Antibiotics: A Review of the Basics

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Objectives
- Describe the clinical significance of a number of terms used in antibiotic therapy
- Explain antibiotic pharmacodynamic / pharmacokinetic principles as they relate to drug choices / dosing regimens
- Compare & contrast basic & clinical pharm of the most common classes of antibiotics used in primary care

Disclosures
This speaker has no financial or other conflicts of interest to disclose

Antimicrobial Therapy
Terms, Definitions And Basic Principles

Bacteriostatic
antibiotics which inhibit the growth of bacteria

Bactericidal
antibiotics which kill bacteria

“Cidal” vs “Static” (in vitro terms)
- Antibiotics labeled as “bactericidal” may actually fail to kill every bacteria on plate within standard 18–24 hours over which the test is conducted
  - Eg. the inoculum is large
- “Bacteriostatic” agents often do kill quite a few bacteria within the standard testing time
  - Sometimes as many as 90%–99% of the inoculum
  - Not enough (>99.9%) under laboratory “rules” to be labeled “bactericidal”

“Cidal” vs “Static”
- Some antibiotics can be bactericidal against certain organisms but only be bacteriostatic against others and vice versa.
  - Eg. macrolides, considered bacteriostatic, have shown in vitro bactericidal activity against non-resistant Streptococcus pneumoniae and S. pyogenes
  - At higher concentrations, bacteriostatic agents are often “cidal” against a number of susceptible organisms
**“Cidal” vs “Static”**

- **Bactericidals** most efficacious against dividing bacteria
- Have greatest efficacy with organisms growing rapidly during the early stages of infection or in mild infections.
- Effectiveness of bactericidal antibiotics often decreases as colony grows larger, growth tends to slow dramatically
  - eg., stationary phase of deep-seeded infections
- Bactericidal activity on freshly inoculated plate may not translate to the same in a long standing infection in the host

**Potential advantages to using bacteriostatic drugs**

- Most bacteriostatic drugs inhibit protein synthesis
  - tetracyclines, clindamycin, macrolides
- Can rapidly diminish synthesis of exotoxins or endotoxins that are the actual mediators of clinical symptoms, morbidity and potential mortality

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**Antimicrobial Therapy**

*Terms, Definitions And Basic Principles*

**Resistance**

Inability for antibiotic to affect a bacteria at concentrations attainable in host

- Intrinsic Resistance
- Acquired Resistance
- Host Resistance

**Intrinsic resistance examples:**

<table>
<thead>
<tr>
<th>Organism</th>
<th>Intrinsic resistance</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaerobic bacteria</td>
<td>Aminoglycosides</td>
<td>Lack of oxidative metabolism to drive uptake of aminoglycosides</td>
</tr>
<tr>
<td>Aerobic bacteria</td>
<td>Metronidazole</td>
<td>Inability to anaerobically reduce drug to its active form</td>
</tr>
<tr>
<td>Gram-negative bacteria</td>
<td>Vancomycin</td>
<td>Lack of uptake resulting from inability of vancomycin to penetrate outer membrane</td>
</tr>
<tr>
<td>Klebsiella spp.</td>
<td>Ampicillin</td>
<td>Production of beta-lactamases that destroy ampicillin before the drug can reach the PBP targets</td>
</tr>
</tbody>
</table>

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**Host (Site) Resistance**

- Bacteria may be sensitive and susceptible to a particular antibiotic in vitro, but infection located at a site where drug concentrations ≥ MIC may not be attainable.
- Ocular fluid, CSF, abscess cavity, prostate, and bone often much lower concentrations than serum levels.
- Examples: 1st & 2nd generation cephalosporins and macrolides do not cross the blood-brain barrier
- Low-oxygen, low-pH, and high-protein environment in abscess may limit clevity of like the aminoglycosides

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**Acquired Resistance**

- Result from the mutation of genes involved in normal physiological processes and cellular structures - or from the acquisition of resistance genes from other bacteria - or from a combination of both
- Traits associated with acquired resistance are found only in some strains or subpopulations of any particular bacterial species.
**Horizontal Transfer Mechanisms**

