A Review of Antibiotic Classes

Gram-Positive Aerobes

COCCI

clusters - *Staphylococci*

pairs - *S. pneumoniae*

chains - group and viridans streptococci

pairs and chains - *Enterococcus sp.*

BACILLI

Bacillus sp.

Corynebacterium sp.

Listeria monocytogenes

Nocardia sp.

Gram-Negative Aerobes

COCCI

Moraxella catarrhalis

Neisseria gonorrhoeae

Neisseria meningitidis

Haemophilus influenzae

BACILLI

E. coli, Enterobacter sp.

Citrobacter, Klebsiella sp.

Proteus sp., Serratia

Salmonella, Shigella

Acinetobacter, Helicobacter

*Pseudomonas aeruginosa**

Anaerobes

"Above Diaphragm"

Peptococcus sp.

Peptostreptococcus sp.

Prevotella

Veillonella

Actinomyces

"Below Diaphragm"

Clostridium perfringens, tetani, and difficile

Bacteroides fragilis, disastonis, ovatus, thetaiotamicron

Fusobacterium

Other Bacteria

- Atypical Bacteria
  - *Legionella pneumophila*
  - *Mycoplasma pneumoniae* or *hominis*
  - *Chlamydia pneumoniae* or *trachomatis*
- Spirochetes
  - *Treponema pallidum* (syphilis)
  - *Borrelia burgdorferi* (Lyme)

Common Bacterial Pathogens by Site of Infection

- Certain bacteria have a propensity to commonly cause infection in particular body sites or fluids
- Antibiotic may be chosen before results of the culture are available based on some preliminary information
  - Site of infection and likely causative organism
  - Gram-stain result (does result correlate with potential organism above)

Bacteria by Site of Infection

Mouth
Peptococcus
Peptostreptococcus
Actinomyces

Skin/Soft Tissue
S. aureus
S. pyogenes
S. epidermidis
Pasteurella

Bone and Joint
S. aureus
S. epidermidis
Streptococci
N. gonorrhoeae
Gram-negative rods

Abdomen
E. coli, Proteus
Klebsiella
Enterococcus
Bacteroides sp.

