Infectious Diseases PRN Focus Session—Infectious Diseases 102: Applying the Basics to Clinical Practice
Activity No. 0217-0000-11-093-L01-P (Knowledge-Based Activity)

Tuesday, October 18
1:15 p.m.–3:15 p.m.
Convention Center: Spirit of Pittsburgh Ballroom A

Moderator: Jason Gallagher, Pharm.D., BCPS
Associate Professor, Clinical Specialist, Infectious Diseases, Director, Infectious Diseases Pharmacotherapy Residency, Temple University, Philadelphia, Pennsylvania

Agenda

1:15 p.m.  Microbiology, Revisited
Conan MacDougall, Pharm.D., MAS, BCPS
Associate Professor of Clinical Pharmacy, University of California–San Francisco, School of Pharmacy, San Francisco, California

1:55 p.m.  Mechanisms of Antimicrobial Resistance
Brian A. Potoski, Pharm.D., BCPS
Associate Professor, University of Pittsburgh School of Pharmacy, Pittsburgh, Pennsylvania

2:35 p.m.  Antimicrobial Pharmacodynamics, from Bench to Bedside
C. Andrew DeRyke, Pharm.D.
Medical Education & Research Liaison, Optimer Pharmaceuticals, Orlando, Florida

Faculty Conflict of Interest Disclosures
C. Andrew DeRyke: employee of Optimer Pharmaceuticals.
Conan MacDougall: no conflicts to disclose.
Brian A. Potoski: no conflicts to disclose.

Learning Objectives

1. Describe the physiological characteristics of bacteria that lead to their pathogenicity and virulence.
2. Determine the relevance of biofilm production in the treatment of infection.
3. Illustrate how normal flora prevent pathogenic invasion by opportunistic bacteria.
4. Explain the four basic mechanisms of resistance employed by bacteria against antibacterial agents.
5. Describe which mechanisms are employed by which bacteria against which drugs.
6. Illustrate the relationship between resistance and virulence, when it exists.
7. Apply knowledge gained in the preceding points to a patient case.
8. Explain the unique aspects that separate antimicrobial pharmacodynamics from that of other therapeutic areas.
9. Describe and define post-antibiotic effects, concentration- and time-dependency, and bactericidal and bacteriostatic effects as they apply to clinical decision making.
10. Choose optimal dosing of an antibiotic based upon its pharmacodynamic profile and minimum inhibitory concentration.
11. Describe instances where pharmacodynamic optimization has been shown to improve clinical outcomes.

Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/am
Microbiology, Revisited
Conan MacDougall, Pharm.D., MAS, BCPS
Associate Professor of Clinical Pharmacy
University of California, San Francisco
macdougallc@pharmacy.ucsf.edu
Conflicts of Interest

- No conflicts to disclose.
Objectives

1) Illustrate how normal flora prevent pathogenic invasion by opportunistic bacteria.

2) Describe the physiological characteristics of bacteria that lead to their pathogenicity and virulence.

3) Determine the relevance of biofilm production in the treatment of infection.
The Normal Flora

- You probably already know...
  ...most bacterial infections are caused by patient’s own bacteria
- You might not know...
  ...the “defensive” role of commensal bacteria
- What you can do about it now...
  ...selective digestive decontamination?
- What’s next...
  ...using estimated risk of resistance to drive drug selection
The Human “Superorganism”

~10\(^{13}\) human cells
~10\(^{14}\) bacterial cells on/in body

Prescott et al, Microbiology 4E, McGraw-Hill, 1999
## Intestinal Microbiome

<table>
<thead>
<tr>
<th>Organism</th>
<th>Log10 organisms (cfu/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oropharynx</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>8-10</td>
</tr>
<tr>
<td><strong>Aerobes</strong></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus</em></td>
<td>6-8</td>
</tr>
<tr>
<td><em>Enterococcus</em></td>
<td>rare</td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>rare</td>
</tr>
<tr>
<td>Yeasts</td>
<td>0-3</td>
</tr>
<tr>
<td><strong>Anaerobes</strong></td>
<td></td>
</tr>
<tr>
<td><em>Peptostreptococcus</em></td>
<td>4-6</td>
</tr>
<tr>
<td><em>Bifidobacterium</em></td>
<td>0-2</td>
</tr>
<tr>
<td><em>Lactobacillus</em></td>
<td>0-3</td>
</tr>
<tr>
<td><em>Clostridium</em></td>
<td>rare</td>
</tr>
<tr>
<td><em>Bacteroides</em></td>
<td>rare</td>
</tr>
</tbody>
</table>

