Antibiotics Review
Safety and Dosing Considerations

Kerry L. LaPlante, Pharm.D., FCCP
Professor of Pharmacy, University of Rhode Island, College of Pharmacy
Adjunct Professor of Medicine, The Warren Alpert Medical School of Brown University
Senior Director of the Rhode Island Infectious Diseases Research (RIID) Program
Co-Director of Antimicrobial Stewardship Program, and Infectious Diseases Pharmacotherapy Specialist, Providence Veterans Medical Center, RI

DISCLOSURES
The information disseminated in this lecture is given in my personal capacity and not in my capacity as a VA employee nor does it necessarily reflect the views of the United States Department of Veterans Affairs

Role: Grant Investigator and Scientific Advisor
Companies: Merck, Pfizer, Allergan, Cempra, Davol/BARD, Ocean Spray, The Medicines Company
OBJECTIVES

1. Understand the role pharmacokinetic and pharmacodynamics play in dosing antibiotics.

2. Understand renal dosing strategies for antibiotics to avoid potential adverse drug events in patients.

3. Describe the most common adverse drug events associated with different classes of antibiotics.

Antibiotic Related Adverse Events

- *Clostridium difficile*, Gastroenteritis/diarrhea
- Antibiotic resistant organisms
- Antibiotic allergy
- General medication adverse events
Pharmacology

- **Pharmacokinetics** = what the body does to the drug
- **Pharmacodynamics** = what the drug does to the body

Antibiotic selection is complicated

- Will it reach the site of action?
- Safety / Toxicity
- How is the immune system?
- Infection or colonization?
- Is there resistance?
- Is the dose maximized?
Considerations in Adjusting Dose

- **CrCl is a starting point**: Remember this is just an estimate
- **Toxicities of the antibiotic**: Amoxicillin vs Aminoglycoside
- **Clinical Condition**: SCr trends, sepsis, stability of the pt
- **Infection type**: Meningittis vs pneumonia
- **Targeted Organism**: Resistant vs. Intermediate resistant vs. susceptible

Route of Administration

Oral and intravenous administration equivalent

- TMP/SMX
- Quinolones
- Tetracyclines
- Clindamycin (~80%)
- Linezolid
- Rifampin
- Metronidazole
- Fluconazole
- Voriconazole
- Valganclovir (=ganclovir)

If the gut works use it! Absorption 30 minutes vs 60-90 minutes
Antibiotics that do NOT Require Renal Dosage Adjustment

- Nafcillin/ Dicloxacillin
- Doxycycline
- Azithromycin
- Tigecycline
- Linezolid

- Metronidazole
- Moxifloxacin
- Ceftriaxone
- Clindamycin

ELIMINATION of DRUGS

The kidney is the most important organ for excreting drugs and their metabolites.

Renal excretion of unchanged drug is a major route of elimination for 25–30% of drugs administered to humans.
ELIMINATION

HALF-LIFE: is the time it takes for a drug to lose half its strength in the body

<table>
<thead>
<tr>
<th>Given one single bolus dose</th>
<th>Amount of Drug remaining..</th>
<th>Say 100mcg given as bolus dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>After one half life (t1/2)</td>
<td>50%</td>
<td>50mcg</td>
</tr>
<tr>
<td>2 half lives (t1/2)</td>
<td>25%</td>
<td>25mcg</td>
</tr>
<tr>
<td>3 half lives (t1/2)</td>
<td>12.5%</td>
<td>12.5mcg</td>
</tr>
<tr>
<td>3.3 half lives (t1/2)</td>
<td>6.25%</td>
<td>6.25mcg</td>
</tr>
<tr>
<td>4 half lives (t1/2)</td>
<td>3.125%</td>
<td>3.125mcg</td>
</tr>
<tr>
<td>5 half lives (t1/2)</td>
<td>1.56%</td>
<td>1.56mcg</td>
</tr>
</tbody>
</table>

Dosing intervals are selected based upon t1/2...

Glomerular Filtration Rate (GFR)

• Usually calculated using a mathematical formula that compares a person’s size, age, sex, and race to serum creatinine levels.

• A GFR under 60 mL/min/1.73 m² may mean kidney disease—the lower the GFR number, the worse the kidney function.

• **Definition**: Rate at which plasma is filtered across the glomerular capsule.

• Determines excretory and homeostatic function

• “Normal”: 90-150 ml/min
GFR and Weight

- Creatinine
  - Synthesized by skeletal muscle
  - Muscular individuals with higher levels
  - Malnourished individuals have lower levels