**Conjugation**
Transfer of DNA via sexual pilus and requires cell-to-cell contact.

**Transduction**
Transfer of DNA from one bacterium into another via bacteriophage.

**Transformation**
Uptake of short fragments of naked DNA by naturally transformable bacteria.

**Clinical Aspects of resistance**
- **MIC**
  - Lowest concentration of antimicrobial that inhibits the growth of the organism after an 18 to 24 hour incubation period
  - Interpreted in relation to the specific antibiotic and achievable drug levels
  - Can not compare MICs between different antibiotics
  - Discrepancies between in vitro and in vivo

**Acquired Resistance examples:**

<table>
<thead>
<tr>
<th>Acquired through:</th>
<th>Resistance observed</th>
<th>Mechanism involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutations</td>
<td>E. coli, H. flu resistance to trimethoprim</td>
<td>Mutations in the chromosomal gene specifying dihydrofolate reductase</td>
</tr>
<tr>
<td>Mutations</td>
<td>S. Pneumonia resistance to penicillins</td>
<td>Mutations in the chromosomal gene specifying PBPs</td>
</tr>
<tr>
<td>Horizontal gene transfer</td>
<td>S. aureus resistance to methicillin (MRSA) and other beta-lactams</td>
<td>Via acquisition of genes on mobile genetic element which code for PBPs not sensitive to ß-lactam inhibition</td>
</tr>
<tr>
<td>Enterobacteriaceae resistance to ß-lactams</td>
<td>Transfer of plasmids containing genes for ESBLs</td>
<td></td>
</tr>
</tbody>
</table>

**Site of Infection**
- **Will the antibiotic get there?**
  - Choice of agent, dose, and route important
  - Oral vs. IV administration
    - Bioavailability, severity of infection, site of infection, function of GI tract
  - Blood and tissue concentrations
    - Ampicillin → ↑ concentrations in bile
    - Fluoroquinolones → ↑ concentrations in bone
    - Quinolones, TMP/SMX, cephalosporins, amoxicillin → ↑ concentrations in prostate
    - Macrolides (clarithromycin, azithromycin) ↑ concentrations in lung

**Site of Infection**
- **Will the antibiotic get there?**
  - Choice of agent, dose, and route important
  - Ability to cross blood-brain barrier
    - Dependent on inflammation, lipophilicity, low mw, low protein binding, low degree of ionization
    - 3rd or 4th generation cephalosporins, chloramphenicol
  - Local infection problems
    - Aminoglycosides inactivated by low pH and low oxygen tension
    - Beta-lactams → inoculum effect

**Culture & Sensitivity Report**
- **Remember:** Sensitivities are *in vitro*

  **Considerations**
  - Tissue penetration
  - Patient Factors:
    - Age / pregnancy / nursing
    - Antibiotic Allergies
    - Renal / hepatic status
    - Compliance risk
    - Potential drug interactions
  - Cost
Concomitant Drug Therapy

- Drug interactions
  - Pharmacokinetic interactions
  - ↑ risk of toxicity
  - Macrolides and CYP3A4, Cotrimoxazole and CYP2C9
  - ↓ efficacy of antimicrobial
  - Divalent cations and fluoroquinolones
  - Pharmacodynamic interactions
  - Cotrimoxazole and ACEI/ARB
- Selection of combination antibiotics (≥ 2 agents) requires understanding of the interaction potential
  - Synergy vs antagonism

Antimicrobial Therapy

Terms, Definitions And Basic Principles

Selective Toxicity

- Use specific, unique targets to destroy or inhibit microorganism without affecting host

Spectrum

- Number of different types of organisms sensitive to an antibiotic

Suprainfection

- Secondary infection arising during the course of primary therapy

Antimicrobial Therapy

Terms, Definitions And Basic Principles

Concentration vs Time-dependent killing

<table>
<thead>
<tr>
<th>Time-Dependent (T&gt;MIC)</th>
<th>Concentration-Dependent</th>
<th>Time Dependent + (concentration enhanced) AUC/MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>No post-antibiotic effect (for gram+)</td>
<td>Cmax/MIC or AUC/MIC</td>
<td>AUC/MIC</td>
</tr>
<tr>
<td>Penicillins, Cephalosporins, Erythromycin</td>
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</table>

Concentration >MIC for 40 – 50% of dosing interval – max killing seen when time above MIC is at least 70% of dosing interval