Colonization Resistance

• Ability to resist overgrowth of potentially pathogenic endogenous & exogenous organisms (primarily aerobes)

• Physical & anatomic barriers
  – Intact mucosa, GI motility

• Chemical & immunologic factors
  – Gastric pH, secretory IgA

• Microbiologic factors
  – Indirect: stimulation of immune response, enhancement of epithelial barrier
  – Direct: Competition for resources, production of antibacterial
Direct Effects of Antimicrobials on GI Flora

Direct Effects of Antimicrobials on GI Flora

Direct Effects of Antimicrobials on GI Flora

<table>
<thead>
<tr>
<th>Drug</th>
<th>B. fragilis</th>
<th>Mean peak blood concentration (mg/L)</th>
<th>Mean fecal concentration (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC$_{50}$</td>
<td>MIC$_{90}$</td>
<td></td>
</tr>
<tr>
<td>Ertapenem</td>
<td>0.25</td>
<td>2</td>
<td>275</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>32</td>
<td>&gt;64</td>
<td>150</td>
</tr>
</tbody>
</table>

Protective anaerobic organisms

Piperacillin/tazobactam

Acquired pathogenic aerobes

Pathogenic aerobes

Fosfomycin

Clindamycin

Selective Digestive Decontamination

Levofloxacin

Selective Digestive Decontamination

• Antimicrobials administered:
  – in patients at high risk (ICU) of infection (VAP), to
  – selectively reduce endogenous potential pathogens (enteric, aerobic), and/or
  – reduce likelihood of colonization with exogenous potential pathogens

• Approach:
  – Selective oropharyngeal decontamination (SOD)
    • Oral administration of non- or- minimally absorbabed antibiotics
      – E.g. Tobramycin + Colistin + Amphotericin
  – Selective digestive decontamination (SDD)
    • SOD + short-duration IV antibiotics (e.g cefotaxime x4 days)
Selective Digestive Decontamination

• ~70 RCTs for SDD, ~11 meta-analyses
• Cochrane review (2009)
  Odds ratios (95% confidence interval)
  – SDD: RTI: 0.28 (0.20-0.38)  Mortality: 0.75 (0.65-0.87)
  – SOD: RTI: 0.44 (0.31-0.63)  Mortality: 0.97 (0.82-1.16)
• Unresolved issues:
  – Single-center RCTs
  – Recruitment bias
  – Various SDD & SOD regimens
  – Long-term ecologic effects
  – Effects in areas with high prevalence of resistance
  – Cost-effectiveness
  – Instinctive revulsion

Selective Digestive Decontamination

• de Smet et al (NEJM 2009)
  – Cluster-randomized trial 13 Dutch ICUs
  – Anticipated ventilation >48 hours or ICU stay >72 hours
  – Assigned SDD/SOD/standard care for all pts x6 months

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Std care</th>
<th>SDD (vs Std Care)</th>
<th>SOD (vs Std Care)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-day mortality</td>
<td>27.5%</td>
<td>26.9% [0.83 (0.72-0.97)]</td>
<td>26.6% [0.86 (0.74-0.99)]</td>
</tr>
<tr>
<td>Bact/fungemia</td>
<td>9.3%</td>
<td>4.3% [0.44 (0.34-0.57)]</td>
<td>6.5% [0.68 (0.53-0.86)]</td>
</tr>
<tr>
<td>eGNR</td>
<td>4.4%</td>
<td>0.9% [0.19 (0.12-0.32)]</td>
<td>3.1% [0.28 (0.16-0.47)]</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>2.8%</td>
<td>2.3% [0.85 (0.57-1.25)]</td>
<td>2.6% [0.91 (0.61-1.36)]</td>
</tr>
<tr>
<td>Systemic antibiotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DDD</td>
<td>33,688</td>
<td>29,663 [-11.9%]</td>
<td>30,299 [-10.1%]</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>4,451</td>
<td>8,473 [+86.6%]</td>
<td>995 [-25.4%]</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>1,334</td>
<td>724 [-45.7%]</td>
<td>3,935 [-13.3%]</td>
</tr>
</tbody>
</table>
### Selective Digestive Decontamination

  - Resistance prevalence surveys from de Smet study
  - Rectal & respiratory samples from all ICU pts

<table>
<thead>
<tr>
<th>Sample</th>
<th>Drug</th>
<th>Resistance prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prior to SDD</td>
<td>During SDD</td>
</tr>
<tr>
<td>Rectal</td>
<td>Ceftazidime</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>Tobramycin</td>
<td>9%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Ceftazidime</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Tobramycin</td>
<td>14%</td>
</tr>
</tbody>
</table>

SDD by Any Other Name?