- BUN
  - Byproduct of protein intake
  - Poor nutrition may lower the BUN level

### Estimating GFR: MDRD and Cockcroft-Gault

<table>
<thead>
<tr>
<th></th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cockcroft-Gault</strong></td>
<td>Long-standing gold standard for the estimation of creatinine clearance</td>
<td>The original study was based on data from 249 male patients with stable renal function. The study used actual body weight, but mentioned that a correction factor of some kind should be used in patients with marked obesity or ascites.</td>
</tr>
<tr>
<td>1976 (All patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Jelliffe 1973</strong></td>
<td>Does not require a patient's height or weight because it describes renal function normalized to a body surface area of 1.73 m².</td>
<td>Published as a &quot;Letter to the Editor&quot;, while this was a landmark equation for its era, its use has become deprecated in favor of newer equations.</td>
</tr>
<tr>
<td>(Stable renal function)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Salazar-Corcoran 1988</strong></td>
<td>Designed to measure creatinine clearance in obese patients (defined as a BMI ≥ 30 m²). Derived from a &quot;fat free mass&quot; equation and was shown to be superior to the Cockcroft-Gault and Jelliffe methods when using total body weight.</td>
<td></td>
</tr>
<tr>
<td>(Obese patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MDRD (four-variable)</strong> 1999</td>
<td>More accurate than the Cockcroft-Gault method (particularly when using total body weight), but it is rarely used for drug dosing because most medications are validated using the Cockcroft-Gault method.</td>
<td>The MDRD equation was only studied in patients with renal dysfunction (GFR &lt; 60 mL/min/1.73 m²). Should not be used in patients with normal renal function.</td>
</tr>
<tr>
<td>(Renal Dysfunction)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
GFR: Declines with Age

- Two individuals, age 30 and age 70
- Both with serum creatinine 1
  - 30 yo: Creatinine clearance 98 ml/min
  - 70 yo: Creatinine clearance 64 ml/min

- GFR declines with aging, and as a result of decreased muscle mass
- Interpreting the serum creatinine by itself can be risky

http://clincalc.com/kinetics/crcl.aspx

Antibiotic Related Adverse Events

- *Clostridium difficile*, Gastroenteritis/diarrhea
- Antibiotic resistant organisms
- Antibiotic allergy
- General medication adverse events
First know the Pathogen, THEN select the antibiotic

• **S. aureus** (MSSA and MRSA)
  - → Skin and soft tissue infections & Pneumonia

• **Streptococcus pneumonia**
  - Community Acquired Pneumonia

• **E. coli** and **K. pneumonia** – ESBLs & CRE

• **C. difficile**

---

**S. aureus**

Has developed resistance to nearly every antibiotic used to treat it

- Produces toxins and biofilms
- Transient or persistent colonizer of skin
Drug Treatments for MRSA

- TMP/SMX (IV, PO)
- Clindamycin (IV & PO)
- Tetracycline’s (PO)
- Linezolid (IV, PO)
- Daptomycin (IV)
- Quinupristin/dalfopristin (IV)
- Tigecycline (IV)

- Glycopeptides:
  - Vancomycin (IV)
  - Dalbavancin (IV)
  - Oritavancin (IV)
  - Telavancin (IV)

- Cephalosporins (anti-MRSA):
  - Ceftaroline (IV)

Fluoroquinolones and MRSA

- MRSA demonstrate susceptibility to quinolones. This encourages consideration of these agents as treatment options.
- *S. aureus* carries a high potential for rapid development of resistance to quinolones.

- Fluoroquinolones uniquely predispose persons to colonization (and subsequent infection) with *S. aureus*
  - Increased risk for colonization and infection (AHR 2.49, 95% CI 1.02-6.07)
  - Increased expression of adherence factors promoting host colonization via over-expression of fibronectin-binding protein
- Fluoroquinolone exposure would have the dual effect of promoting *S. aureus* colonization while selectively eradicating MSSA strains; the net effect of which is to favor MRSA colonization

Trimethoprim – sulfamethoxazole
(Bactrim, Co-Trimoxazole)

- MRSA - most common first line outpt antibiotic in adults and pediatric population - active against ~90% MRSA
- In vitro activity against *E. faecalis*, but not *E. faecium*
  - Conflicting susceptibility and clinical failures reported
- PO and excellent bioavailability
- Poor activity against streptococcus (GAS, Beta hemolytic strep, ect)

**Adults:** 1-2 DS tablets (160mg TMP/800mg SMX) PO q 8-12h

**TMP/SMX**

**Toxicities**
- GI: N, V, D
- **Hypersensitivity** (fever, rash) 5% (higher in HIV+)
  - Contains sulfates, may trigger asthma in sulfate sensitive pts.
- **Hyperkalemia** (in 21% of adults): TMP reduces distal renal tubular secretion K+
  (monitor esp other meds that cause hyperK)
- **Increases in SCR:** Trimethoprim interferes with creatinine secretion which may lead to a rise in serum creatinine concentration than can be misinterpreted as a fall in GFR/ CrCl.

**Renal impairment:** CrCl greater than 30 mL/min, give usual dose; CrCl 15-30 mL/min, give one-half the usual dose; CrCl less than 15 mL/min, not recommended
### Linezolid (Zyvox)

<table>
<thead>
<tr>
<th>Class</th>
<th>Oxazolidinone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiological Spectrum</td>
<td>Gram-positive aerobes and anaerobes. <em>Staphylococcus spp</em> (MSSA, MRSA), Enterococcus (including VRE), Strep (cidal)</td>
</tr>
<tr>
<td>Does not cover</td>
<td><em>Gram negatives</em></td>
</tr>
</tbody>
</table>
| Uses                | • SSTI, PNA,  
|                     | • CA-MRSA pneumonia – necrotizing pneumonia in a seriously ill pt |
| Increasing uses/Interest | • VISA and VRSA  
|                     | • Pt “failing vancomycin therapy - 7-9 days of persistent bacteremia??, use in combination with another agent?”  
|                     | • Pneumonia: worsening infiltrate or clinical sx while on vancomycin after 2 to 3 days of vancomycin therapy.  
|                     | • Documented VRE infections |
| Should not be used  | MRSA or VRE decolonization |
| Monitoring          | • CBC weekly → Bone marrow suppression (within the first two weeks of therapy)  
|                     | → life of a platelet, average life span of circulating platelets is 7 to 10 days.  
|                     | • Optic neuritis and irreversible sensory motor polyneuropathy (prolonged tx i.e., >28 days)  
|                     | • Serotonin syndrome when co-administered with serotonergic agents (SSRIs, TCAs, MAOI, amphetamines, etc) |
| Dosing              | 600mg PO/IV q12h → no renal dose adjustments necessary |