AUC/MIC > 125 for gram+ bacteria

> 25-50 for gram- cocci

Cmax/MIC >10

Bacterial Morphology & Antibiotics

Gram POSITIVE

- Cell Wall Synthesis
- Beta Lactams
- Vancomycin
- Bacitracin

Gram NEGATIVE

- DNA Replication
- Mupirocin
- Metronidazole
- Fluoroquinolones
- Sulfonamides
- Trimethoprim
- Folic Acid Synthesis
- Tetracyclines
- Clindamycin
- Macrolides
- β-Lactams
- Tetacyclines, clindamycin

Antibiotic Targets

Cell Wall Synthesis

DNA Replication

Protein Synthesis

mRNA synthesis

β-Lactams

Metronidazole

Sulfonamides

Fluoroquinolones

Folic Acid Synthesis

Sulfonamides

Trimethoprim

Tetracyclines

Clindamycin

Macrolides

β-Lactams

Tetracyclines, clindamycin

Cell Membrane Disruption

Image source: Agins
**Antibiotics: A Review of the Basics**

### Antibiotic Generations

<table>
<thead>
<tr>
<th>Generation</th>
<th>Gram (+)</th>
<th>Gram (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>&gt; gram (-)</td>
<td>&gt; gram (+)</td>
</tr>
<tr>
<td>3rd</td>
<td>&gt; gram (-)</td>
<td>&gt; gram (+)</td>
</tr>
</tbody>
</table>

- Penicillins, cephalosporins, macrolides
- Fluoroquinolones

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### Beta Lactams

![Beta Lactam Structures](image)

#### Characteristics

- **Same MOA:** Inhibit cell wall synthesis
- **Bactericidal** (except against Enterococcus sp.);
  - **Time-dependent killers**
    - Amount of **Time above MIC** correlates with efficacy
  - Short elimination half-life (few exceptions)
- **Cross-hypersensitivity**

#### Mechanism

- **Beta- Lactam antibiotics have affinity for PBPs**
- Structurally similar to peptidoglycan building blocks
- Covalent binding to serine residue at catalytic site

#### Types of Resistance

1. **Production of beta-lactamase enzymes**
   - Most important and most common
   - Hydrolyzes beta-lactam ring = inactivation
2. **Alteration in PBPs leading to decreased binding affinity or increased expression of enzyme** (e.g., MRSA)
Resistance to Beta-lactams

1. Beta-Lactamase

Penicillinases
Cephaosporinases
Extended-Spectrum β-lactamases
metallo-β-lactamases

2. Alteration in PBPs

Mutations in genes leading to PBPs with decreased binding affinity for beta-lactams

MRSA
Methacillin resistance staph aureus
PRSP
Penicillin resistant strep pneumonia

Beta-Lactams - Side Effects

- Generally well tolerated –
  - Mostly GI – upset stomach, diarrhea, nausea, etc.
  - Risk of suprainfection (more with broad-spectrum)
- Hypersensitivity – 3 to 9 %
  - Mild to severe allergic reactions
  - Higher incidence with parenteral administration or procaine formulation
  - Cross-reactivity exists among all penicillins and even other β-lactams
  - Desensitization is possible

New Report on Penicillin Allergy

- Penicillin “allergy” history often inaccurate
- Of 30 million US patients reported to be penicillin-allergic, an estimated 28.5 million actually are not!
  - 19 of 20 pts who think they are allergic to penicillin are misinformed
- Subjects with a penicillin “allergy” history:
  - Spend significantly more time in the hospital.
  - Are exposed to significantly more antibiotics previously associated with C difficile and VRE.
  - fluoroquinolones, clindamycin, and vancomycin
- Testing for penicillin allergy may result in cost savings, improved patient care, and fewer drug-resistant bacteria

Natural Penicillins
(penicillin G, penicillin VK)

Gram-positive
S. aureus (pen-sens)
S. pneumoniae (pen-sens)
Group streptococci
viridans streptococci
Atypicals
Spirochetes (syphilis, lyme)

Gram-negative
negligible

Anaerobes
Above the diaphragm
Clostridium sp.
**Natural Penicillins** (penicillin G, penicillin VK)