Urinary Tract
E. coli, Proteus
Klebsiella
Enterococcus
Staph saprophyticus

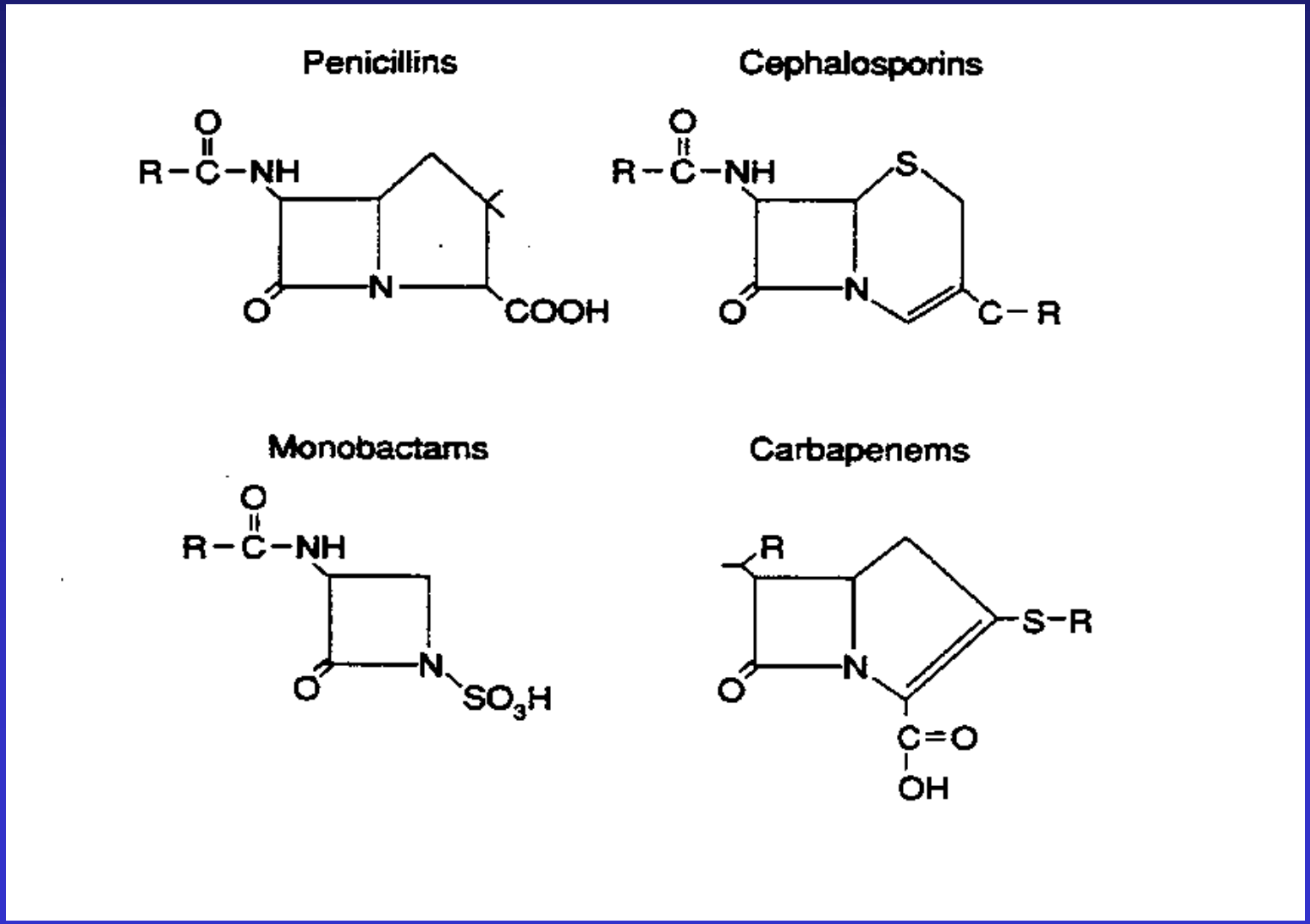
Upper Respiratory
S. pneumoniae
H. influenzae
M. catarrhalis
S. pyogenes

Lower Respiratory Community
S. pneumoniae
H. influenzae
K. pneumoniae
Legionella pneumophila
Mycoplasma, Chlamydia

Lower Respiratory Hospital
K. pneumoniae
P. aeruginosa
Enterobacter sp.
Serratia sp.
S. aureus

Meningitis
S. pneumoniae
N. meningitidis
H. influenza
Group B Strep
E. coli
Listeria

Beta-Lactam Structure



β-Lactam Characteristics

- Same MOA: Inhibit cell wall synthesis
- Bactericidal (except against Enterococcus sp.); time-dependent killers
- Short elimination half-life
- Primarily renally eliminated (except nafcillin, oxacillin, ceftriaxone, cefoperazone)
- Cross-allergenicity - except aztreonam

ALL β-lactams

- Mechanism of Action
  - interfere with cell wall synthesis by binding to penicillin-binding proteins (PBPs) which are located in bacterial cell walls
  - inhibition of PBPs leads to inhibition of peptidoglycan synthesis
  - are <u>bactericidal</u>

ALL β-lactams

- Mechanisms of Resistance
  - production of beta-lactamase enzymes
    - most important and most common
    - hydrolyzes beta-lactam ring causing inactivation
  - alteration in PBPs leading to decreased binding affinity
  - alteration of outer membrane leading to decreased penetration

Antimicrobial Spectrum of Activity

- General list of bacteria that are killed or inhibited by the antibiotic
  - are established during early clinical trials of the antibiotic
  - local, regional and national susceptibility patterns of each bacteria should be evaluated; differences in antibiotic activity may exist
- Individualized susceptibilities should be performed on each bacteria if possible

Natural Penicillins
(penicillin G, penicillin VK)

Gram-positive

pen-susc *S. aureus*

pen-susc *S. pneumoniae*

Group streptococci

viridans streptococci

Enterococcus

Other

Treponema pallidum (syphilis)

Gram-negative

Neisseria sp.