### Daptomycin

**Approved 2003**

<table>
<thead>
<tr>
<th>Class</th>
<th>Lipopeptide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiological Spectrum</td>
<td>Gram-positive aerobes and anaerobes. <em>Staphylococcus spp</em> (MSSA, MRSA, MSSE and MRSE), <em>Enterococcus spp</em>. (including VRE → static mostly)</td>
</tr>
<tr>
<td>Does not cover</td>
<td>No gram negative anaerobic and aerobic activity (no <em>Pseudomonas, Acinetobacter or Gram negative anaerobe activity</em>)</td>
</tr>
<tr>
<td>Uses</td>
<td>ABSSSI and Gram positive bactremia and Rt sides IE</td>
</tr>
</tbody>
</table>
| Increasing uses/Interest | Osteo, Vanco MIC ≥ 1mcg/mL  
|                     | 2 minute once daily out pt infusion |
| Should not be used  | Pneumonia – inactivation by lung surfactant |
| Monitoring          | CPK (at start and weekly) and for Eosinophilic pneumonia – pt says “I cannot breath” while on dapto… |
| Dosing              | IE and Bacteremia 6 to 10 to 12mg/kg IV q24 or 48h (if CrCl <30ml/min)  
|                     | **DOsing IS INCREASING!** |
Ceftaroline fosamil (TEFLARO®) IV only (approved 2010)

<table>
<thead>
<tr>
<th>Class/MOA</th>
<th>broad-spectrum cephalosporin</th>
</tr>
</thead>
</table>
| Dose & Adjustments | • 600mg IV q12h (ABSSSI and CABP)  
  • Dosage adjustment is required in patients with moderate or severe renal impairment, and in patients with end-stage renal disease. Maintain interval (q12h) decrease dose.  
  • 600mg q8h (?_MSSA/MRSA bacteremia’s (unapproved use)) |
| Spectrum | • Gram-positive and Gram-negative bacteria commonly associated with ABSSSI (including MRSA) and CABP (including Streptococcus pneumoniae bacteremia) |
| Does not cover | • Pseudomonas, Enterococcus, Acinetobacter or Gram negative anaerobes (i.e. Bacteroides fragilis) |
| Safety | • In pooled clinical trials, no AR occurred in >5% of patients,  
  • recent cases – agranulocytosis when + clindamycin combo > 2 weeks |
| Monitoring | • Direct Coombs' test seroconversion  
  • Seroconversion from a negative to a positive direct Coombs' test seen in ~10% of pts in 4 pooled phase 3 clinical trials  
  • No adverse reactions representing hemolytic anemia were reported. |
| Drug-Drug Interactions | • No clinical drug-drug interaction studies have been conducted  
  • There is minimal potential for drug-drug interactions between ceftaroline and CYP450 substrates (not a substrate, inducer or inhibitor) |
| Special groups | • Pregnancy Category B, Phase 3 for Pediatric Subjects, Obese, and Meningitis underway: ClinicalTrials.gov |

Ceftaroline is now (2015) FDA approved for patients with ABSSSI with baseline S. aureus bacteremia and allows for a shorter intravenous (IV) infusion time (5min).

Vancomycin 1958-present

• Initial forms were very impure and had a lot of side effects  
• Bactericidal against most organisms  
• Concentration-independent killing profile  
• Low toxicity except when combined with aminoglycosides  
• Questionable activity against vanco-tolerant strains  
• Less effective than beta-lactams against beta-lactam sensitive organisms

Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists

2/15/2017
Overall Summary

• Increasing trough serum vancomycin concentrations to 15–20 mg/L to obtain an increased AUC/MIC of ≥400 may be desirable but is currently not supported by clinical trial data.

• Target attainment of an AUC/MIC of ≥400 is not likely in patients with S. aureus infections who have an MIC of ≥2 mg/L; therefore, treatment with alternative agents should be considered.

• Higher trough serum vancomycin levels may also increase the potential for toxicity, but additional clinical experience will be required to determine the extent of this potential.

Dosing and Monitoring Vancomycin

• 15 mg/kg × actual body weight, rounded to nearest 250mg
• Choose dosing interval based on creatinine clearance

Vancomycin Levels

• Vancomycin levels are not needed in patients with stable renal function who are on standard doses of Vancomycin.

• Vancomycin Peak levels are not indicated.