**Common Clinical Uses**
- **Streptococcal infections** (without bacteremia)
  - Mild-to-moderate infections of the upper respiratory tract, scarlet fever, mild erysipelas
- **Pneumococcal infections**
  - Mild to moderately severe infections of the respiratory tract
- **Staphylococcal infections** (pen-sensitive).
  - Mild infections of the skin and soft tissues

**Aminopenicillins** (ampicillin, amoxicillin)

**Increased activity against gram (-) aerobes**

**Gram-positive**
- *S. aureus* (pen-sens)
- Group streptococci
- viridans streptococci
- Enterococcus sp.

**Atypical**
- Spiriches (syphilus, lyme)

**Carboxypenicillins** (carbenicillin, ticarcillin)

Developed to further increase activity against resistant gram-negative aerobes

**Gram-positive**
- Proteus mirabilis
- Salmonella, Shigella
- some E. coli
- H. influenzae (**β**L neg)
- Enterobacter sp.
- Pseudomonas aeruginosa

**Gram-negative**
- M. Caterrhalis
- N. meningitidis
- Proteus mirabilis
- E. coli (some strains)
- Salmonella

**Ureidopenicillins** (piperacillin, azlocillin)

Developed (from Ampcillin) to further increase activity against resistant gram-negative aerobes

**Gram-positive**
- viridans strep
- Group strep
- some Enterococcus

**Anaerobes**
- Fairly good activity

**Gram-negative**
- Proteus mirabilis
- Salmonella, Shigella
- E. coli
- H. influenzae
- Enterobacter sp.
- Pseudomonas aeruginosa
- Serratia marcescens
- some Klebsiella sp.

**β-Lactamase Inhibitor – Penicillin Combinations**

- **Clavulanic Acid** + **Amoxicillin**
  - Augmentin
  - *Amp + S = Unasyn*
  - *Pip + T = Zosyn*
  - *Tic + C = Timentin*
Cephalosporins

- Divided into 5 groups “Generations”
- Generations differ in ~
  - Antimicrobial activity
  - Spectrum
  - Resistance to beta-lactamase
  - CNS penetration

1st Generation Cephalosporins

Best activity against gram-positive aerobes, with limited activity against a few gram-negatives

<table>
<thead>
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<th>Gram-negative</th>
</tr>
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<td>S. aureus* (meth-sens)</td>
<td>E. Coli (some)</td>
</tr>
<tr>
<td>S. pneumoniae* (pen-sens)</td>
<td>K. pneumoniae</td>
</tr>
<tr>
<td>Group streptococci</td>
<td>P. mirabilis</td>
</tr>
<tr>
<td>viridans streptococci</td>
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</table>

* May retain activity with B-lactamase producing strains

General Clinical Uses:

- Uncomplicated, community-acquired infections of the skin and soft tissue and urinary tract.
- Respiratory tract infections caused by penicillin-sensitive S. pneumonia.
- Parenteral 1st generation agents are used for surgical wound prophylaxis (ie. Ancef).

First Generation Cephalosporins

1st

cefalotin (Keflin)
cefalexin (Keflex) po
cefadroxil (Duricef) po
cephazolin (Ancef)

Second Generation Cephalosporins

In general, less active against gram (+) aerobes, but more active against gram (-)

Cephamycins & Carbacephems also included in the group

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<td>H. influenzae</td>
</tr>
<tr>
<td></td>
<td>M. Catarrhalis</td>
</tr>
<tr>
<td></td>
<td>E. aerogenes</td>
</tr>
<tr>
<td></td>
<td>Neisseria sp. (some)</td>
</tr>
</tbody>
</table>

Second Generation Cephalosporins

CEFPOZIL PO
CEFLOXIN PO / IM
CEFAZOLIN PO

Carbacephem
loracarbef (Lorabid) po

Cephamycins

Next slide

Third Gen Cephalosporins

- Less active against gram-positive, but greater activity against gram-negative aerobes
- Ceftriaxone (Rocheepin) and ceftaxime (Claforen) retain good activity against gram-positive aerobes, including pen-resistant S. pneumoniae
- Those with anti-pseudomonal activity have decreased activity against Gram-positive organisms
- Several agents are strong inducers of extended spectrum beta-lactamases (ESBLs)
**3 Third Gen Cephalosporins**