Anaerobes

Above the diaphragm

Clostridium sp.

Penicillinase-Resistant Penicillins
(nafcillin, oxacillin, methicillin)

Developed to overcome the penicillinase enzyme of *S. aureus* which inactivated natural penicillins

Gram-positive

methicillin-susceptible *S. aureus*

Group streptococci

viridans streptococci

Aminopenicillins
(ampicillin, amoxicillin)

Developed to increase activity against gram-negative aerobes

Gram-positive

pen-susc *S. aureus*

Group streptococci

viridans streptococci

Enterococcus sp.

Listeria monocytogenes

Gram-negative

Proteus mirabilis

S*almonella, Shigella*

some *E. coli*

βL- *H. influenzae*

Carboxypenicillins
(carbenicillin, ticarcillin)

Developed to further increase activity against resistant gram-negative aerobes

Gram-positive	**Gram-negative**
marginal	*Proteus mirabilis* S*almonella, Shigella* some *E. coli* βL- *H. influenzae* *Enterobacter sp.* *Pseudomonas aeruginosa*

Ureidopenicillins
(piperacillin, azlocillin)

Developed 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
S*almonella, Shigella*
E. coli
βL- *H. influenzae*
Enterobacter sp.
Pseudomonas aeruginosa
Serratia marcescens
some *Klebsiella sp.*

β-Lactamase Inhibitor Combos
(Unasyn, Augmentin, Timentin, Zosyn)

Developed to gain or enhance activity against β-lactamase producing organisms

Gram-positive

S. aureus

Anaerobes

Bacteroides sp.

Gram-negative

H. influenzae

E. coli

Proteus sp.

Klebsiella sp.

Neisseria gonorrhoeae

Moraxella catarrhalis

Classification and Spectrum of Activity of Cephalosporins

- Divided into 4 major groups called "Generations"
- Are divided into Generations based on
  - antimicrobial activity
  - resistance to beta-lactamase

First Generation Cephalosporins

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

Gram-positive

meth-susc *S. aureus*

pen-susc *S. pneumoniae*

Group streptococci

viridans streptococci

Gram-negative

E. coli

K. pneumoniae

P. mirabilis

Second Generation Cephalosporins

- Also includes some cephamycins and carbacephems
- In general, slightly less active against gram-positive aerobes, but more active against gram-negative aerobes
- Several second generation agents have activity against anaerobes

Second Generation Cephalosporins
Spectrum of Activity

Gram-positive

meth-susc *S. aureus*

pen-susc *S. pneumoniae*

Group streptococci

viridans streptococci

Gram-negative

E. coli

K. pneumoniae

P. mirabilis

H. influenzae

M. catarrhalis

Neisseria sp.

Second Generation Cephalosporins
Spectrum of Activity

The cephamycins (cefoxitin, cefotetan, and cefmetazole) are the only 2nd generation cephalosporins that have activity against anaerobes

Anaerobes

Bacteroides fragilis

Bacteroides fragilis group

Third Generation Cephalosporins
Spectrum of Activity

- In general, are even less active against gram-positive aerobes, but have greater activity against gram-negative aerobes
- Ceftriaxone and cefotaxime have the best activity against gram-positive aerobes, including pen-resistant *S. pneumoniae*
- Several agents are strong inducers of extended spectrum beta-lactamases

Third Generation Cephalosporins
Spectrum of Activity

Gram-negative aerobes

E. coli, *K. pneumoniae*, *P. mirabilis*

H. influenzae, *M. catarrhalis*, *N. gonorrhoeae* (including beta-lactamase producing); *N. meningitidis*

Citrobacter sp., *Enterobacter* sp., *Acinetobacter* sp.

