Antibiotic Review

George C. Mejicano, MD, MS
Professor of Medicine
Senior Associate Dean for Education
School of Medicine
One of the best ways to learn about all of the numerous types of antibiotics is to place them into different categories based upon their mechanism of action.
All drugs in a given antibiotic class have the same mechanism of action because they share the same target site. Subtle alterations in chemical structure are associated with specific differences between drugs in the same class (such as different half lives or spectrums).
<table>
<thead>
<tr>
<th>Structure</th>
<th>Group</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure" /></td>
<td>Penam</td>
<td>Penicillins</td>
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<tr>
<td><img src="image2.png" alt="Structure" /></td>
<td>Clavam</td>
<td>Beta-lactamase inhibitors (clavulanic acid)</td>
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<tr>
<td><img src="image3.png" alt="Structure" /></td>
<td>Carbapenem</td>
<td>(Thienamycin, imipenem)</td>
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<tr>
<td><img src="image4.png" alt="Structure" /></td>
<td>Cephem</td>
<td>Cephalosporins</td>
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<tr>
<td><img src="image5.png" alt="Structure" /></td>
<td>Oxacephem</td>
<td>(Latamoxef)</td>
</tr>
<tr>
<td><img src="image6.png" alt="Structure" /></td>
<td>Monobactam</td>
<td>(Aztreonam)</td>
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</table>
Target: Cell Wall

- $\beta$-lactams
- Glycopeptides
- Bacitracin
- Isoniazid
- Fosfomycin
- Cycloserine
Target: Cell Membrane

- Polymyxin – topical drug
- Colistin
- Cyclic lipopeptides – daptomycin
Target: Folate Synthesis Pathway

- Trimethoprim
- Sulfonamides
- Pyrimethamine – for *T. gondii*
Target: Bacterial Ribosome

- 30 S ribosome
  - Aminoglycosides and tetracyclines
- 50 S ribosome
  - Macrolides, clindamycin, & chloramphenicol
- Initiation complex
  - Oxazolidinones – linezolid
Target: Nucleic Acids

- Fluoroquinolones
- Rifamycins
- Metronidazole
How do Bacteria Become Resistant to Antibiotics?
Cellular Division of Bacteria

Requires the synthesis of cell wall, nucleic acids, and numerous proteins
Four Major Mechanisms of Antibiotic Resistance

- Enzyme inactivation
- Altered target site
- Altered bacterial membrane
- Antibiotic efflux pump
Enzyme Inactivation

β-lactamase can inactivate drugs such as penicillins and cephalosporins (H. influenza, E. coli, Klebsiella & Staphylococcus species)

Bacteria that can produce β-lactamase

β-lactamase can open β-lactam ring of antibiotic

Antibiotic inactivated
**Klebsiella pneumoniae**

MIC’s to β-lactamases

<table>
<thead>
<tr>
<th>β-lactamase</th>
<th>Ceftazidime</th>
<th>Ceftriaxone</th>
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<tbody>
<tr>
<td>TEM-1</td>
<td>0.12</td>
<td>&lt; 0.06</td>
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<tr>
<td>TEM-10</td>
<td>&gt; 256</td>
<td>0.5</td>
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<tr>
<td>TEM-12</td>
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<td>0.25</td>
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<tr>
<td>TEM-26</td>
<td>256</td>
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<tr>
<td>SHV-1</td>
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<td>SHV-4</td>
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<tr>
<td>SHV-5</td>
<td>&gt; 256</td>
<td>128</td>
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</table>

[ID Clin N Amer 1997;11:875]
Enzyme Inactivation

Acetylase, phosphorylase, and adenylase enzymes can modify aminoglycosides

Example: *Pseudomonas* may produce phosphorylase (APH) that results in the addition of a phosphate group. This causes inactivation of the antibiotic.