No preventive antibiotics for anyone

Single-dose surgical prophylaxis

Preemptive antibiotics for cirrhotic patients with ascites

SDD for ventilated ICU patients?

Multi-dose surgical prophylaxis “until drains out”

Prophylaxis for neutropenic patients

Broad-spectrum prophylaxis on admission
What’s Next: Quantifying Collateral Damage of Antimicrobials

- Implicit calculation of risks & benefits
  - Risk (abx tx) = Risk (untreated infection) - Risk (ADR) - “Risk” (cost) [- Risk (antibiotic resistance)]
  - Risk (antibiotic resistance) not well-defined

- Paul et al J Antimicrob Chemother 2006
  - Created computerized expert system
  - Assigned “antibiotic resistance coefficients” for each drug
  - Used in selection of “optimal” antibiotic regimen

What’s Next: Quantifying Collateral Damage of Antimicrobials

Virulence Factors

• You probably already know...
  ...whether a bacterium causes disease often related to its production of virulence factors

• You might not know...
  ...how virulence factors contribute to disease process

• What you can do about it now...
  ...protein synthesis inhibitors as antitoxins

• What’s next...
  ...anti-virulence-factor antibodies in development
Invasion

Adhesins

Proteases
Glycanases

Type III secretion signaling
Defense

Capsule

Sequestration inside vacuole

Survival inside phagolysosome
Damage

- Superantigens
- Unrestrained immune activation
- Pore-formers
- Cell lysis
- Second messenger activators
- Protein synthesis inhibitors
- Paralysis
- Neurotransmitter release inhibitors (proteases)
- Various effects
# Bacterial Exotoxins and Countermeasures

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Organism</th>
<th>Class</th>
<th>Countermeasure</th>
</tr>
</thead>
</table>
| Diphtheria toxin       | *C. diptheriae* | Protein synthesis inhibitor | Diphtheria antitoxin  
|                        |              |                        | Diphtheria toxoid vaccine                           |
| Tetanus toxin          | *C. tetani*  | Protease               | Tetanus antitoxin  
|                        |              |                        | Tetanus toxoid vaccine                              |
| Botulinum toxin        | *C. botulinum* | Protease               | Botulinum antitoxin                                 |
| Lethal factor          | *B. anthracis* | Protease               | Anthrax killed vaccine                              |
| Pertussis toxin        | *B. pertussis* | 2\(^{nd}\) messenger activator | Pertussis acellular vaccine                        |
| Panton-Valentine leukocidin | *S. aureus* | Pore-former            |                                                    |
| Pyogenic exotoxin      | *S. pyogenes* | Superantigen           |                                                    |
| Shiga toxin            | *E. coli*    | Protein synthesis inhibitor |                                                |
| Exotoxin A             | *Pseudomonas* | Protein synthesis inhibitor |                                               |
| Toxin A/B              | *C. difficile* | 2\(^{nd}\) messenger activator |                                               |
Protein Synthesis Inhibitors as Antitoxins

Cell-wall-active agents

Protein synthesis inhibitors

[Diagram showing relationships between cell wall active agents, protein synthesis inhibitors, and antitoxins]
Protein Synthesis Inhibitors as Antitoxins: 
*In Vitro* Data

Protein Synthesis Inhibitors as Antitoxins: Animal Models

Protein Synthesis Inhibitors as Antitoxins: Clinical Data

<table>
<thead>
<tr>
<th>Subpopulation</th>
<th>Cell wall agents only</th>
<th>Protein synthesis inhibitors with or without cell wall agents</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial infections</td>
<td>12/25 (48%)</td>
<td>10/12 (83%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Deep infections</td>
<td>1/7 (14%)</td>
<td>10/12 (83%)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>No surgery</th>
<th>Surgical intervention</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial infections</td>
<td>9/22 (41%)</td>
<td>3/3 (100%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Deep infections</td>
<td>0/6 (0%)</td>
<td>1/1 (100%)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Protein Synthesis Inhibitors as Antitoxins: Beyond Streptococci?

