant of successful delivery to site of infection
Measures of Antibiotic Effect

I. **Spectrum of Activity** - based on the # of bacterial species drug is active against

II. **Bacterial Sensitivity** - ability of bacterial strain to replicate following antibiotic exposure

III. **Therapeutic Index** - ratio of min. conc. likely to produce an adverse effect to min. conc. to produce desired effect
   - Can be affected by host factors

IV. **Ability to Penetrate** - delivery of antibiotic to site of infection
   - Can be most difficult challenge of antibiotic therapy
PK & PD Antibiotic Principles

What do we need to know?
Pharmacokinetics refers to what the body does to the drug.

Pharmacodynamics refers to what the drug does to the body/pathogen (antimicrobial)
PK/PD Relationship of Antibiotics

Fig. 1 Schematic representation of the complexity of interactions between patient, pathogen and antibiotic

**Note:**

- PK/PD of antimicrobial agents describes the triangular relationship amongst the potency of a drug against a microorganism, subject exposure to a drug (the concentration of antibiotic available for effect over time) and drug effects.

- In this relationship, the receptor of the antibiotic is located within the microorganism, instead of on a cell in the human body. Thus, the intended beneficial effects on the host will be secondary to the killing or growth inhibition of the pathogen. In this view, antimicrobial therapy is only one of the factors contributing to curing a patient.
PK/PD Metrics: Putting It All Together
Dr. Harry Eagle: Founding Father of PK/PD Principles

- Initially identified PK-PD principles in the 1940s and 1950s

- Used animal models to identify:
  - Time dependence of penicillin bactericidal activity
  - Concentration dependence of streptomycin and bacitracin activity
  - Mixed time vs. conc. pattern for tetracyclines

- Recognized implications of these observation for patients

- Work established that both time and concentration play an important role in antibiotic effectiveness
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>Proportion of drug absorbed into systemic circulation after administration. Drugs administered intravenously are usually 100% bioavailable; other dosage forms may be less bioavailable.</td>
</tr>
<tr>
<td>$C_{\text{min}}$</td>
<td>Minimum serum concentration of drug</td>
</tr>
<tr>
<td>$C_{\text{max}}$</td>
<td>Peak serum concentration of drug achieved following administration of a single dose</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>Time to peak serum concentration</td>
</tr>
<tr>
<td>$V_d$</td>
<td>Volume of distribution. A relative measure of the distribution of the drug throughout the body. $V_d&gt;3\text{L}$ indicates drug is distributed outside of the plasma.</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the serum concentration–time curve</td>
</tr>
<tr>
<td>$t_{\frac{1}{2}}$</td>
<td>Elimination half-life; time required for serum concentration of the drug to be reduced by 50%</td>
</tr>
<tr>
<td>$T&gt;\text{MIC}$</td>
<td>Amount of time that the serum concentration is above the minimum inhibitory concentration required for bactericidal/bacteriostatic effects; applicable to antimicrobials only.</td>
</tr>
</tbody>
</table>
Pharmacokinetic/Pharmacodynamic (PK/PD) Breakpoints

• Refer to the antibacterial concentrations calculated from PK/PD parameters and the dimension of those parameters for predicting efficacy *in vivo*.

• The specific PK/PD factors correlating with bacteriological efficacy depend on the nature of drug action in bacterial killing/inhibition
  • Concentration-dependent or time-dependent.

• The efficacy of a given antibiotic utilized to eradicate a specific bacterial infection combines the use of the resulting MIC, along with PK/PD values associated with standard dosing:
  • MIC is a good indicator of the potency of an antibiotic, but it indicates nothing about the time course of antimicrobial activity.
  • PK parameters quantify the serum level time course of an antibiotic.
Concentration vs. Time Curve

- Concentration dependent (Cmax/MIC)
- Adsorption Phase
- AUC/MIC
- Elimination Phase ($T_{1/2}$)
- Time dependent ($T>$MIC)
- Cmax (peak)
- T>MIC
- T>MIC (MIC)
- INJECTION

Concentration dependent (Cmax/MIC)
Note:

- $C_{\text{max}}$ = peak concentration after single drug dose
- $C_{\text{min}}$ = lowest concentration before the next drug dose (trough)
- AUC = area under the serum concentration time curve
- MIC = minimal inhibitory concentration; antibiotic concentration resulting in inhibition of visible growth of microbes
- $T > \text{MIC}$ = time of concentration greater than MIC
- AUC/MIC = persistent serum drug concentration vs. MIC
### Predictors of Bacterial Eradication: Pharmacokinetic/Pharmacodynamic Parameters

<table>
<thead>
<tr>
<th>Bacterial Killing/Persistent Effect*</th>
<th>Therapy Goal</th>
<th>PK/PD Measurement</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration-Dependent/Prolonged Persistent Effect</td>
<td>High Peak Serum Concentration</td>
<td>Peak/MIC</td>
<td>Aminoglycosides; Daptomycin; Quinolones; Metronidazole</td>
</tr>
<tr>
<td>Time-Dependent/No Persistent Effect</td>
<td>Long Duration of Exposure</td>
<td>Time Above MIC</td>
<td>β-lactams (Penicillins; Cephalosporins; Carbapenems); Monobactams</td>
</tr>
<tr>
<td>Time-Dependent/ Moderate to Long Persistent Effect</td>
<td>Enhanced Amount of Drug</td>
<td>24-h AUC/MIC</td>
<td>Clindamycin; Erythromycin/Azithromycin/Clarithromycin; Linezolid; Tetracyclines; Vancomycin</td>
</tr>
</tbody>
</table>

*Post-Antibiotic Effect (PAE) is the persistent suppression of bacterial growth following antibiotic exposure.

The three pharmacodynamic properties of antibiotics include:

- **Time-dependent killing:**
  - Period of time that it takes for a pathogen to be killed by exposure to an antibiotic.
  - Maximum suppression of the organism is maintained as long as antibiotic concentration remains above the MIC.

- **Concentration-dependent killing:**
  - Direct relationship between antibiotic concentration and bactericidal effect.
  - Goal is to maximize concentration to attain highest possible concentration at infection site.

- **Post antibiotic effect (PAE):**
  - Describes persistent suppression of bacterial growth after antimicrobial exposure.
Goal of PK/PD Metrics

• Establish the **PK/PD Target** required for effective antimicrobial therapy

• Identify which **PK/PD parameter** (T> MIC, AUC/MIC, Peak/MIC) best predicts in vivo antimicrobial activity.

• Determine the **magnitude** of the PK/PD parameter required for in vivo efficacy (changes in cfu or survival in animals and clinical/microbiological cure in humans).
Use of Animal Models in PK/PD Evaluation of Antibiotics

- Identifying PK/PD parameters correlating with efficacy
  - Dose-fractionation studies to reduce inter-dependence among the various parameters
    - Usually 3, 6, 12 and 24 h intervals
    - With long half-life drugs 12, 24, 36 and 72 h intervals have been used
Use of Animal Models in PK/PD Evaluation of Antibiotics

• Determining magnitudes of the PK/PD parameters required for efficacy and identifying factors that affect the magnitude

• Changes in cfu (short durations of therapy) vs. survival (longer courses)

• Clinical/microbiological efficacy in humans
PK/PD Indices of Major Antibiotic Classes
β-lactams (T>MIC)

- In vivo animal studies have demonstrated that β-lactams have a slow continuous kill characteristic
  - Related to time serum concentration exceeds the MIC
  - Effect independent of peak levels
  - Administered in multiple daily doses to optimize PD end-point

- In vitro killing curve studies:
  - Activity rapidly saturated at concentrations = 4 times MIC; increasing concentrations had no increased killing effect
  - No PAE on *Streptococcus* spp. and GNB (carbapenems are the exception).
\textbf{β-lactams: Optimizing Exposure}

- Optimum level of exposure varies for different agents within the β-lactam class

- Required \%\(T>MIC\) for efficacy:
  - 50\%-70\% for \textit{cephalosporins}
  - 50\% for \textit{penicillins}
  - 40\% for \textit{carbapenems}