Aminoglycoside (gentamicin, tobramycin, amikacin)
Alteration in Target Site

Altered Penicillin Binding Proteins (PBPs)

Actively growing *S. pneumoniae*:

- PBPs facilitate cell wall formation for new cell

Without antibiotic:

Antibiotic binds to “2b” PBPs

Susceptible *S. pneumoniae*

Antibiotic cannot bind to altered PBPs, growth continues (i.e. the organism is antibiotic resistance)

Drug resistant *S. pneumoniae*

Antibiotic binds to “2b” PBPs

Cannot make adequate cell wall, growth stops

**Drug resistant** *S. pneumoniae*
Alteration in Target Site

*Altered Pentapeptides*

- Glycopeptides (such as vancomycin) work by binding to pentapeptides that are critically important precursors of the bacterial cell wall.
- Vancomycin resistant enterococci (VRE) carry genes that result in an increase in altered pentapeptides that do not bind glycopeptides as efficiently.
  - *vanA*: resistant to vancomycin and teicoplanin.
  - *vanB*: resistant to vancomycin, susceptible to teicoplanin.
Alteration in Target Site

Alteration in Ribosomal Target Sites

- Example: *S. pneumoniae* versus macrolides

**Normal Macrolide Method of Action:**
Macrolide binds to 50 S ribosome of *S. pneumoniae* and inhibits bacterial protein synthesis

**Macrolide Resistance:**
*S. pneumoniae* acquires gene that results in methylation of ribosomes. Macrolide is unable to bind to altered ribosomes and cannot interfere with protein synthesis.
Mechanisms of Resistance

Altered Bacterial Membrane

- Bacteria can limit access to a site by virtue of their membrane characteristics
- Reduced permeability results in resistance to $\beta$-lactams, TMP-SFX, and quinolones
- Common pathogens:
  - *Pseudomonas aeruginosa* has a membrane that is impermeable to many $\beta$-lactam antibiotics
  - *Enterobacter* species have altered porin proteins
  - Penicillin-resistant *Neisseria gonorrhoea*
MODE OF ACTION AND RESISTANCE OF BETA-LACTAM ANTIBIOTICS IN GRAM-NEGATIVE BACTERIA

- Beta-lactam antibiotics
- Porins
- Outer membrane
- Periplasm
- Cytoplasmic membrane
- Beta-lactamases
- Penicillin-binding proteins
Mechanisms of Resistance

Antibiotic Efflux Mechanism

- Gram-negative enteric bacilli
- *S. pneumoniae* vs. macrolides – relatively new
- Antibiotics: tetracyclines, quinolones, macrolides

**Efflux Pump:** The antibiotic permeates the cell but is actively pumped back out
Another Method to Inactivate an Antibiotic

- Change the oxygen saturation
  - Metronidazole only works in an anaerobic environment because it must get reduced into its active form
  - The aminoglycosides enter bacterial cells through an aerobic uptake mechanism; in an anaerobic environment, this class of drugs won’t work because they can’t get in
Spectrum of Activity

- Drugs with activity against only Gram-positive organisms
  - Vancomycin
  - Semi-synthetic penicillins (e.g. nafcillin, methicillin, oxacillin and dicloxacillin)
  - Daptomycin
Spectrum of Activity

- Drugs with activity against only Gram-negative organisms
  - Aminoglycosides (when used alone)
  - Aztreonam (monobactam)
  - Colistin
Spectrum of Activity

- Drugs with activity against anaerobes
  - Clindamycin
  - Metronidazole
  - Cephamycins – subgroup of 2\textsuperscript{nd} generation cephalosporins that share MTTP side chain
  - Carbapenems
  - $\beta$-lactam + $\beta$-lactam inhibitor combinations
  - Vancomycin – only Gram-positive anaerobes
Spectrum of Activity

- Drugs with activity against Gram-positive, Gram-negative and anaerobic organisms (i.e. broad spectrum antimicrobials)
  - Cephalosporins
  - Carbapenems
  - $\beta$-lactam + $\beta$-lactam inhibitor combinations
  - Tetracyclines
  - Macrolides
  - Newer fluoroquinolones
Spectrum of Activity

- Drugs with activity against the atypical agents of community acquired pneumonia
  - Macrolides
  - Fluoroquinolones
  - Tetracyclines
Spectrum of Activity

- Drugs with activity against mycobacteria
  - Isoniazid
  - Rifampin and rifabutin
  - Pyrazinamide
  - Ethambutol
  - Clarithromycin
  - Fluoroquinolones
Drug Toxicity