• Trough levels are indicated for patients on vancomycin whose renal function is changing, patients on an unusual dosing regimen, patients is morbidly obese.
### Selecting a Dosing Interval (estimates)

<table>
<thead>
<tr>
<th>Estimated CrCl (ml/min)</th>
<th>Dosing Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 100</td>
<td>q6 to 8</td>
</tr>
<tr>
<td>80-100</td>
<td>q8</td>
</tr>
<tr>
<td>50-79</td>
<td>Q12h</td>
</tr>
<tr>
<td>&lt;25ml/min</td>
<td>Q36 or q48</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Estimation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodialysis (check pre-dialysis level)</td>
<td>Give an initial loading dose of 15 -20 mg/kg Re-dose patient with 12-15 mg/kg when serum level ≤ 15 mcg/mL</td>
</tr>
<tr>
<td>Peritoneal dialysis</td>
<td></td>
</tr>
</tbody>
</table>

### Vancomycin Troughs

**Troughs not recommended for patients:**
- receiving therapy < 4 days
- receiving oral vancomycin therapy (minimal drug absorbed)

**Trough concentrations ONLY if:**
- requiring therapy > 4 days
- patients with severe or life threatening infections receiving concomitant nephrotoxic drugs (e.g. cyclosporine, amphotericin B, aminoglycosides)
- morbidly obese patients
First know the Pathogen, THEN select the antibiotic

- *S. aureus* (MSSA and MRSA)
  - → Skin and soft tissue infections & Pneumonia
- *Streptococcus pneumonia*
  - Community Acquired Pneumonia
- *E. coli* and *K. pneumonia* – ESBLs & CRE
- *C. difficile*

Optimizing the Management of Community-Acquired Respiratory Tract Infections (RTI)

- Acute Bacterial Sinusitis (ABS)
- Community-Acquired Pneumonia (CAP)
- Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB)

Common Causative Pathogens
Rapid Resolution of Symptoms (CAP/ABS)
Longer Infection-free Interval (ABECB)
Common Bacterial Pathogens
CAP, ABECB, ABS

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>CAP1,2</th>
<th>ABECB3</th>
<th>ABS4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus pneumoniae</td>
<td>32-42%</td>
<td>35.3%</td>
<td>20-43%</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>19-26%</td>
<td>34.1%</td>
<td>22-35%</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>4-6%</td>
<td>17.6%</td>
<td>2-10%</td>
</tr>
</tbody>
</table>

*Atypical pathogens are also common in CAP. Serological findings from 551 CAP outpatients suggested the presence of Mycoplasma and Chlamydia spp. in 25 and 11% of patients, respectively.2

Key Pathogen in RTIs
Streptococcus pneumoniae
Scanning Electron Micrograph

Considerations for CAP Diagnosis and Treatment

- Criteria for diagnosis*
  - Clinical features (e.g., cough, fever, sputum production, and pleuritic chest pain)
  - Positive chest radiograph
  - Routine diagnostic tests for etiologic diagnosis are optional for outpatients

- Risk factors for MDRSP impact treatment choice†
  - Age >65 years
  - Use of antimicrobials within the previous 3 months
  - Alcoholism
  - Medical comorbidities
  - Immunosuppressive illness or therapy
  - Exposure to a child in a day care center

- Experts recommend use of the most active agents within each therapeutic class

*When a fluoroquinolone is appropriate, more active agents are given preference because of their benefit in decreasing the risk of selection for antibiotic resistance.

†Moderate recommendation; level III evidence

2007 IDSA/ATS CAP Guidelines: Empirical Antibiotics for Outpatients

Previously healthy
No risk factors* for drug-resistant S. pneumoniae

Risk factors* for drug-resistant S. pneumoniae

In region with a high rate (>25%) of infection with high-level (MIC ≥16µg/mL) macrolide-resistant S. pneumoniae, consider use of agents listed for patients with risk factors

- Azithromycin
- Clarithromycin
- Erythromycin
- Doxycycline

- Respiratory fluoroquinolone†
  - Moxifloxacin
  - Gemifloxacin
  - Levofloxacin (750 mg)
  - β-lactam + macrolide†

Outpatient

* Risk factors: Presence of comorbidities such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected); or other risks for DRSP infection in adults (age >65 years; use of antimicrobials within the previous 3 months; alcoholism; medical comorbidities; immunosuppressive illness or therapy; and/or exposure to a child in a day care center).

† β-lactam: High-dose amoxicillin, amoxicillin-clavulanate, cephalaxin, cefuroxime 500 mg bid. Macrolide: azithromycin, clarithromycin, erythromycin, doxycycline.


Erythromycin activity against S. pneumoniae (Macrolide marker)

- 2005: 32%
- 2006: 34%
- 2007: 31%
- 2008: 59%
- 2009: 37%
- 2010: 39%
- 2011: 50%
- 2012: 62%
- 2013: 40%
- 2014: 50%

Year

Recommendation
- a-strong
- b-weak

Evidence
- 1-level I evidence
- 2-level II evidence
- 3-level III evidence
Fluoroquinolones

Fluoroquinolones bind to two enzymes, inhibiting DNA replication: Topoisomerase IV and DNA gyrase.