**Gram-negative aerobes**
- E. coli, K. pneumoniae, P. mirabilis, H. influenzae, M. catarrhalis, N. gonorrhoeae (incl beta-lactamase +)
- N. meningitidis, Citrobacter sp., Enterobacter sp., Acinetobacter sp., M. morganii, S. marcescens

**Pseudomonas** ceftazidime (Fortaz)

**Gram+ cocci**
- ceftriaxone (Rochepin)
- cefotaxime (Claforen)
- cefpodoxime (Vantin)
- cefixime (Suprax)

**Third Gen Cephalosporins**

**General Clinical Uses**
- For infections involving gram-negative bacteria, particularly hospital-acquired infections or complicated community-acquired infections of the respiratory tract, blood, intra-abdominal, skin and soft tissue and urinary tract.

**Drugs of choice for Meningitis**
- cefdinir (Omnicef) (PO)
- cefixime (Suprax) (PO)
- ceftibuten (Cedax) (PO)
- cefpodoxime (Vantin) (PO)
- ceftazidime (Fortaz)
- cefotaxime (Claforan)

**Fourth Gen Cephalosporins**
- Greater activity against both Gram-negative & Gram-positive organisms than 3rd-gen agents
- Good activity against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and multiple drug resistant *Streptococcus pneumoniae*
- Stability against beta-lactamases
  - Poor inducer of extended-spectrum beta-lactamases
- cefepime (Maxipime) - currently only one available

**Cephalosporin Side Effects**
- GI - diarrhea, nausea, electrolyte disturbances, and/or pain and inflammation at injection site, superinfection
- Hypersensitivity –
  - Studies suggest 1% to 3% incidence of allergic rx’s independent of history of PCN allergy
  - Cross rx with PCN allergy reported as high as 10%

**vancomycin**
- Glycopeptide antibiotic obtained from the actinobacteria species *Amycolatopsis orientalis*
- Inhibits synthesis of cell wall phospholipids and prevents cross-linking of peptidoglycans at a different site than B-lactams
- Active against gram positive bacteria only
  - Highly resistant *Strep. pneumo*, *Clostridia*, *Enterococcus*, *Staph. epi* and MRSA

**Common Clinical Uses:**
- Serious infections caused by susceptible organisms resistant to penicillins
  - methicillin-resistant *Staph aureus* MRSA
  - multi-resistant *Staph epidermidis* MRSE
- Pseudomembranous colitis (relapse or unresponsive to metronidazole treatment)
- Treatment of infections caused by gram-positive microorganisms in patients with serious allergies to beta-lactam antimicrobials
**Antibiotics: A Review of the Basics**

**vancomycin**
- **Adverse effects**
  - Pain / thrombophlebitis (IV administration)
  - Red man syndrome
  - Due to histamine release (non-IgE mediated)
  - Pruritus, erythematosus rash that involves the face, neck, and upper torso.
  - Slow injection and prophylactic antihistamines
  - Ototoxic – may potentiate known ototoxic agents.
- **Renal excretion** (90-100% glomerular filtration).
  - Normal half-life 6-10 hours.
  - Half life is over 200 hours in pts with ESRD

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**Tetracylines**
- From various *Streptomyces* strains
  - "Broad Spectrum" antibiotics
  - **gram (+)** (except Enterococcus)
  - **gram (-)**
  - **Atypicals**
  - Inhibit protein synthesis / Bacteriostatic
- Naturally-occurring
  - Short-acting ($t_1/2 < 6$ hrs)
  - Tetracycline
  - Oxytetracycline
  - Demeclocycline ($t_1/2$ 10 hr)
- Semi-synthetic
  - Long-acting ($t_1/2 > 16$ hrs)
  - Doxycycline
  - Minocycline

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**Tetracylines**
- Dosycycline / Minocycline
  - Absorption less affected by food, somewhat lower potential for causing photosensitivity, no dosage adjustments required in renal impairment
  - Minocycline 5x more lipophilic than doxycycline
  - May not distribute into tissues like the bladder or prostate, may be less effective for UTIs, prostatitis or epididymitis.
  - Both shown to have potent anti-inflammatory effects on neutrophil chemotaxis and inhibitory effects on cytokines and matrix metalloproteinases