- Kidney toxicity (often reversible but may require acute dialysis)
  - Aminoglycosides
  - β-lactams
  - Sulfonamides – typically only seen with high dose intravenous antibiotic therapy
Drug Toxicity

- Auditory toxicity (can be irreversible)
  - Aminoglycosides – vestibular system too
  - Erythromycin – typically only seen with high dose intravenous antibiotic therapy
  - Vancomycin
Drug Toxicity

- Bone marrow suppression
  - β-lactams – typically only seen with high dose intravenous antibiotic therapy
  - Chloramphenicol – severest form is aplastic anemia, which is irreversible
  - Sulfonamides
Drug Toxicity

- Liver toxicity (often reversible but may lead to fulminant liver failure)
  - Erythromycin estolate
  - Isoniazid
  - Rifampin
  - Pyrazinamide
Drug Toxicity

• Hypersensitivity reactions (Types I – IV)
  ▪ β-lactams
  ▪ Sulfonamides
Drug Toxicity

- Gastrointestinal tract toxicity
  - Erythromycin – dyspepsia and vomiting
  - Amoxicillin – diarrhea
  - Cephalosporins – diarrhea
  - Doxycycline – vomiting
  - Clindamycin – diarrhea
Drug Toxicity

- Central nervous system toxicity
  - Imipenem lowers seizure threshold
Drug Toxicity

- Few drugs are approved in children because clinical trials in the pediatric age groups are very difficult to do.
- Drugs to avoid in children:
  - Tetracyclines – discolors teeth and impairs bone development
  - Fluoroquinolones – causes damage to cartilage of juvenile rodents
Drug Toxicity

• Few drugs are approved for use in pregnancy because clinical trials in this group are considered very risky

• Rule of thumb
  ▪ Only erythromycin and β-lactams are considered safe in pregnancy
  ▪ Exception: imipenem

• Drugs to avoid during pregnancy (or while trying to conceive)
  ▪ Tetracyclines
  ▪ Fluoroquinolones
Pregnancy Category

- Each drug is given a pregnancy category by the United States Food and Drug Administration (FDA)
  - Category A
  - Category B
  - Category C
  - Category X
Antibiotic Update: A Case Based Approach

George C. Mejicano, MD, MS
Department of Medicine
Patient with fevers and a red streak going up his thigh
Penicillin

- Pharmacology: Relatively poor absorption
- Spectrum: Oral anaerobes, spirochetes, *S. pneumoniae*, and most *E. coli*; but NOT *H. influenzae*, *M. catarrhalis*, or *Enterococci*
- Side effects: Rash and diarrhea
- Indications: Drug of choice for strep throat, skin and soft tissue infections due to various strep species, syphilis, and leptospirosis
Patient with sinus pressure & purulent nasal discharge
Amoxicillin

- **Pharmacology:** Excellent absorption (does not reach ileum to treat *Salmonella*)
- **Spectrum:** Enterococci, oral anaerobes, *S. pneumoniae*, spirochetes, and most *E. coli*; but NOT *H. influenzae* or *M. catarrhalis*
- **Side effects:** Rash, diarrhea, and colitis secondary to *C. difficile*
- **Indications:** Remains the drug of choice for otitis media and sinusitis
Therapy for Acute Sinusitis

Gold standard: Amoxicillin

CDC Recommendation: Amoxicillin

Amoxicillin therapy should be the first-line treatment of acute bacterial sinusitis

Canadian Sinusitis Symposium, 1997
This patient sustained a dog bite. The animal is captured (last Td was 3 yrs ago)
Amoxicillin-Clavulanate

- **Pharmacology:** Blocks beta-lactamases
- **Spectrum:** *S. aureus, H. influenzae, M. catarrhalis* are added to amoxicillin
- **Side effects:** Diarrhea, rash, thrush, and *C. difficile* colitis
- **Indications:** Bite wounds, skin and soft tissue infections, and bacterial URTI’s
Patient with red, swollen and sore elbow that has a draining sinus; cx grows MSSA
Dicloxacillin

- Pharmacology: Beta-lactamase resistant (dicloxacillin > cloxacillin)
- Spectrum: S. aureus & Streptococci; little anaerobic activity
- Side effects: Rash & fever; dicloxacillin allergy = penicillin allergy
- Indications: For Staphylococcus aureus infections, use higher dose (500 mg po QID)
Cephalosporins