## What’s Next: Novel Virulence Factor Countermeasures

<table>
<thead>
<tr>
<th>Factor</th>
<th>Organism</th>
<th>Countermeasure</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panton-Valentine leukocidin</td>
<td><em>S. aureus</em></td>
<td>Linezolid</td>
<td>Clinical practice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PVL subunit vaccine</td>
<td>Animal models</td>
</tr>
<tr>
<td>Pyogenic exotoxin</td>
<td><em>S. pyogenes</em></td>
<td>Clindamycin</td>
<td>Clinical practice</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Engineered soluble T-cell receptor</td>
<td>Preclinical development</td>
</tr>
<tr>
<td>Shiga toxin</td>
<td><em>E. coli</em></td>
<td>Urtoxazumab, monoclonal antibody</td>
<td>Phase II trial</td>
</tr>
<tr>
<td>Exotoxin A</td>
<td><em>Pseudomonas</em></td>
<td>Exotoxin A toxoid vaccine</td>
<td>Animal models</td>
</tr>
<tr>
<td>Toxin A/B</td>
<td><em>C. difficile</em></td>
<td>Humanized anti-toxin monoclonal antibodies</td>
<td>Phase II trial</td>
</tr>
</tbody>
</table>
Biofilms

- You probably already know...
  - ...infections associated with prosthetic materials are difficult to eradicate

You might not know...
- ...how biofilms are associated with antibiotic resistance

- What you can do about it now...
  - ...rifampin as an anti-biofilm agent

- What’s next...
  - ...quorum-sensing inhibitors
Biofilm Architecture

1. Adsorption
2. Irreversible attachment
3. Mature microcolony formation
4. Growth and division
5. Multispecies consortia

Processes:
- Planktonic bacteria
- Extracellular polymeric substance ("slime")
- Dispersion
- Chemoattraction
- Signal molecules
- Water channel
# Biofilms in Human Infections

<table>
<thead>
<tr>
<th>Native Tissue</th>
<th>Prosthetic Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular access fistulas</td>
<td>Vascular catheters</td>
</tr>
<tr>
<td>Prostate gland</td>
<td>Urinary catheters</td>
</tr>
<tr>
<td>Heart valves (often w/abnormalities)</td>
<td>Artificial heart valves (metal &amp; bioprosthetic)</td>
</tr>
<tr>
<td>Lungs in cystic fibrosis</td>
<td>Orthopedic implants</td>
</tr>
<tr>
<td>Periodontitis</td>
<td>Contact lenses</td>
</tr>
</tbody>
</table>
Biofilms and Antibiotic Resistance

<table>
<thead>
<tr>
<th>Drug</th>
<th>% Planktonic MSSA Strains Inhibited</th>
<th>% Biofilm MSSA Strains Inhibited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin</td>
<td>100%</td>
<td>18%</td>
</tr>
<tr>
<td>Linezolid</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>100%</td>
<td>9%</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>100%</td>
<td>27%</td>
</tr>
</tbody>
</table>

- Mechanisms of resistance
  - Reduced penetration
  - Altered metabolism
  - Upregulation of efflux pumps
  - Higher inocula

Rifampin as Anti-Biofilm Agent

## Rifampin as Anti-Biofilm Agent

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active vs organisms in various metabolic states</td>
<td>Extensive drug interactions</td>
</tr>
<tr>
<td>Bactericidal activity</td>
<td>Added toxicity</td>
</tr>
<tr>
<td>Penetrates into biofilm well</td>
<td>Rapid emergence of resistance as monotherapy &amp; with high organism burden</td>
</tr>
<tr>
<td>Displays additive to synergistic activity in many combinations</td>
<td>Combination activity not always predictable; indifferent to antagonistic in some organisms/models</td>
</tr>
<tr>
<td>Extensive tissue distribution</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Data Supporting Adjunctive Use of Rifampin in Biofilm Infections

<table>
<thead>
<tr>
<th>Infection</th>
<th>Data</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Native tissue</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Native valve endocarditis</td>
<td>Randomized controlled trial</td>
<td>+/-</td>
</tr>
<tr>
<td>Chronic osteomyelitis</td>
<td>Cohort</td>
<td>+/-</td>
</tr>
<tr>
<td><strong>Prosthetic material</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular catheter (prevention)</td>
<td>Randomized controlled trial</td>
<td>++</td>
</tr>
<tr>
<td>Prosthetic valve endocarditis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S. epidermidis</em></td>
<td>Cohort studies, case series</td>
<td>+</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>Case series</td>
<td>+</td>
</tr>
<tr>
<td>Ventricular shunts</td>
<td>Case series</td>
<td>+</td>
</tr>
<tr>
<td>Orthopedic implants</td>
<td>Randomized controlled trial</td>
<td>++</td>
</tr>
</tbody>
</table>

++=very beneficial +=beneficial +/-=equivocal

Staphylococcal knee/hip PJI <1 year
Debridement & retention
Randomized, double-blind (?)