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**Tetracylines**
- Respiratory tract infections [CAP or bronchitis]
  - Due to Mycoplasma, S pneumoniae, H influenzae, Klebsiella species)
  - UTIs caused by mycoplasma or chlamydia
  - Genital chlamydial infections
  - SSSIs
  - Acne, infections due to S. aureus, including CA-MRSA
  - Doxycycline one of three choices for (early-stage) treatment Lyme Disease
  - Drug of choice for treatment of rickettsial infections like Rocky Mountain Spotted Fever

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**Macrolides**
- Erythromycin
  - Derived from *Streptomyces erythreus*
- Clarithromycin & Azithromycin
  - Structural analogs
    - Broader spectrum of activity
    - Better pharmacokinetic properties – better bioavailability, better tissue penetration, prolonged half-lives
    - Improved tolerability

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**Adverse Effects:**
- GI irritation
- Suprainfection (esp. Candida, also C.diff)
- Photosensitivity (esp. natural tetracyclines)
- May worsen renal failure (except doxy / mino)
- Dizziness / headaches (minocycline)
  - Dose-related, typically appear in 2 – 3 days, women > men
  - In children - discoloration of teeth, depression of bone growth
Macrolides

Mechanism of Action
- Inhibit bacterial protein synthesis
- Macrolides typically are bacteriostatic
- May be bactericidal when present at high concentrations against susceptible organisms
- Time-dependent activity

Macrolides

Antibacterial spectrum:
- Erythromycin
  - Gram positives: Staph. (MRSA is resistant), Strep., Treponema, Corynebacteria
  - Atypicals: Mycoplasma, Ureaplasma, Chlamydia
- Clarithromycin - similar to erythromycin
  - Increased activity against gram negatives (H. flu, Moraxella, H. pylori) & atypicals (above plus MAV)
- Azithromycin
  - Decreased activity against gram positive cocci.
  - Increased activity against H. flu and M. cat.

Macrolides

Empiric use in URIs
1. Spectrum (particularly for C and A) covers S. pneumoniae, H. influenzae, and M. catarrhalis - three most common pathogens causing community-acquired pneumonia (CAP), otitis and bacterial sinusitis
2. Coverage of atypicals (mycoplasma, chlamydia and legionella) also associated with CAP
3. Ability to concentrate in respiratory tract tissue and upper airways.

Macrolides

Drug Interactions
Erythromycin and Clarithromycin – powerful inhibitors of CYP 3A4
- Some Statins (ator, sim, lov)
- Carbamazepine
- Warfarin (R)
- OAB drugs
- CCBs
- Buspirone
- Methadone, oxycodone
- Cyclosporine
- PDE5 Inhibitors
- Some Benzos
- Others

Macrolides

Side Effects
- Gastrointestinal – up to 33%
  - Nausea, vomiting, diarrhea, dyspepsia
  - Most common with erythro; less with others
- Cholestatic hepatitis - rare
  - > 1 to 2 weeks of erythromycin estolate
- Other: Bad Taste - Clarithromycin
  - Ototoxicity (high dose erythro in patients with URI);
  - QTc prolongation (all 3); hypersensitivity rare

Co-trimoxazole

- Sulfamethoxazole + trimethoprim [SXT, TMP-SMX, TMP-SMZ, Bactrim, Septra]
- Synthetic antimicrobial agents not derived from a “natural” source
- Fixed dose ratio 5:1 (S:T)
- Agents block two different steps in folic acid synthetic pathway
- No consensus - bactericidal or bacteriostatic

Alan P. Agins, Ph.D. 2017
**Fluoroquinolones**

**Mechanism:**
- Synthetic – not from microorganism
- Inhibit bacterial replication / transcription
- Bactericidal !!!
- Conc–dependent killing / Post Antibiotic effect
- Serum concentrations need to average 4X the MIC for each 24-hr period to produce almost 100% kill

**Fluoroquinolones**

**First-generation** - Nalidixic acid, etc.
- Discovered during synthesis of Chloroquine
- No gram pos. activity
- Poor oral absorption & tissue-penetration
- UTIs – E.coli, Proteus, Shigella, Enterobacter, etc

**Second-generation (1<sup>st</sup> gen Fluoro)**
- Ciprofloxacin, Norfloxacin, Ofloxacin
- Gram Negative Rod coverage (inc. pseudomonas)
- Some Gram Positive coverage
- Limited atypical coverage