Fluoroquinolone

Topoisomerase IV

DNA gyrase

Fluoroquinolones

- Ciprofloxacin – think Gram-negatives
- Levofoxacin – workhorse general activity
- Gatifloxacin – no more...March 2006
- Moxifloxacin – CAP, no urine concentrations (also no renal dose adjustment)
- Gemifloxacin – PO only

QT prolongation, dysglycemias, photo-toxicity, C. diff colitis, all seem to be a class effect with the FQ’s
Use with caution for patients at risk

Fluoroquinolones Uses

- UTI (not moxi)
- Respiratory (do not use cipro unless pseudomonas or atypical)
- No for Skin infections...staph can evolve resistance on therapy
- Bone, excellent penetration (with susceptible organisms)
- Prostatitis
- MDR TB
Fluoroquinolone Problems

- Broad spectrum encourages empiric use for questionable indications
- Delays the diagnosis of TB
- CNS symptoms, including seizures
- QT prolongation
- Tendon rupture
- Hypersensitivity
- Drug interactions

Azithromycin
(Zithromax, Z-Pak, Z-max)

- Was the World's best-selling antibiotic!
- Upper and lower RTI. Also effective against certain STD’s, such as non-gonococcal urethritis and cervicitis
- PO and IV availability
- Due to ion trapping and the high lipid solubility, during active phagocytosis, large concentrations of drug are released. Tissue cons can be over 50 times higher than in plasma (no use in bacteremia)
- Most common side effects are gastrointestinal; diarrhea (4-5%), nausea (3%), abdominal pain (2-3%) and vomiting

Caution in pts with prolonged QT intervals or meds that prolong QT interval (Amiodarone, Flecainide etc.)
Cardiovascular risks of azithromycin?

• In 2011, approximately 40.3 million people in the United States (roughly one eighth of the population) received an outpatient prescription for the macrolide azithromycin, according to IMS Health.

FDA Post marketing surveillance label changes noted:
• Risks of QT-interval prolongation and associated ventricular arrhythmia torsades de pointes.

Risk factors, patients with/on:
• Prolongation, hypokalemia, hypomagnesemia, bradycardia
• Certain antiarrhythmic agents, including class IA (e.g., quinidine and procainamide) and class III (e.g., amiodarone and sotalol)
• Can azithromycin prolong a correct QT interval?

Ray et al 2012 NEJM

Azithromycin updates

• Conflicting findings about azithromycin and cardiac safety, particular azithromycin-induced QTc interval prolongation and torsade de pointes.

• The FDA wants healthcare providers to consider azithromycin-induced fatal cardiac arrhythmias for patients already at risk for cardiac death and other potentially arrhythmogenic cardiovascular conditions.

• Factors that link to azithromycin-induced/associated QTc interval prolongation and torsade de pointes.
  • Female sex, older age, heart disease,
  • QTc interval prolonging drugs and metabolic inhibitors,
  • Hypokalemia, and bradycardia.

• Current knowledge: Subjects had at least two additional risk factors. Elderly women with heart disease appear to be at particularly risk

Azithromycin should still be prescribed responsibly (it is not intended for anti-viral, anti-pyretic, anti-tussive, or anti-anxiety therapy)
Doxycycline

- Hepatic metabolism, can be use in pts w/ poor renal function
- Lyme disease: 100 mg twice daily PO for 14 days

- Increased nausea on empty stomach
- **Oral**: (tablets and suspension) take with adequate fluid to prevent esophageal irritation and ulceration
- **Oral**: (tablets and suspension) may take with food, milk, or carbonated beverage if gastric irritation occurs

Absorption decreased by milk, antacids, iron supplements, cholestyramine, and things containing iron, calcium, magnesium, aluminum, drug interactions with anticonvulsants, warfarin

First know the Pathogen, THEN select the antibiotic

- *S. aureus* (MSSA and MRSA)
  - → Skin and soft tissue infections & Pneumonia

- *Streptococcus pneumonia*
  - Community Acquired Pneumonia

- *E. coli* and *K. pneumonia* – ESBLs & CRE

- *C. difficile*

Extended Spectrum Beta-Lactamase Production in Gram Negative Bacteria
# Fosomycin (Monuril)

<table>
<thead>
<tr>
<th>Class</th>
<th>phosphonic antibiotics: inhibits bacterial cell wall biogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiological Spectrum</td>
<td>Synthetic broad spectrum bactericidal antibiotic - in vitro activity against Gram negatives and gram-positives including E. coli, Klebsiella spp, Proteus, Pseudomonas spp and VRE.</td>
</tr>
<tr>
<td>Does not cover</td>
<td>Acinetobacter, gram positives</td>
</tr>
<tr>
<td>Uses</td>
<td>• uncomplicated UTI in pts with multiple antibiotic allergies</td>
</tr>
<tr>
<td></td>
<td>• uncomplicated VRE infections</td>
</tr>
<tr>
<td>Increasing uses/Interest</td>
<td>• Salvage therapy for URI due to multi-drug resistant gram negative organisms (e.g., Pseudomonas spp, ESBL and CRE)</td>
</tr>
<tr>
<td></td>
<td>• Systematic review: 81.3% (748/608) Klebsiella pneumoniae isolates producing ESBL were susceptible to fosfomycin. In two clinical studies, oral treatment with fosfomycin-trometamol (salt) - effective against complicated or uncomplicated lower UTI caused by ESBL-producing E.coli in, cumulatively, 75 (93.8%) of the 80 patients evaluated. -Falagas ME Lancet Infect Dis. 2010 Jan;10(1):43-50.</td>
</tr>
<tr>
<td>Should not be used</td>
<td>Oral formulation - any infections outside of urinary tract (does not achieve adequate concentrations at other sites)</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Well tolerated (N,D, headache, dyspepsia and dizziness)*.</td>
</tr>
<tr>
<td></td>
<td>* rapidly absorbed with an oral bioavailability of 30-37% depending on fed state</td>
</tr>
<tr>
<td>Dosing</td>
<td>Uncomplicated UTI: 3g (1 sachet) PO once</td>
</tr>
<tr>
<td></td>
<td>Complicated: 3g (1 sachet) PO every 2-3 days (up to 21 days)</td>
</tr>
<tr>
<td></td>
<td>• Renal adjustment may be necessary in pts with CrCl &lt;50mL/min.</td>
</tr>
<tr>
<td></td>
<td>• Powder should be mixed with 90-120mL of cold water, stirred to dissolve and taken immediately</td>
</tr>
</tbody>
</table>