18 patients
Plus Rifampin
2 weeks
Rifampin/Ciprofloxacin

Flucloxacillin (MSSA)
or Vancomycin (MRSA)

15 patients
Plus Placebo
2 weeks
Placebo/Ciprofloxacin

Hips x3 months
Knees x6 months
Or until failure

Clinical cure (lack of symptoms, CRP<5, stable joint)
24 months after initial therapy

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>RIF</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per-protocol</td>
<td>12/12</td>
<td>7/12</td>
<td>0.02</td>
</tr>
<tr>
<td>Intention-to-treat</td>
<td>16/18</td>
<td>9/15</td>
<td>0.10</td>
</tr>
<tr>
<td>Rifampin resistance</td>
<td>0/0</td>
<td>3/4</td>
<td>--</td>
</tr>
</tbody>
</table>
What’s Next: Quorum-Sensing Inhibitors

Summary

• The “War on Bugs”
  – Old paradigm: thermonuclear warfare – kill all bugs dead
  – New paradigm: neutron bomb – kill bad bugs, leave infrastructure
  – Future paradigm: electromagnetic pulse – disrupt communication & cooperation

• What are we doing now?
  – Best evidence – least used: Selective digestive decontamination
  – Moderate evidence – standard of care: rifampin for prosthetic device infections
  – Weak evidence – variously used: clindamycin for toxigenic Strep infections
Antimicrobial Pharmacodynamics: from Bench to Bedside

C. Andrew DeRyke, Pharm.D.
Optimer Pharmaceuticals, Inc.
Orlando, FL
Conflict of Interest

Employee of Optimer Pharmaceuticals, Inc.
Learning Objectives

• Explain the unique aspects that separate antimicrobial pharmacodynamics from that of other therapeutic areas.

• Describe and define post-antibiotic effects, concentration- and time-dependency, and bactericidal and bacteriostatic effects as they apply to clinical decision making.

• Choose optimal dosing of an antibiotic based upon its pharmacodynamic profile and minimum inhibitory concentration.

• Describe instances where pharmacodynamic optimization has been shown to improve clinical outcomes
Pharmacokinetics

“PK is what the body does to the drug”

- **Absorption**
- **Distribution**
- **Metabolism**
- **Elimination**

- **Concentration**
- **C<sub>max</sub>**
- **AUC**
- **Elimination half-life** (t<sub>1/2</sub>, k<sub>10</sub>)
- **C<sub>min</sub>**

AUC = Area under the concentration-time curve
C<sub>max</sub> = Maximum plasma concentration
C<sub>min</sub> = Minimum plasma concentration
Pharmacodynamics
“PD describes the critical interaction between drug and bug”

Describes the relationship between drug concentration and pharmacologic effect

– Antimicrobial Effect
  • Antimicrobial PD is unique since only class of drugs that exert that intended activity on another living organism other than our own cells
  • Links PK and drug effect on bacteria (minimum inhibitory concentration)

– Toxicity (toxicodynamics)
Minimum Inhibitory Concentration (MIC)

Known quantity of bacteria placed into each tube

Lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism

- 0.25 µg/mL
- 0.5 µg/mL
- 1.0 µg/mL
- 2.0 µg/mL
- 4.0 µg/mL
- 8.0 µg/mL
- 16 µg/mL

Increasing antibiotic concentration
How is Resistance Reported?

• Minimum Inhibitory Concentration (MIC):
  – The most refined means of measuring in vitro antibacterial activity
  – Difficult to interpret for most clinicians

• Clinical Laboratory Standards Institute (CLSI) establishes tentative MIC breakpoints:
  – Susceptible (S)
  – Intermediate (I): low level of resistance
  – Resistant (R): high level of resistance

• FDA defines final breakpoints when agent is approved

• Discordance is not uncommon:
  – e.g., vancomycin, doripenem, cephalosporins against Gram-negatives
Determination of Clinical Breakpoints (where % S comes from)

- Indicate at which MIC the chance of eradication (success) prevails significantly over failure
- Several approaches to determination:
  - Populations of pathogens with higher MICs in the bimodal or normal distribution
  - Clinical trial data documenting success or failure with higher MIC strains
  - Pharmacodynamics
Wrong way to interpret

“I review the profile and pick the antimicrobial agent with the lowest MIC”
## MIC susceptibility breakpoints against *Pseudomonas aeruginosa*

<table>
<thead>
<tr>
<th>MICs (µg/mL)</th>
<th>S</th>
<th>I</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piperacillin-tazobactam</td>
<td>≤ 64</td>
<td></td>
<td>≥128</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≤ 1</td>
<td>2</td>
<td>≥ 4</td>
</tr>
</tbody>
</table>

Resident: “So an MIC of 16 µg/mL is very resistant to ciprofloxacin but quite sensitive to piperacillin-tazobactam. How does this make sense?”
Comparing concentration-time profile (drug exposure) of Pip-tazo & Ciprofloxacin