• First generation: Mostly Gram positive activity
• Second generation: Preserved Gram positive activity and enhanced Gram negative activity plus/minus anaerobic activity
• Third generation: Enhanced Gram negative activity but weaker Gram positive activity
• Fourth generation: Enhanced Gram positive and Gram negative activity
Cephalosporin Activity by Generation

<table>
<thead>
<tr>
<th></th>
<th>First</th>
<th>Second</th>
<th>Third</th>
<th>Fourth</th>
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<tbody>
<tr>
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<td>Staph</td>
<td>++++</td>
<td>++++</td>
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<td>++++</td>
</tr>
<tr>
<td>GNRs</td>
<td>+</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
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</table>
1st Generation Cephalosporins

- **Spectrum:**
  - Mostly Gram positive organisms such as Group A Streptococcus and *S. aureus*

- **Disadvantages:**
  - Lots of diarrhea; leads to increased resistance

- **Indications:**
  - Intravenous cefazolin used extensively to prevent surgical wound infections
  - Oral cephalexin has essentially no indications
2nd Generation Cephalosporins

- **Spectrum:**
  - Spirochetes, almost all streptococci, most *E. coli, H. influenzae*, and *M. catarrhalis*
  - Cephamycin group (cefotetan, cefoxitin, and cefmetazole) has decent anaerobic activity

- **Disadvantages:**
  - Diarrhea and thrush

- **Indications:**
  - Second line for sinusitis and otitis media; complex UTI’s but quinolones are better
A Sample of the Second Generation Cephalosporins

- **Cefprozil**: Expensive & not very active against *H. influenzae*
- **Cefoxitin**: Excellent choice for pelvic inflammatory disease (PID)
- **Cefuroxime**: Suspension has bitter taste; excellent *S. aureus* activity (drug of choice for orthopedic & cardiac surgery prophylaxis)
3rd Generation Cephalosporins

- **Spectrum:**
  - Very broad, but variable *S. aureus* activity
  - IV ceftazidime hits *Pseudomonas aeruginosa*

- **Disadvantages:**
  - Diarrhea, thrush, and rash

- **Oral Indications:**
  - Cefixime: only gonorrhea (now off market)
  - Cefpodoxime: otitis, bronchitis, & sinusitis
Male patient with painful and copious urethral discharge
IV 3rd Generation Cephalosporins

• Ceftriaxone
  • Can be given IV or IM
  • Excellent CNS penetration
  • Long half life allows once daily dosing (not in meningitis)
  • Excreted in the bile and can cause biliary sludging

• Cefotaxime:
  • Usually dosed every eight hours
  • Excreted in the urine
  • Spectrum equivalent to ceftriaxone

• Ceftazadime:
  • Major use is against Pseudomonas aeruginosa
**4th Generation Cephalosporins**

- Cefepime is the only one approved in the USA
- Typically dosed 1-2 grams IV q 12 hours
- Excellent *S. aureus* activity
- Poor activity against anaerobes
- Excellent against Gram negative organisms
  - Use 2 grams IV q 8 hours for *P. aeruginosa*
  - Active even in organisms that produce extended spectrum beta lactamases (ESBLs)
- Adjust dose in patients with renal dysfunction
Patient with fever & sore throat who has a severe allergy to penicillin
Erythromycin

• Prototype macrolide that inhibits protein synthesis (bacteriostatic)

• Spectrum
  • Gram positive cocci; diphtheria; pertussis; spirochetes; *Mycoplasma, Chlamydia* and *Chlamydophilia* species; *L. pneumophila*; but not *H. influenzae*, *Moraxella catarrhalis*, or *Enterococcus* species
Erythromycin

• Disadvantages:
  • Emerging resistance of many streptococci
  • GI upset is major problem
  • Drug interactions with many drugs including: cyclosporin, digitalis, theophylline, warfarin, astimizole, and carbatamazapine

• Indications:
  • Bowel prep for GI surgery; diphtheria; pertussis; atypical pneumonia; chlamydia & strep throat in penicillin-allergic persons
Clarithromycin

- **Spectrum:**
  - Same as erythromycin plus MAI
    - *Mycobacterium avium-intracellulare*