---

**Beers Criteria for Potentially Inappropriate Medication Use in Older Adults**

The intentions of the criteria: Improve medication selection; educate clinicians and patients; reduce adverse drug events; and serve as a tool for evaluating quality of care, cost, and patterns of drug use of older adults.
### 2015 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

<table>
<thead>
<tr>
<th>Organ System, Therapeutic Category, Drugs</th>
<th>Rationale</th>
<th>Recommendation</th>
<th>Quality of Evidence</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrofurantoin</td>
<td>Potential for pulmonary toxicity, hepatotoxicity, and peripheral neuropathy, especially with long-term use; safer alternatives available</td>
<td>Avoid in individuals with creatinine clearance &lt;30 mL/min or for long-term suppression of bacteria</td>
<td>Low</td>
<td>Strong</td>
</tr>
</tbody>
</table>

 Recommendation and rationale modified since 2012

### Table 2. 2015 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

<table>
<thead>
<tr>
<th>Organ System, Therapeutic Category, Drugs</th>
<th>Rationale</th>
<th>Recommendation</th>
<th>Quality of Evidence</th>
<th>Strength of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton-pump inhibitors</td>
<td>Risk of Clostridium difficile infection and bone loss and fractures</td>
<td>Avoid scheduled use for &gt;8 weeks unless for high-risk patients (e.g., oral corticosteroids or chronic NSAID use), erosive esophagitis, Barrett's esophagitis, pathological hypersecretory condition, or demonstrated need for maintenance treatment (e.g., due to failure of drug discontinuation trial or H2 blockers)</td>
<td>High</td>
<td>Strong</td>
</tr>
</tbody>
</table>

Medications Added Since 2012 Beers Criteria
INTRODUCTION to ESBL’s

1. ESBL are enzymes that break down many common antibiotics, making the antibiotics ineffective.

2. Infections with ESBL producing organisms have been associated with poor outcomes.

3. Carbapenems constitute the best treatment option for infections caused by ESBL’s.

4. Difficulty of reliably identifying ESBL-producing organisms in clinical laboratories, making it likely that their prevalence is underestimated.

Evolution of Resistance

- What are Beta-Lactams?
  - What are Beta-lactamases?
    - What are Extended Spectrum Beta-lactamases?
      - Carbapenem-resistant enterobacteriaceae (CRE)
Beta-Lactams

4 major classes

Penicillins
Generation Cephalosporins (1st, 2nd, 3rd, 4th)
Carbapenems (meropenem, imipenem ertapenem and doripenem)
Monobactams (aztreonam)

Plasmid Transfer

Escherichia coli or Klebsiella

Klebsiella
TEM’s & SHV’s Family of Extended Spectrum Beta-Lactams

4 major classes of antibiotics

Penicillins
First, Third and Fourth Generation Cephalosporins
Carbapenems (meropenem imipenem and doripenam)
Monobactams (aztreonam)

Drugs with Most Reliable Activity Against ESBL-producing Enterobacteriaceae

Carbapenems –
only consistently proven tx option

Possibly
Piperacillin/tazobactam, cefepime (inoculum effect)
amikacin,
tigecycline (not P. mirabilis),
fluoroquinolones
Imipenem/ Meropenem

• Activity
  • Broad spectrum activity against Gram (+), Gram (-), and anaerobes
  • Inactive against MRSA, resistant enterococci, Stenotrophomonas, Burkholderia, Legionella, Chlamydia, Mycoplasma, C. diff
  • Meropenem is more active against Enterobacteriaceae and less active against Gram-positive bacteria

• Side effects
  • Seizures with renal impairment and with meningitis
  • cross-reactive allergy to penicillin

Ertapenem

<table>
<thead>
<tr>
<th>Class</th>
<th>Carbapenems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiological Spectrum</td>
<td>Many Gram-negative bacteria, ESBLs and AmpC's</td>
</tr>
<tr>
<td>Does not cover</td>
<td>No <em>Pseudomonas, Acinetobacter</em> or Enterococcus</td>
</tr>
<tr>
<td>Uses</td>
<td>Intra-abdominal, diabetic foot with osteo, ESBL UTI's, pyelonephritis if not severely ill</td>
</tr>
<tr>
<td>Increasing uses/Interest</td>
<td>Combo carbapenam therapy for CRE’s (ideally with third agent)</td>
</tr>
</tbody>
</table>

  ➔ case reports, ertapenem plus doripenem or meropenem successfully to treat select pan-drug resistant and colistin-resistant KPC *K. pneumoniae* infections (bacteremia, ventilator-associated pneumonia, and urinary tract infection).