- **Piperacillin-tazobactam 3.375 g IV**
  - **CIP Cmax** = 4.6 µg/mL
  - **P/T Cmax** = 96 µg/mL

- **Ciprofloxacin 400 mg IV**
  - **P/T MIC** = 16 µg/mL

**Graph details:**
- X-axis: Time (hours)
- Y-axis: Free Drug Conc (µg/mL)
- Key points:
  - Time 0: Initial concentration
  - Time 1-8: Concentration over time
Comparing concentration-time profile (drug exposure) of Pip-tazo & Ciprofloxacin

CIP MIC = 0.25 µg/mL
Wrong way to interpret

“I review the profile and pick the antimicrobial agent with the lowest MIC”

Rationale as to why this is not logical:
1. We don’t give the same mg or g dose of different antibiotics to patients
   - Piperacillin 4g (e.g. 4.5g dose) is 10 times more drug than Ciprofloxacin 400 mg
2. The resultant serum drug exposure (e.g., concentration-time curve) is different for different antibiotics
3. The MICs which harbor resistance mechanisms are different for different drug/bug combos
4. In vitro, in vivo animal, and clinical outcomes data show clinical and microbiological success for drug/bug combos at different MICs
Basics of Antimicrobial Pharmacodynamics
Concentration-Dependent vs. Independent Bacterial Killing

Common Pharmacodynamic Indices

AUC = Area under the concentration–time curve
MIC = Minimum Inhibitory Concentration
$C_{\text{max}}$ = Maximum or peak plasma concentration
$C_{\text{min}}$ = Minimum or trough plasma concentration
# Pharmacodynamic parameters predictive of outcome

<table>
<thead>
<tr>
<th>$C_{\text{max}}$:MIC</th>
<th>AUC:MIC</th>
<th>T&gt;MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Examples</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Azithromycin</td>
<td>Penicillins</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Fluoroquinolones</td>
<td>Cephalosporins</td>
</tr>
<tr>
<td>Polymyxins</td>
<td>Ketolides</td>
<td>Carbapenems</td>
</tr>
<tr>
<td></td>
<td>Linezolid</td>
<td>Monobactams</td>
</tr>
<tr>
<td></td>
<td>Daptomycin</td>
<td>Macrolides</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tigecycline</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organism kill</th>
<th>Therapeutic goal</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration-dependent</td>
<td>Maximize exposure</td>
<td>Optimize duration of exposure</td>
</tr>
<tr>
<td>Concentration or Time-dependent</td>
<td>Maximize exposure</td>
<td></td>
</tr>
<tr>
<td>Time-dependent</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Vesga *et al. ICAAC* 1997.
Definitions

- **Bactericidal:**
  - MBC/MIC is $\leq 4$
  - CLSI: $> 3 \log (99.9\%)$ reduction in CFU/mL in 18-24 hours of incubation in liquid media

- **Bacteriostatic:**
  - MBC/MIC $> 16$
  - CLSI: $< 3 \log (99.9\%)$ reduction in CFU/mL in 18-24 hours of incubation in liquid media

MIC = minimal inhibitory concentration
CLSI = Clinical & Laboratory Standards Institute
CFU = colony-forming unit.
Determination of Bactericidal Activity: The time kill method

- **Control**
- **Static**
- **Cidal**

99.9% Kill
## Bactericidal vs. Bacteriostatic

<table>
<thead>
<tr>
<th>Bacteriostatic</th>
<th>Bactericidal</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Erythromycin</td>
<td>• Penicillins</td>
</tr>
<tr>
<td>• Tetracyclines</td>
<td>• Carbapenems</td>
</tr>
<tr>
<td>• Clindamycin</td>
<td>• Cephalosporins</td>
</tr>
<tr>
<td>• Sulfa drugs</td>
<td>• Aminoglycosides</td>
</tr>
<tr>
<td>• Trimethoprim</td>
<td>• Vancomycin</td>
</tr>
<tr>
<td>• Chloramphenicol</td>
<td>• Fluoroquinolones</td>
</tr>
<tr>
<td>• Tigecycline</td>
<td>• Metronidazole</td>
</tr>
<tr>
<td></td>
<td>• Ketolides</td>
</tr>
</tbody>
</table>
Bactericidal vs. Bacteriostatic

- Bactericidal antibiotics are not required to treat the vast majority of infections, exceptions include:
  - Endocarditis
  - Meningitis
  - Neutropenia (?)