- **Indications:**
  - Community acquired pneumonia & MAI
  - Not very good for otitis media, sinusitis, or bronchitis (little effect on *H. influenzae*)
Clarithromycin

• Advantages:
  • Less GI upset but diarrhea still a problem
  • Fewer interactions with other drugs

• Disadvantages:
  • High cost
  • Poor activity against *H. influenzae* and some isolates of resistant *S. pneumoniae*
  • Avoid food to improve absorption
Patient with cervical discharge
Azithromycin

- Similar to macrolides but has much longer half life and also much higher tissue levels

- Spectrum
  - Same as clarithromycin

- Indications:
  - Community acquired pneumonia and MAI
  - Not very good for otitis media, sinusitis, or bronchitis (little effect on *H. influenzae*)
Azithromycin

- **Advantages:**
  - Less GI side effects than erythromycin
  - Improved adherence due to long half life
  - Minimal drug-drug interactions

- **Disadvantages:**
  - High cost
  - Poor activity against *H. influenzae* and some isolates of drug resistant *S. pneumoniae*
Patient with fever, dysuria, & left flank pain (WBC casts in urine)
Fluoroquinolones

- **Spectrum:**
  - Varies by specific agent but generally broad spectrum with excellent activity against many atypical organisms and Gram negative bacilli

- **Advantages:**
  - Long half-life and excellent absorption

- **Disadvantages:**
  - High acquisition cost; bind to minerals; cartilage damage (avoid in children)
Ciprofloxacin

- Oral form close to going generic
- Advantages:
  - Agent of choice for *Legionella* species
  - Superb for Gram negatives, including *Pseudomonas auriginosa*
  - Very well absorbed
- Disadvantages:
  - Low serum levels, rash, GI upset
Patient with fevers, shortness of breath, and productive cough
New Fluoroquinolones

- Potent and broad spectrum antimicrobials
- More active against staphylococci and streptococci than older fluoroquinolones
- Similar in vitro activity against all types of *S. pneumoniae*, including penicillin and macrolide resistant strains
- Available agents: Levofloxacin (Levaquin)  
  Gatifloxacin (Tequin)  
  Moxifloxacin (Avelox)
Activity of New Fluoroquinolones Against Other Microorganisms

- Maintain potent activity against *Enterobacteriaceae, Haemophilus influenzae* and *Moraxella catarrhalis*
- Active against atypical pneumonia pathogens (*Legionella pneumophila, Chlamydothilia pneumoniae, and Mycoplasma pneumoniae*)
- Expanded anaerobic activity seen in both gatifloxacin and moxifloxacin
# Newer Fluoroquinolones: Pharmacokinetic Properties

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<thead>
<tr>
<th>Parameter</th>
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<th>GATI</th>
<th>MOXI</th>
<th>GEMI</th>
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<tr>
<td>Dose (mg)</td>
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<td>400</td>
<td>400</td>
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<tr>
<td>Peak (mg/L)</td>
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<td>3.5</td>
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<tr>
<td>Prot Binding (%)</td>
<td>25</td>
<td>20</td>
<td>45</td>
<td>60</td>
</tr>
<tr>
<td>AUC (mg x hr/L)</td>
<td>48</td>
<td>35</td>
<td>40</td>
<td>8</td>
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<tr>
<td>Bioavailability (%)</td>
<td>98</td>
<td>90</td>
<td>85</td>
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<td>Half-life (hr)</td>
<td>7</td>
<td>8</td>
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<tr>
<td>Elimination (Renal, Hepatic)</td>
<td>R</td>
<td>R</td>
<td>H</td>
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Fluoroquinolones: End of an Era?

“The committee is concerned about misuse and overuse of fluoroquinolones and feels that, if abuse of this class of drugs continues unabated, we may see the demise of fluoroquinolones as useful antibiotics within the next 5-10 years.”

