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”

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>Total</td>
<td>8-10</td>
</tr>
<tr>
<td>Aerobes</td>
<td></td>
</tr>
<tr>
<td>Streptococcus</td>
<td>6-8</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>rare</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>rare</td>
</tr>
<tr>
<td>Yeasts</td>
<td>0-3</td>
</tr>
<tr>
<td>Anaerobes</td>
<td></td>
</tr>
<tr>
<td>Peptostreptococcus</td>
<td>4-6</td>
</tr>
<tr>
<td>Bifidobacterium</td>
<td>0-2</td>
</tr>
<tr>
<td>Clostridium</td>
<td>0-3</td>
</tr>
<tr>
<td>Bacteroides</td>
<td>rare</td>
</tr>
<tr>
<td></td>
<td>0-3</td>
</tr>
</tbody>
</table>


~10^13 human cells
~10^14 bacterial cells on/in body

Prescott et al., Microbiology 4E, McGraw-Hill, 1999
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

<table>
<thead>
<tr>
<th>Drug</th>
<th><em>B. fragilis</em></th>
<th>Mean peak blood concentration (mg/L)</th>
<th>Mean fecal concentration (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ertapenem</td>
<td>0.25</td>
<td>2</td>
<td>275</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>&gt;64</td>
<td>150</td>
<td>258</td>
</tr>
</tbody>
</table>

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 absorbable 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

  - 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>
<th>Prior to SDD</th>
<th>During SDD</th>
<th>After SDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal</td>
<td>Cefazidime</td>
<td>6%</td>
<td>5%</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>12%</td>
<td>7%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tobramycin</td>
<td>9%</td>
<td>7%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>Cefazidime</td>
<td>10%</td>
<td>4%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin</td>
<td>10%</td>
<td>5%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tobramycin</td>
<td>14%</td>
<td>6%</td>
<td>12%</td>
<td></td>
</tr>
</tbody>
</table>


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 Chemotherapy 2006
  - Created computerized expert system
  - Assigned “antibiotic resistance coefficients” for each drug
  - Used in selection of “optimal” antibiotic regimen


SDD by Any Other Name?

- No preventive antibiotics for anyone
- Single-dose surgical prophylaxis
- Multi-dose surgical prophylaxis “until drains out”
- Preemptive antibiotics for cirrhotic patients with ascites
- Prophylaxis for neutropenic patients
- SDD for ventilated ICU patients?
- Broad-spectrum prophylaxis on admission

What’s Next: Quantifying Collateral Damage of Antimicrobials

- 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>38-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/Sepsis</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>CR-1</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% [0.65 (0.31-1.64)]</td>
<td>2.6% [0.91 (0.61-1.64)]</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>133,688</td>
<td>20.66 [11.9%]</td>
<td>30,299 [10.1%]</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>4,451</td>
<td>8,473 [4.6%]</td>
<td>995 [2.5%]</td>
</tr>
<tr>
<td>Carbenapenem</td>
<td>1,334</td>
<td>724 [45.7%]</td>
<td>3,935 [13.3%]</td>
</tr>
</tbody>
</table>

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ACCP 2011 Annual Meeting
Infectious Diseases 102: Applying the Basics to Clinical Practice 5
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

Defense

Bacterial Exotoxins and Countermeasures

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Organism</th>
<th>Class</th>
<th>Countermeasure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria toxin</td>
<td><em>C. diphtheriae</em></td>
<td>Protein synthesis inhibitor</td>
<td>Diphtheria antitoxin</td>
</tr>
<tr>
<td>Tetanus toxin</td>
<td><em>C. tetani</em></td>
<td>Protease</td>
<td>Tetanus antitoxin</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td><em>C. botulinum</em></td>
<td>Protease</td>
<td>Botulinum antitoxin</td>
</tr>
<tr>
<td>Lethal factor</td>
<td><em>B. anthracis</em></td>
<td>Protease</td>
<td>Anthrax killed vaccine</td>
</tr>
<tr>
<td>Pertussis toxin</td>
<td><em>B. pertussis</em></td>
<td>2nd messenger activator</td>
<td>Pertussis acellular vaccine</td>
</tr>
<tr>
<td>Panton-Valentine leokoxin</td>
<td><em>S. aureus</em></td>
<td>Pore-former</td>
<td></td>
</tr>
<tr>
<td>Pyogenic exotoxin</td>
<td><em>S. pyogenes</em></td>
<td>Superantigen</td>
<td></td>
</tr>
<tr>
<td>Shiga toxin</td>
<td><em>E. coli</em></td>
<td>Protein synthesis inhibitor</td>
<td></td>
</tr>
<tr>
<td>Exotoxin A</td>
<td><em>Pseudomonas</em></td>
<td>Protein synthesis inhibitor</td>
<td></td>
</tr>
<tr>
<td>Toxin A/B</td>
<td><em>C. difficile</em></td>
<td>2nd messenger activator</td>
<td></td>
</tr>
</tbody>
</table>

Damage

Protein Synthesis Inhibitors as Antitoxins
Protein Synthesis Inhibitors as Antitoxins:

*In Vitro* Data


Protein Synthesis Inhibitors as Antitoxins:

*Animal Models*


Protein Synthesis Inhibitors as Antitoxins:

*Clinical Data*

Subpopulation | Cell wall agents only | Protein synthesis inhibitors with or without cell wall agents | P-value |
---|---|---|---|
Superficial infections | 12/25 (48%) | 10/12 (83%) | 0.07 |
Deep infections | 1/7 (14%) | 10/12 (83%) | 0.006 |
No surgery | 9/22 (41%) | 3/3 (100%) | 0.04 |
Superficial infections | 0/6 (0%) | 1/1 (100%) | 0.14 |

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

Biofilms in Human Infections

Native Tissue | Prosthetic Device
--- | ---
Vascular access fistulas | Vascular catheters
Prostate gland | Urinary catheters
Heart valves (often w/abnormalities) | Artificial heart valves (metal & bioprosthetic)
Lungs in cystic fibrosis | Orthopedic implants
Periodontitis | Contact lenses

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

Pros

<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>S. epidermidis</td>
<td>Cohort studies, case series</td>
<td>+</td>
</tr>
<tr>
<td>S. aureus</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>

Forrest GH, et al. (Clin Microbiol Rev 2010;23:14-34)
Staphylococcal knee/hip PJI <1 year Debridement & retention Randomized, double-blind (?)

18 patients
Plus Rifampin
2 weeks
Rifampin/Ciprofloxacin
Hips x3 months

15 patients
Flucloxacillin (MSSA) or Vancomycin (MRSA)
Knees x6 months
Or until failure
Placebo/Ciprofloxacin

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

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”

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)

Conflict of Interest

Employee of Optimer Pharmaceuticals, Inc.
**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**

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>S</th>
<th>I</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25 µg/mL</td>
<td>≤ 64</td>
<td>≥ 128</td>
<td></td>
</tr>
<tr>
<td>0.5 µg/mL</td>
<td>≤ 1</td>
<td>2</td>
<td>≥ 4</td>
</tr>
</tbody>
</table>

**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, orphalosporins 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”

**Comparing concentration-time profile (drug exposure) of Pip-tazo & Ciprofloxacin**

- **P/T Cmax = 96 µg/mL**
- **CIP Cmax = 4.6 µg/mL**
- **P/T MIC = 16 µg/mL**

**MIC susceptibility breakpoints against *Pseudomonas aeruginosa***

Resident: “So an MIC of 16 µg/mL is very resistant to ciprofloxacin but quite sensitive to piperacillin-tazobactam. How does this make sense?”
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

Common Pharmacodynamic Indices

Pharmacodynamic parameters predictive of outcome

Examples

Vesga et al. ICAAC 1997.
### Definitions

- **Bactericidal:**
  - MBC/MIC is ≤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

---

### Bactericidal vs. Bacteriostatic

**Bacteriostatic**
- Erythromycin
- Tetracyclines
- Ceftriaxone
- Sulfonamides
- Trimethoprim
- Chloramphenicol
- Ticarcillin

**Bactericidal**
- Penicillins
- Carbapenems
- Cephalosporins
- Aminoglycosides
- Vancomycin
- Fluoroquinolones
- Metronidazole
- Ketolides

**Magnitude of persistent inhibitory effects of antimicrobial activity**

**Post-antibiotic Effect (PAE)**

**Application of Antimicrobial Pharmacodynamics at the Bedside**

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**Application of Antimicrobial Pharmacodynamics at the Bedside**

**Infectious Diseases 102: Applying the Basics to Clinical Practice**

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**References**

**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


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**Intermittent Infusion**

Piperacillin/Tazobactam 3.375g IV Q6H


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**Probability of Achieving 50% fT>MIC**

Pip/Tazo 4.5g Q6H (0.5 H infusion)

Adapted from Delpeyre CA et al. Drugs Microbiol (Apr 2007) 58: 337-44.

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**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) vs. Time (24-hour period)

Time (h)

Free drug Conc (µg/mL)

Intermittent Dosing
Continuous Infusion

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

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

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

Cefepime Pharmacodynamics

Probability of achieving 50% T>MIC for VAP patients (CrCL 50 mL/min – 120 mL/min)
Outcomes of Patients with Gram-Negative Bloodstream Infections Treated with Cefepime

<table>
<thead>
<tr>
<th>Cefepime MIC (µg/mL)</th>
<th>28-day mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 µg/mL (n=116)</td>
<td>23%</td>
</tr>
<tr>
<td>2 µg/mL (n=18)</td>
<td>29%</td>
</tr>
<tr>
<td>4 µg/mL (n=11)</td>
<td>27%</td>
</tr>
<tr>
<td>8 µg/mL (n=16)</td>
<td>56%</td>
</tr>
<tr>
<td>≥16 µg/mL (n=15)</td>
<td>53%</td>
</tr>
</tbody>
</table>


Once-Daily Gentamicin vs Conventional (Q8H) Regimen


Vancomycin Pharmacodynamics in Patients with MRSA Pneumonia

Evaluating Vancomycin AUC/MIC at the bedside
Example: 53 y F, 95 kg, non-ICU; CLCR = 66 mL/min
Vancomycin 1500 mg daily; MRSA bacteremia, MIC = 1µg/mL