- Clinical experience with new agents in patients with highly resistant strains is more valuable than classifications based on *in vitro* studies

Post-antibiotic Effect (PAE)
Magnitude of persistent inhibitory effects of antimicrobial activity

![Graph showing PAE = 5.8 Hrs](image-url)

- **Control**
- **Antibiotic**

**Log$_{10}$ CFU/thigh**

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

T>MIC
Application of Antimicrobial Pharmacodynamics at the Bedside
T>MIC

Concentration

0

Time (hours)

MIC

T>MIC
Beta-Lactams: Targeted PD Exposure

• The optimum level of exposure varies for different agents within the beta-lactam class

• Required %T>MIC for efficacy:
  ~ 50%–70% for cephalosporins
  ~ 50% for penicillins
  ~ 40% for carbapenems

Intermittent Infusion
Piperacillin/Tazobactam 3.375g IV Q6H

- Healthy Volunteers

% $f_T > MIC = 50\%$
% $f_T > MIC = 83\%$

MIC = 16 µg/mL
MIC = 2 µg/mL

Intermittent Infusion 
Piperacillin/Tazobactam 3.375g IV Q6H

Healthy Volunteers- % fT>MIC = 50%
Hyperdynamic Patients- % fT>MIC = 33%

MIC = 16 µg/mL

Free Drug Conc (µg/mL)

Time (hours)

Probability of Achieving 50% $fT>MIC$

Pip/Tazo 4.5g Q6H (0.5 H infusion)

Adapted from DeRyke CA et al. Diagn Microbiol Infect Dis 2007; 58: 337-44.
30-day Mortality among patients with *Pseudomonas aeruginosa* bacteremia
Stratified by piperacillin-tazobactam MIC

Maximizing T>MIC

• Higher dose
• Increased dosing frequency
• Increased duration of infusion
Intermittent vs. Continuous Infusion Regimens

Intermittent Dosing Interval

Free drug Conc (µg/mL)

Antibiotic concentration exceeding the MIC

MIC$_1$

MIC$_2$

Time (24-hour period)

Intermittent Dosing

Continuous Infusion
Piperacillin/tazobactam 3.375gm administered as a 0.5h or 4h Infusion

Free drug Concentration (µg/mL)

Rapid Infusion (30 min)

Extended Infusion (4 h)

Time (h)

0 2 4 6 8

Free drug Concentration (µg/mL)

0.1 1.0 10.0 100.0

MIC
Pip/tazo for *P. aeruginosa* Infections: Clinical Implications of Extended Infusion Dosing

Continuous vs. Extended Infusion Implementation in Clinical Practice

Extended or Prolonged

- **Pros**
  - Daily antibiotic free-interval (50% of day)
  - Less frequent administration compared to intermittent
  - Same dose/delivery package as intermittent doses
  - Ambulatory patient

- **Cons**
  - Daily intravenous access
  - Labor, supplies and administration resources
  - Timing of administration for non-compatible drugs

Continuous

- **Pros**
  - Once daily administration
  - Reduced costs for labor, supplies, and administration

- **Cons**
  - Dedicated line
  - Compatibility issues
  - Stability and drug waste
  - Ambulatory patient

Cefepime Pharmacodynamics

Probability of achieving 50% $fT>MIC$ for VAP patients (CrCL: 50 mL/min – 120 mL/min)

- 100% Target Attainment
- 90% Target Attainment

Outcomes of Patients with Gram-Negative Bloodstream Infections Treated with Cefepime

$C_{\text{max}}$ : MIC

$C_{\text{max}}$ = Maximum plasma concentration

Concentration

Time (hours)

MIC

$C_{\text{max}}$ : MIC
Once-Daily Gentamicin vs Conventional (Q8H) Regimen

AUC = Area under the concentration–time curve

AUC:MIC

Concentration

Time (hours)

MIC
Vancomycin Pharmacodynamics in Patients with MRSA Pneumonia

Evaluating Vancomycin AUC/MIC at the bedside

Example: 53 y F, 95 kg, non-ICU, $\text{CL}_{\text{CR}} = 66 \text{ mL/min}$

Vancomycin 1500 mg daily; MRSA bacteremia, MIC = 1$\mu$g/mL

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Estimate $\text{CL}_{\text{CR}}$</th>
<th>66 mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 2</td>
<td>Estimate Vanco CL†</td>
<td>$75%$ of $\text{CL}_{\text{CR}} = 50$ mL/min Convert to L/h = 3.0 L/h</td>
</tr>
<tr>
<td>Step 3</td>
<td>Estimate AUC</td>
<td>$\text{AUC} = \frac{\text{Dose}}{\text{CL}}$ $\text{AUC} = \frac{1500}{3.0} = 500$</td>
</tr>
<tr>
<td>Step 4</td>
<td>Estimate AUC/MIC</td>
<td>$\frac{\text{AUC}}{\text{MIC}} = \frac{500}{1} = 500$</td>
</tr>
</tbody>
</table>