  *KPC enzyme may have increased affinity for ertapenem than other carbapenems ➔ KPC preferentially deactivates ertapenem which hinders degradation and improves the activity of the concomitant carbapenem.

Should not be used

Monitoring Phlebitis……well tolerated.

Dosing 1g IV or IM q24h (dose adjust for worsening renal function)
Ceftazidime + Avibactam (AVYCAZ™)
Avibactam - a non-beta-lactam beta-lactamase inhibitor

<table>
<thead>
<tr>
<th>Class/MOA</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval</td>
<td>• complicated urinary tract infections (cUTIs), vs. versus imipenem-cilastatin</td>
</tr>
<tr>
<td></td>
<td>• complicated intra-abdominal infections (cIAIs), meropenem vs. CAF/AVI + metronidazole</td>
</tr>
<tr>
<td></td>
<td>&quot;New Treatment for Serious Infections in Patients Who Have Limited or No Alternative Treatment Options &quot;</td>
</tr>
<tr>
<td>Dose &amp; Adjustments</td>
<td>CAZ-AVI IV as a two hour infusion (2000 mg/500 mg, every 8 hours),</td>
</tr>
<tr>
<td>Spectrum</td>
<td>Gram-negative infections, including extended-spectrum beta-lactamases (ESBLs; Ambler class A, B, C, and D enzymes including CTX-M types) and Klebsiella pneumoniae carbapenemases (KPCs)</td>
</tr>
<tr>
<td>Does not cover</td>
<td>MRSA, MSSA, enterococcus</td>
</tr>
<tr>
<td>Safety</td>
<td>The most common adverse reactions (incidence of &gt; 10% in either indication) were vomiting, nausea, constipation, and anxiety</td>
</tr>
<tr>
<td>Monitoring</td>
<td>TBD?</td>
</tr>
</tbody>
</table>

First know the Pathogen, THEN select the antibiotic

- **S. aureus** (MSSA and MRSA)
  - → Skin and soft tissue infections & Pneumonia

- **Streptococcus pneumonia**
  - Community Acquired Pneumonia

- **E. coli and K. pneumonia** – ESBLs & CRE

- **C. difficile**
~ Clostridium difficile ~

Designated an **URGENT** Global Threat by the CDC

“THREAT LEVEL
URGENT:
immediate public health threat that requires urgent and aggressive action”

CDC=Centers for Disease Control and Prevention.


---

Pathophysiology

The Canadian Medical Journal: July 2004 171
Antimicrobials Predisposing Patients to CDI

Among symptomatic patients with CDI:

• 96% of patients received antimicrobials within the 14 days before onset

• 100% received an antimicrobial within the previous 3 months

All antibiotic pose increased risk to *Clostridium difficile* infection!

Olson MM, et al Infect Control Hosp Epidemiol 1994
Cohen SH, Infect Control Hosp Epidemiol 2010

---

**CDI Treatment guidelines: SHEA & IDSA 2010**

<table>
<thead>
<tr>
<th>Clinical definition</th>
<th>Clinical data</th>
<th>Treatment recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode, mild or moderate</td>
<td>WBC ≤ 15,000 cells/µL and SCr ≤ 1.5x premorbid level</td>
<td>Metronidazole 500mg PO TID x 10-14 days</td>
</tr>
<tr>
<td>Initial episode, severe</td>
<td>WBC ≥ 15,000 cells/µL or SCr ≥ 1.5x premorbid level</td>
<td>Vancomycin 125mg PO QID x 10-14 days</td>
</tr>
<tr>
<td>Initial episode, severe, complicated</td>
<td>Hypotension or shock, ileus, megacolon</td>
<td>Vancomycin 500mg QID PO or by nasogastric tube + metronidazole 500mg q8h IV. If complete ileus, consider adding rectal instillation of Vancomycin</td>
</tr>
<tr>
<td>First recurrence</td>
<td>...</td>
<td>Same as for initial episode</td>
</tr>
<tr>
<td>Second recurrence</td>
<td>...</td>
<td>Vancomycin in a tapered and/or pulsed regimen</td>
</tr>
</tbody>
</table>

Cohen SH, Infect Control Hosp Epidemiol. 2010
### American Journal of Gastroenterology 2013

<table>
<thead>
<tr>
<th>Severity</th>
<th>Criteria</th>
<th>Treatment</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to moderate</td>
<td>Diarrhea plus any additional sign or symptom not</td>
<td>MET 500mg PO TID x 10 days If unable to take MET, VAN 125mg</td>
<td>Switch to Vancomycin 125mg PO QID x 10 days</td>
</tr>
<tr>
<td></td>
<td>meeting severe or complicated criteria</td>
<td>PO QID x 10 days if no improvement in 5-7 days</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Serum albumin &lt;3g/dL + one of the following: WBC ≥ 15,000 cells/mm³ or abdominal tenderness</td>
<td>VAN125mg PO QID x 10 days</td>
<td>...</td>
</tr>
<tr>
<td>Severe and complicated</td>
<td>Any of the following attributable to CDI:</td>
<td>VAN 500mg PO QID + MET 500mg IV q8h, and Vancomycin per rectum (500mg in 500mL saline as enema) QID</td>
<td>Surgical consultation suggested</td>
</tr>
<tr>
<td>Recurrent CDI</td>
<td>Recurrence within 8 weeks of completion of therapy</td>
<td>Repeat MET or VAN pulse regimen</td>
<td>Consider FMT after 3 recurrences</td>
</tr>
</tbody>
</table>