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**Co-trimoxazole**

- Folate necessary for one-carbon transfer in purines and pyrimidine de novo synthesis
- Thymidine (for DNA) and Uridine (for mRNA) most sensitive to blockade

**Co-trimoxazole**

- **Adverse Effects**
  - GI Upset and allergic rashes most common
  - Photodermatitis
  - Hypersensitivity (incl SJ syndrome)
  - Hematologic:
    - Hemolytic anemia (G6PDH deficient pts.), neutropenia, thrombocytopenia
  - Renal: toxic nephrosis

**Co-trimoxazole**

- **Interactions**
  - Highly protein bound
  - Neonates - Kernicterus
  - Can displace other protein bound drugs – warfarin, phenytoin, lamotrigine, valproate, NSAIDs
  - TMP may hyperkalemic effect of ACEIs/ARBs
  - Both Sulfa and TMP are inhibitors of CYP2C9
  - Phenytoin
  - S-warfarin
  - Some antidiabetic drugs
  - others

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**Co-trimoxazole**

- **Common Clinical Uses:**
  - upper and lower RTIs, GU and UTIs, GI infections, skin and wound infections, septicemias, etc
  - UTIs, prostatitis
  - AOM, AECB, etc
  - CA-MRSA, impetigo,
  - Shigellosis, PCP (acute and prophylaxis in HIV), Traveler's Diarrhea, toxoplasmosis, etc

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**Co-trimoxazole**

**Broad Spectrum:**
- S. aureus, S. pneumonia, H. flu, Neisseria species, E.Coli, Shigella, Pneumocystis carinii

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**Sulfa**

**Mechanism:**
- Synthetic – not from microorganism
- Inhibit bacterial replication / transcription
- Bactericidal !!!
- Conc–dependent killing / Post Antibiotic effect
- Serum concentrations need to average 4X the MIC for each 24-hr period to produce almost 100% kill
### Fluoroquinolones

#### Third-generation Quinolones

- **Levofloxacin (Levaquin)**
  - Active enantomer of ofloxacin
  - Spectrum similar to 2nd-gen – plus -
    - "atypicals" & gram+
    - Strep, Staph, Enterococci

#### Fourth-generation Quinolones

- **Moxifloxacin (Avelox)**
  - Greater gram+ coverage
  - Less effective against pseudomonas and enterobacter

### Fluoroquinolones Adverse Effects

- Gastrointestinal – 5%
  - Nausea, vomiting, diarrhea, dyspepsia
- Central Nervous System
  - Headache, dizziness, confusion, tremors, restlessness, agitation, insomnia, anxiety, paranoia, panic attacks, hallucinations, toxic psychosis, seizures
  - Peripheral neuropathy (rare)
  - Can be irreversible (new FDA WARNING)

### Fluoroquinolones Common Clinical Uses

- Acute bacterial exacerbations of chronic bronchitis
- Community-acquired pneumonia
- Uncomplicated skin and skin structure infections
- Nongonococcal urethritis and cervicitis
- Mixed Infections of the urethra and cervix
- Acute pelvic inflammatory disease
- Uncomplicated cystitis
- Complicated urinary tract infections
- Prostatitis
- Acute, uncomplicated urethral & cervical gonorrhea

### Fluoroquinolones Drug Interactions

- **Divalent / trivalent cations**
  - Impair PO absorption of fluoroquinolones – can lead to Clinical Failure
  - Ca, Fe, Mg, Al, Zn, etc
  - Antacids, enteral feedings
  - Administer doses 2 to 4 hours apart; FQ first
- **Cytochrome P450 CYP1A2 inhibition**
  - Caffeine, theophylline, cyclosporine, (R) warfarin - ↑ levels, ↑ toxicity
  - Ciprofloxacin most likely

### Fluoroquinolones Interactions / Warnings

- NSAIDs increase risk of severe CNS adverse reactions, including but not limited to seizures
- Benzodiazepine-dependent pts may experience precipitated withdrawal symptoms
- Suprainfection
  - Quinolones in comparison to other antibiotic classes rank amongst the highest for risk of causing colonization with MRSA and C Difficile
Fluoroquinolones warnings
- QTc interval prolongation
- CNS effects – neuro / psychiatric
- Hypoglycemia
- Hepatotoxicity
- Hypersensitivity reactions
- Peripheral neuropathy
- Photosensitivity/phototoxicity
- Suprainfection (C. difficile and CDAD)
- Tendon inflammation/rupture [Boxed]