† Creatinine clearance and vancomycin clearance are NOT a 1:1 ratio

## Vancomycin Dosing Worksheet

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name:</td>
<td>ACCP</td>
</tr>
<tr>
<td>Age (years)</td>
<td>53</td>
</tr>
<tr>
<td>Sex (Male = 1, Female = 0)</td>
<td>0</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.5</td>
</tr>
<tr>
<td>Height (in)</td>
<td>64.0</td>
</tr>
<tr>
<td>Height (m)^2</td>
<td>2.64062</td>
</tr>
<tr>
<td>Actual Weight (kg)</td>
<td>95</td>
</tr>
<tr>
<td>Ideal Body Weight (kg)</td>
<td>54.1</td>
</tr>
<tr>
<td>Dosing Weight</td>
<td>54.1</td>
</tr>
<tr>
<td>Percent obese</td>
<td>1.75</td>
</tr>
<tr>
<td>Adjusted Body Weight (kg)</td>
<td>70.5</td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>1.1</td>
</tr>
<tr>
<td>Serum Albumin &gt;=3.0 (Yes = 1, No=0)</td>
<td>1</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td><strong>Female</strong></td>
</tr>
<tr>
<td>Creatinine Clearance (ml/min)</td>
<td>77</td>
</tr>
<tr>
<td>Creatinine Clearance (adjusted)</td>
<td>77</td>
</tr>
<tr>
<td>Creatinine Clearance (L/h)</td>
<td>3.9</td>
</tr>
<tr>
<td>Salazar-Corcoran Estimate</td>
<td>88</td>
</tr>
</tbody>
</table>

### Sawchuk-Zaske

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Regimen:</td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td>1500</td>
</tr>
<tr>
<td>Interval</td>
<td>24</td>
</tr>
<tr>
<td>Creatinine Clearance (adjusted)</td>
<td>0.269105</td>
</tr>
<tr>
<td>e^-k(tau)</td>
<td>3</td>
</tr>
<tr>
<td>Time of infusion</td>
<td>1.5</td>
</tr>
<tr>
<td>1-e^-k(t')</td>
<td>0.08</td>
</tr>
<tr>
<td>1-e^-k(tau)</td>
<td>0.73</td>
</tr>
<tr>
<td>e^-k(tau - t')</td>
<td>0.29</td>
</tr>
<tr>
<td>Vancomycin Parameters</td>
<td></td>
</tr>
<tr>
<td>Vancomycin Clearance (ml/min)</td>
<td>approx. 0.7-0.8*ClCr 49</td>
</tr>
<tr>
<td><strong>Vancomycin Clearance (L/h)</strong></td>
<td>3.0</td>
</tr>
<tr>
<td>Vancomycin Vd (L)</td>
<td></td>
</tr>
<tr>
<td>0.57 L/kg (ABW) (Clcr &gt;60ml/min)</td>
<td>54.2</td>
</tr>
<tr>
<td>0.83L/kg (ABW) (Clcr&lt;60ml/min)</td>
<td>78.9</td>
</tr>
<tr>
<td>Is Clcr&gt;60ml/min?</td>
<td>YES</td>
</tr>
<tr>
<td>Elimination rate constant (k) hr-1</td>
<td>0.055</td>
</tr>
<tr>
<td>Terminal half life (h)</td>
<td>12.7</td>
</tr>
<tr>
<td>Time to steady-state (h)</td>
<td>63</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax</td>
<td>36.4</td>
</tr>
<tr>
<td>Cmin</td>
<td>10.6</td>
</tr>
<tr>
<td>AUC(0-tau)</td>
<td></td>
</tr>
<tr>
<td>ln trap</td>
<td>35</td>
</tr>
<tr>
<td>log trap</td>
<td>471</td>
</tr>
<tr>
<td>total</td>
<td>506</td>
</tr>
<tr>
<td>1-e^-k(t')</td>
<td>0.08</td>
</tr>
<tr>
<td>1-e^-k(tau)</td>
<td>0.73</td>
</tr>
<tr>
<td>e^-k(tau - t')</td>
<td>0.29</td>
</tr>
<tr>
<td>elimination rate constant (k) hr-1</td>
<td>0.055</td>
</tr>
<tr>
<td>terminal half life (h)</td>
<td>12.7</td>
</tr>
<tr>
<td>Time to steady-state (h)</td>
<td>63</td>
</tr>
</tbody>
</table>