Infectious Diseases Society of America
Community Acquired Pneumonia Committee
December 1, 2003    [CID 2003; 37:1405-33]
### Action of Fluoroquinolones

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<tr>
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<th>Topoisomerase IV</th>
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<tr>
<td>Ciprofloxacin</td>
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<td>Levofloxacin</td>
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<tr>
<td>Gatifloxacin</td>
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<td>Moxifloxacin</td>
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</tr>
<tr>
<td>Gemifloxacin</td>
<td>+</td>
<td>+</td>
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</table>
Patient with fever after camping
Doxycycline

• Spectrum:
  • *S. pneumoniae* (although resistance is on the rise), *H. influenzae*, and anaerobes
  • Many unusual diseases (Brucellosis; Lyme disease; Plague; Ehrlichiosis; Malaria; Rickettsial infections; Tularemia; *Mycoplama, Legionella, & Chlamydia* spp)

• Indications:
  • PID, NGU, Chlamydia, Lyme disease, etc,
Doxycycline

- **Advantages:**
  - Absorption not altered by food
  - Little catabolism compared to other tetracyclines

- **Disadvantage:**
  - Damages developing teeth and binds to bone

- **Bottom line:** A very important drug!
HIV patient with fever & cough
Trimethoprim-Sulfamethoxazole

• Spectrum:
  • Most *S. pneumoniae* and *H. influenzae*; some *S. aureus*; many Gram-negatives (including *Stenotrophamomonas maltophilia*); *Listeria* species and *Pneumocystis jiroveci*

• Side effects:
  • Rash (sometimes severe); renal problems with high doses, & rare myelosuppression
Trimethoprim-Sulfamethoxazole

- **Advantages:**
  - Long half life, low cost, excellent absorption

- **Indications:**
  - UTI’s and prostatitis; as an adjunctive drug for *S. aureus*; prophylaxis for transplant and HIV patients; PCP; and enteric infections
  - For GU and GI infections, fluoroquinolones are typically considered superior drugs
Patient with fever, cough & foul breath
Clindamycin

• Spectrum:
  • Excellent for anaerobes, *S. aureus* (especially CA-MRSA), and most *S. pneumoniae*
  • Not Coagulase-negative staphylococci, Enterococci, or Gram-negative rods

• Advantage:
  • Superb absorption and penetration
Clindamycin

• Disadvantages:
  • Antibiotic associated diarrhea and pseudo-membranous colitis due to *C. difficile*

• Indications:
  • Gram-positive cocci in penicillin-allergic patients (such as endocarditis prophylaxis); drug of choice for aspiration pneumonia; lung abscess; recurrent strep throat and furunculosis; trichomononaisis; occasionally used for *S. aureus* osteomyelitis; and very useful to reduce toxin release
Stool from patient with diarrhea has these organisms in it
Metronidazole

• **Spectrum:**
  – Oral and GI anaerobes; protozoa (such as *Giardia*, amoeba, and *Trichomonas*)

• **Indications:**
  – Drug of choice for *C. difficile*; anaerobic infections above the neck and below the diaphragm; bacterial vaginosis; giardiasis; trichomoniasis; amebiasis; endovascular infections due to *Bacteroides* species
Metronidazole

- Advantages:
  - Low cost and excellent absorption

- Disadvantages:
  - Nausea; metallic taste; disulfuram reaction; may cause neuropathy if taken for long periods
Oxazolidinone - Linezolid

- New class that inhibits formation of the initiation complex for protein synthesis
- Mostly bacteriostatic drug, but it is bactericidal against *S. pneumoniae*
- Best drug for MRSA pneumonia and VRE
- Dose: 600 mg oral or IV twice daily
- Monitor platelets if duration > two weeks
- Very expensive antibiotic ($84 per day)!
Ertapenem

- Long half-life carbapenem
- Once daily dosing
- High protein binding
- Low toxicity
- Not for *Acinetobacter* species or *Pseudomonas aeruginosa*
Daptomycin

• New drug class (cyclic lipopeptide)
• Rapidly bactericidal with a novel mechanism of action: acts by binding to cell membrane and disrupting the cell membrane potential
• Minimal resistance and side effects
• Dose: 4 mg/kg once daily
  – Q 48 h for creatinine clearance < 30
  – No adjustment for liver dysfunction
Conclusions

- Pharmacodynamics help to explain why some antibiotics work better than others
- Simple & inexpensive medications are still the agents of choice for many infections
- Drug metabolism may help optimize therapy
- Judicious use of antibiotics will help control costs and minimize the spread of resistance
Thank You!!