- The presence of neutrophils reduces the \(T>MIC\) required for efficacy by 5\%-10\%.
Aminoglycosides ($C_{\text{max}}$/MIC)

- $C_{\text{max}}$/MIC between 8 and 12
  - Higher concentrations do not increase efficacy

- Significant PAE
  - Single daily dose optimal to increase aminoglycoside activity.
  - Can be associated with increased risk of renal toxicity and ototoxicity.
  - Monitoring of $C_{\text{min}}$ is advocated to minimize drug side effects.
Fluoroquinolones: Concentration Dependent

- Can be dosed to optimize both $C_{\text{max}}$/MIC and AUC/MIC values
  - Suggested $C_{\text{max}}$/MIC >10
  - Levofloxacin/gatifloxacin AUC/MIC in patients with *S. pneumoniae* CAP has been described to be $\geq 33.7$

- Although $C_{\text{max}}$/MIC and AUC/MIC ratio predict efficacy, indices are sometimes co-linear and cannot be separated.
Levofloxacin/
Gatifloxacin AUC/MIC

Table 4.
Clinical and Microbiological Responses Stratified by Free-Drug
AUC$_{24}$/MIC Ratios$^a$

<table>
<thead>
<tr>
<th>Free-drug AUC/MIC Ratio Range</th>
<th>No. Patients</th>
<th>No. (%) Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Clinical Cure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Microbiological Cure</td>
</tr>
<tr>
<td>21–30</td>
<td>8</td>
<td>6 (75)</td>
</tr>
<tr>
<td>31–40</td>
<td>6</td>
<td>4 (66)</td>
</tr>
<tr>
<td>41–100</td>
<td>13</td>
<td>13 (100)</td>
</tr>
<tr>
<td>101–150</td>
<td>9</td>
<td>8 (89)</td>
</tr>
<tr>
<td>151–200</td>
<td>4</td>
<td>4 (100)</td>
</tr>
<tr>
<td>201–250</td>
<td>4</td>
<td>3 (75)</td>
</tr>
<tr>
<td>251–300</td>
<td>4</td>
<td>4 (100)</td>
</tr>
<tr>
<td>301–350</td>
<td>3</td>
<td>3 (100)</td>
</tr>
<tr>
<td>&gt;350</td>
<td>7</td>
<td>6 (86)</td>
</tr>
</tbody>
</table>

$^a$AUC = area under the curve, MIC = minimum inhibitory concentration. Reprinted, with permission, from reference 39.

Key Concepts: PK/PD Indices

- PK/PD parameters correlate with bacteriological and clinical outcome in animal models and in humans.

- PK/PD parameters can be used to select agents with maximum potential for bacterial eradication.

- Currently available agents vary significantly in achieving PK/PD parameters necessary for bacterial eradication.
Can PK/PD be used in everyday clinical practice? Could this optimize antibiotic utilization?
Pharmacodynamic Measures of Antimicrobial Effects

- PK/PD relationships vital in translation of microbiological activity and achieving successful treatment outcomes
- Studies over the past 20+ years have more clearly defined the PK/PD properties of the major antibiotic classes
- Important to the general design of dosing, development of new antibiotics and reduction of the selection of resistant microorganisms.
Patient Specific Approach

- PK partially dictates dosage requirements and becomes vital to obtain accurate estimate of PK parameters to aid in antimicrobial activity.

- PK parameters are generally derived from general population and are used to set dosing.

- Best case scenario would be to derive patient specific PK/PD parameters.
  - Time and cost limiting factors
  - Usu. limited to patients with severe infections
PK/PD Considerations for Critically Ill Patients

Critical illniss has greatest effect on volume of distribution and excretion

In critically ill patients, therapy should target MIC of problematic pathogens, such as Enterobacteriaceae and Pseudomonas aeruginosa, which are associated with high mortality.