Surawicz CM, *Am J Gastroenterol* 2013

### European Society of Clinical Microbiology and Infectious Diseases (ESCMID) - 2014

- **Non-severe CDI**
  - Oral antibiotic treatment
  - Fidaxomycin 200 mg tid 10 days
  - Vancomycin 125 mg tid 10 days
- **Risk of first recurrence**
  - Oral antibiotic treatment
  - Metronidazole 500 mg
- **Multiple recurrences**
  - Oral antibiotic treatment
  - Fidaxomycin 200 mg bid 10 days
  - Vancomycin 125 mg qid 10 days
- **Non-severe disease or complicated course**
  - Oral antibiotic treatment
  - Vancomycin 125 mg bid 10 days

Recommended courses of metronidazole not recommended (increased risk for peripheral neuropathy)

Debast SB *Clin Microbiol Infect* 2014
<table>
<thead>
<tr>
<th>Table related to CDI treatment</th>
<th>Metronidazole for CDI</th>
<th>Vancomycin PO for CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage (CDI)</strong></td>
<td>Metronidazole 500mg PO TID x10-14d</td>
<td>Vancomycin 125mg PO QID x 10-14d</td>
</tr>
<tr>
<td><strong>Adjust dose</strong></td>
<td>No/No (renal / hepatic)</td>
<td>No/No (renal/hepatic) may accumulate with low RFx</td>
</tr>
<tr>
<td><strong>PK</strong></td>
<td>PO admin - fecal concentrations</td>
<td>PO admin - fecal concentrations</td>
</tr>
<tr>
<td></td>
<td>9.3 mg/g in watery stools</td>
<td>Vancomycin 125mg QID</td>
</tr>
<tr>
<td></td>
<td>1.2 mg/g formed stools</td>
<td>600-1000 mcg/g fecal concentration</td>
</tr>
<tr>
<td></td>
<td>IV = same, some reported higher</td>
<td></td>
</tr>
<tr>
<td><strong>MIC</strong>_{90} = 1-2mcg/mL</td>
<td><strong>MIC</strong>_{90} = 1-2mcg/mL</td>
<td></td>
</tr>
<tr>
<td><strong>Resistance to C difficile</strong></td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

**Micro**

- Predominantly Gram-negative anaerobes: *(i.e., Bacteroides species, fusobacteria, and also Clostridia spp (Gram-positive))*
- Predominantly Gram-positive anaerobes *(i.e. Lactobacillus spp, also, Bacteroides fragilis group, B. melaninogenicus, B. bivius, Fusobacterium spp., Peptococcus spp, Peptostreptococcus spp Clstridium perfringens, C. difficile and Propionibacterium acnes)*

**Considerations**

- Low selection for VRE
- Side effect: nausea?
- Long duration – polyneuropathy (3d to 21d+)
- *minimal systemic absorption, limits toxicity*

Pepin Clinical Infectious Diseases 2008; 46:1493–8

---

**DIFICID®(fidaxomicin) - FDA Approved May 2011**

First medication for the management (CDI) to be approved by the FDA in >20 years

<table>
<thead>
<tr>
<th>Class/MOA</th>
<th>Narrow spectrum macrolide antibiotic, protein synthesis inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uses</strong></td>
<td><em>Clostridium difficile</em> associated diarrhea (CDAI)</td>
</tr>
<tr>
<td><strong>Dose &amp; Adjustments</strong></td>
<td>200 mg tablet PO twice daily for 10 days, with or without food.</td>
</tr>
<tr>
<td><strong>Spectrum</strong></td>
<td><em>Clostridia spp. Including all types of C. difficile</em></td>
</tr>
<tr>
<td><strong>Does not cover</strong></td>
<td>Gram-negative organisms, <em>Bacteroides</em> spp. and <em>Candida</em> spp. Moderate: <em>Staphylococcus aureus</em>, coagulase-negative staphylococci (CoNS), <em>Enterococcus faecalis</em> and <em>Enterococcus faecium</em></td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>The most common adverse reactions reported in clinical trials are nausea (11%), vomiting (7%), abdominal pain (6%), gastrointestinal hemorrhage (4%), anemia (2%), and neutropenia (2%) – little to no systemic absorption</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Acute hypersensitivity reactions (angioedema, dyspnea, pruritus, and rash) have been reported.</td>
</tr>
<tr>
<td><strong>Drug-Drug Interactions</strong></td>
<td>None noted, several tested</td>
</tr>
<tr>
<td><strong>Special groups</strong></td>
<td>Not approved in &lt;18 year old</td>
</tr>
</tbody>
</table>

DIFICID®(fidaxomicin) [prescribing information]. Optimer, 2013.
Antibiotics Review
Safety and Dosing Considerations

Kerry L. LaPlante, Pharm.D., FCCP
Professor of Pharmacy, University of Rhode Island, College of Pharmacy
Adjunct Professor of Medicine, The Warren Alpert Medical School of Brown University
Senior Director of the Rhode Island Infectious Diseases Research (RIID) Program
Co-Director of Antimicrobial Stewardship Program, and Infectious Diseases Pharmacotherapy
Specialist, Providence Veterans Medical Center, RI