Step 1
Estimate CLCR
66 mL/min

Step 2
Estimate Vanco CL1
75% of CLCR = 50 mL/min
Convert to 1/L/h = 3.0 L/h

Step 3
Estimate AUC
AUC = Dose/CL
AUC = 1500/3 = 500

Step 4
Estimate AUC/MIC
AUC/MIC = 500/1 = 500

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Sex (Male = 1, Female = 0)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.5</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Ideal Body Weight (kg)</td>
<td>54.1</td>
<td></td>
</tr>
<tr>
<td>Percent obese</td>
<td>1.75</td>
<td></td>
</tr>
<tr>
<td>Adjusted Body Weight (kg)</td>
<td>70.5</td>
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</tr>
<tr>
<td>Serum Creatinine</td>
<td>1.1</td>
<td>Sawchuk-Zaske</td>
</tr>
<tr>
<td>Serum Albumin</td>
<td>1</td>
<td>Yes = 1, No = 0</td>
</tr>
<tr>
<td>Creatinine Clearance (ml/min)</td>
<td>77</td>
<td>66</td>
</tr>
<tr>
<td>Interval</td>
<td>24</td>
<td>0 269105</td>
</tr>
<tr>
<td>Creatinine Clearance (L/h)</td>
<td>3.9</td>
<td>e^-k(tau) 0.05</td>
</tr>
<tr>
<td>Time of infusion</td>
<td>1.5</td>
<td>1-e^-k(t') 0.08</td>
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<tr>
<td>Cmax</td>
<td>36.4</td>
<td>37.0</td>
</tr>
<tr>
<td>Cmin</td>
<td>10.6</td>
<td>10.7</td>
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<tr>
<td>Vancomycin Parameters</td>
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</tr>
<tr>
<td>Vancomycin Vd (L)</td>
<td>0.57</td>
<td>L/kg (ABW) (Clcr &gt; 60 ml/min) 54.2</td>
</tr>
<tr>
<td>Vancomycin Vd (L)</td>
<td>0.83</td>
<td>L/kg (ABW) (Clcr &lt; 60 ml/min) 54.2</td>
</tr>
<tr>
<td>Vancomycin AUC(0-tau)</td>
<td>506</td>
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</tr>
<tr>
<td>Vancomycin half-life (h)</td>
<td>12.7</td>
<td></td>
</tr>
<tr>
<td>Time to steady-state (h)</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Elimination rate constant (k) hr^-1</td>
<td>0.055</td>
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</tr>
<tr>
<td>Terminal half-life (h)</td>
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<td></td>
</tr>
<tr>
<td>Time to steady-state (h)</td>
<td>63</td>
<td></td>
</tr>
</tbody>
</table>

### Calculations

- **Adjusted Body Weight (kg)**: 
  \[ \text{Adjusted Body Weight} = \text{Ideal Body Weight} \times (\text{Actual Body Weight} / \text{Ideal Body Weight}) \]

- **Serum Albumin**:
  - Yes = 1, No = 0

- **Creatinine Clearance (ml/min)**:
  \[ \text{Creatinine Clearance} = \frac{\text{Creatinine x Weight (kg)}}{\text{Height (cm) x 1000}} \]

- **Creatinine Clearance (L/h)**:
  \[ \text{Creatinine Clearance} = \frac{\text{Creatinine x Weight (kg)}}{\text{Height (cm) x 1000} x 60} \]

### Notes

- **Age**: 53 years
- **Sex**: Male (0)
- **Height**: 162.5 cm
- **Weight**: 95 kg
- **Ideal Body Weight**: 54.1 kg
- **Percent obese**: 1.75%
- **Adjusted Body Weight**: 70.5 kg
- **Serum Creatinine**: 1.1 mg/dL (Sawchuk-Zaske)
- **Serum Albumin**: 1 (Yes = 1, No = 0)
- **Creatinine Clearance (ml/min)**: 77 ml/min, 66 ml/min
- **Interval**: 24 hours, 0 269105
- **Creatinine Clearance (L/h)**: 3.9 L/h, e^-k(tau) 0.05
- **Time of infusion**: 1.5 hours, 1-e^-k(t') 0.08
- **Cmax**: 36.4 mg/L, 37.0 mg/L
- **Cmin**: 10.6 mg/L, 10.7 mg/L
- **Vancomycin Vd (L)**: 0.57 L/kg (ABW) (Clcr > 60 ml/min) 54.2
- **Vancomycin Vd (L)**: 0.83 L/kg (ABW) (Clcr < 60 ml/min) 54.2
- **Vancomycin AUC(0-tau)**: 506
- **Vancomycin half-life (h)**: 12.7 hours
- **Time to steady-state (h)**: 63 hours
- **Elimination rate constant (k) hr^-1**: 0.055
- **Terminal half-life (h)**: 12.7 hours
- **Time to steady-state (h)**: 63 hours

### Other Information

- **ACCP 2011 Annual Meeting**
- **Infectious Diseases 102: Applying the Basics to Clinical Practice**