Critically Ill Patients

Variable PK

Variability in Antimicrobial Concentration

Less Likely to Reach PD Targets

Increased Risk of Treatment Failure

Increased Risk of Antimicrobial Resistance
Table 3
Ideal approach to adjust the dose

Initial dosing regimen (chosen by patient’s physician)
Blood sampling (two or more post-distributional samples)
Pharmacokinetic analysis (peak, AUC, CL)
Obtain MIC of micro-organism
Adjust dose or/and intervals (PK/PD)
Re-determine concentrations
Adjust again

# Antibiotic Optimization: Dosing

<table>
<thead>
<tr>
<th>Antibiotic class</th>
<th>Pharmacodynamic (PD) profile</th>
<th>PD parameter</th>
<th>Clinical optimization strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>concentration-dependent</td>
<td>( \frac{f_{\text{Cmax}}}{\text{MIC}} \geq 10 ) to 12; total AUC/MIC ( \geq 156 )</td>
<td>High-dose, once-daily or extended interval dosing; dosing strategy can use a nomogram (Hartford Nomogram) or be individualized using therapeutic drug monitoring and MIC</td>
</tr>
</tbody>
</table>
| \( \beta \)-lactams penicillins carbapenems cephalosporins | time-dependent time-dependent time-dependent | \( f_{T>MIC} \geq 50 \)
\( f_{T>MIC} \geq 30-40 \)
\( f_{T>MIC} \geq 50-70 \) | Continuous or prolonged infusion; can be combined with greater doses to treat higher MIC organisms |
| Fluoroquinolones | concentration-dependent      | \( \frac{f_{\text{Cmax}}}{\text{MIC}} \geq 10 \) to 12; total AUC/MIC \( > 125 \) for gram-negatives; \( \frac{f_{\text{AUC}}}{\text{MIC}} > 30-50 \) for gram-positives | Increase dose related to MIC; however careful of increases in toxicity associated with higher concentrations; Use the most potent agent (i.e., lowest MIC) to maximize AUC/MIC ratio |
| Glycopeptides/Lipopeptides daptomycin vancomycin | concentration-dependent time-dependent | \( \frac{f_{\text{AUC}}}{\text{MIC}}; \frac{f_{\text{Cmax}}}{\text{MIC}} \) total AUC/MIC \( > 400 \) | Maximize dose in relation to MIC; Maximize over daily dose in relation to MIC; target trough concentrations of 15-20 mcg/ml |
| Macrolides/Azalides | time-dependent | AUC/MIC | N/A |
| Oxazolidinone (linezolid) | time-dependent | total AUC/MIC \( > 110 \) | Maximize overall daily dose in relation to MIC; standard dose optimized for most susceptible bacteria up to MIC of 2 mcg/ml. |
| Polymyxins | concentration-dependent | \( \frac{f_{\text{AUC}}}{\text{MIC}} > 12 \) to 15; total AUC/MIC \( > 60 \) | Maximize overall daily dose in relation to MIC while considering nephrotoxicity; Consider algorithm for loading and maintenance doses by Garonzik (70) |
| Tetracyclines/Glycylcyclines doxycycline tigecycline | time-dependent time-dependent | AUC/MIC \( * \) \( \frac{f_{\text{AUC}}}{\text{MIC}} \) | Approved dosage optimized for most susceptible bacteria in intra-abdominal infections and complicated skin infections; if tolerated, increase overall daily dose to 200mg daily to maximize pharmacodynamics for more serious infections or Acinetobacter spp. |

* Clinically relevant AUC/MIC targets for these antibiotics have not been well established

Table 1: Summary of antibiotic classes, pharmacodynamics parameter, exposure threshold and strategy to optimize pharmacodynamics.
Summary Thoughts

• Each antibiotic has its own pharmacokinetic profile

• Each class of antibiotic has a different pharmacodynamic profile based on the cidal/static characteristics on bacteria

• Individualized dosing regimens using known PK/PD characteristics are important to optimize patient outcomes and minimize antimicrobial resistance

• PK profiles change over time (particularly in critically ill patients); possibly warranting periodic reconsideration of dosing regimens
Optimizing Antibiotic Use through Pharmacokinetic and Pharmacodynamic Principles

Natalie Williams-Bouyer, Ph.D.
Associate Professor
Department of Pathology
Division of Clinical Microbiology
UTMB Health
Galveston, Texas