Fluoroquinolones & Neuropathy
- Fluoroquinolones (all) pose risk for producing permanent peripheral neuropathy
- Onset is rapid, often within few days of treatment initiation
  - FDA stated some patients who d/c drug continued to experience nerve damage symptoms for > a year
- FDA advises clinicians to switch patients to another class of antibiotics if they develop symptoms of peripheral neuropathy
  - unless the clinician believes the benefits of fluoroquinolone treatment outweigh the risks

Fluoroquinolones & dysglycemia
- Caused removal of gatifloxacin (Tequin) from market
- More likely to occur in diabetic patients
  - especially elderly + renal insufficiency
- Hypoglycemia (early) > hyperglycemia (later)
- hypoglycemia may be profound/difficult to manage
- Moxifloxacin (1%) > levofloxacin (.9%) > cipro (.8%)
- Use caution when using FQs in diabetic patients

Fluoroquinolones & Tendons
- Fluoroquinolones use increases the likelihood of tendon rupture by 3 to 4 fold
- Most at risk:
  - Pts > 60 yrs old
  - Pts taking corticosteroids (systemic)
  - Transplantation pts (kidney, heart or lung)
- Patients who experience pain, swelling, inflammation of a tendon or tendon rupture should stop taking the medications and call their provider

Clindamycin
- Semi-synthetic derivative of Lincomycin
- Inhibits protein synthesis (including toxin production)
- Bacteriostatic
- Covers gram- anaerobes & some gram+ aerobes
  - aerobic gram (-) bacteria resistant to clindamycin
    - Pseudomonas, Legionella, H. influenzae and Moraxella)
- Used for respiratory, skin and soft tissue infections, peritonitis, oral infections, acne, BV
- Option for CA-MRSA

Clindamycin
- Topical, PO, IV
- Side effects:
  - Diarrhea, vomiting, and nausea
    - More common if the individual lies down for an extended period of time within 30 minutes of taking Clindamycin.
  - Rash, neutropenia / thrombocytopenia,
  - Most noted antibiotic for causing pseudomembranous colitis
**Metronidazole**

- Bactericidal –
- Pro-drug, need to be “reduced” to active drug
- Causes uncoiling of DNA
- Will work in both growing and dormant infections

**Anaerobic Bacteria**
- *Bacteroides* sp., *Clostridium* sp., *Helicobacter pylori*

**Facultative Anaerobe**
- *Gardnerella* (vaginalis)

**Anaerobic Parasites / Protozoa**
- *Trichomonas vaginalis*, *Giardia lamblia*

**Adverse Effects**

**Gastrointestinal**
- Nausea, vomiting, stomatitis, metallic taste

**CNS**
- Peripheral neuropathy, seizures, encephalopathy
- Use caution in preexisting CNS disorders
- Requires discontinuation of metronidazole

**Other**
- Possibly carcinogenic [Black Boxed Warning]
- Based on animal data

**Drug Interactions**

- An inhibitor of CYP2C9 hepatic enzymes
- Warfarin → anticoagulant effect
- Phenytoin → phenytoin concentrations

- The issue with Alcohol
  - Disulfiram reaction ???
  - No evidence for → acetaldehyde in serum
  - May be due to Serotonin Syndrome
  - More likely in pts taking SSRIs/SNRIs

**Nitrofurantoin**

**Macrodantin, Macrobid**

**Uses:** UTIs, UTI prophylaxis
- Only clinically proven for use against
  - *E. coli* or *Staph. saprophyticus*
- Concentrates in urine
- Renal impairment - concentration achieved in urine may be sub-therapeutic
- Inhibits several bacterial enzyme systems including acetyl coenzyme A interfering with metabolism and possibly cell wall synthesis

**Side Effects:**

- Nausea, vomiting, fever, rash
- Peripheral neuropathy
- Hypersensitivity pneumonitis
- Chronic use may cause progressive pulmonary interstitial fibrosis
  - Watch for pulmonary involvement early
- SEs much more common in the elderly
- Colors urine a dark orange-brown