Morganella morganii, *Serratia marcescens*, *Providencia*

Pseudomonas aeruginosa (ceftazidime and cefoperazone)

Fourth Generation Cephalosporins

- 4th generation cephalosporins for 2 reasons
  - Extended spectrum of activity
    - gram-positives: similar to ceftriaxone
    - gram-negatives: similar to ceftazidime, including *Pseudomonas aeruginosa*; also covers beta-lactamase producing *Enterobacter* sp.
  - Stability against β-lactamases; poor inducer of extended-spectrum β -lactamases
- Only cefepime is currently available

Carbapenems
Spectrum of Activity

- Most broad spectrum of activity of all antimicrobials
- Have activity against gram-positive and gram-negative aerobes and anaerobes
- Bacteria not covered by carbapenems include MRSA, VRE, coagulase-negative staph, *C. difficile*, *S. maltophilia*, *Nocardia*

Monobactams
Spectrum of Activity

Aztreonam bind preferentially to PBP 3 of gram-negative aerobes; has little to no activity against gram-positives or anaerobes

Gram-negative

E. coli, K. pneumoniae, P. mirabilis, S. marcescens

H. influenzae, M. catarrhalis

Enterobacter, Citrobacter, Providencia, Morganella

Salmonella, Shigella

Pseudomonas aeruginosa

β-lactams
Pharmacology

- Concentration-independent bacterial killing – Time above MIC correlates with efficacy
- Absorption
  - Many penicillins degraded by gastric acid
  - Oral β-lactams are variably absorbed; food delays rate and extent of absorption
    - Pen VK absorbed better than oral Pen G
    - Amoxicillin absorbed better than ampicillin

β-lactams
Pharmacology

- Distribution
  - Widely distributed into tissues and fluids
  - Pens only get into CSF in the presence of inflamed meninges; parenteral 3rd and 4th generation cephs, meropenem, and aztreonam penetrate the CSF
- Elimination
  - most eliminated primarily by the kidney, dosage adjustment of these agents is required in the presence of renal insufficiency
  - Nafcillin, oxacillin, ceftriaxone, and cefoperazone are eliminated primarily by the liver; piperacillin also undergoes some hepatic elimination
  - ALL β-lactams have short elimination half-lives (< 2º), except for a few cephalosporins (ceftriaxone)

β-Lactams
Special Pharmacologic Considerations

- Some preparations of parenterally-administered penicillins contain sodium; must be considered in patients with CHF or renal insufficiency

Sodium Penicillin G	2.0 mEq per 1 million units
Carbenicillin	4.7 mEq per gram
Ticarcillin	5.2 mEq per gram
Piperacillin	1.85 mEq per gram

- Imipenem is combined with cilastatin to prevent hydrolysis by enzymes in the renal brush border

β-Lactams
Adverse Effects

- Hypersensitivity – 3 to 10 %
  - Higher incidence with parenteral administration or procaine formulation
  - Mild to severe allergic reactions – rash to anaphylaxis and death
  - Antibodies produced against metabolic by-products or penicillin itself
  - Cross-reactivity exists among *all penicillins and even other β-lactams*
  - Desensitization is possible

β-Lactams
Adverse Effects

- Neurologic – especially with penicillins and carbapenems (imipenem)
  - Especially in patients receiving high doses in the presence of renal insufficiency
  - Irritability, jerking, confusion, seizures
- Hematologic
  - Leukopenia, neutropenia, thrombocytopenia – prolonged therapy (> 2 weeks)

β-Lactams
Adverse Effects

- Gastrointestinal
  - Increased LFTs, nausea, vomiting, diarrhea, pseudomembranous colitis (*C. difficile* diarrhea)
- Interstitial Nephritis
  - Cellular infiltration in renal tubules (Type IV hypersensitivity reaction – characterized by abrupt increase in serum creatinine; can lead to renal failure
  - Especially with methicillin or nafcillin

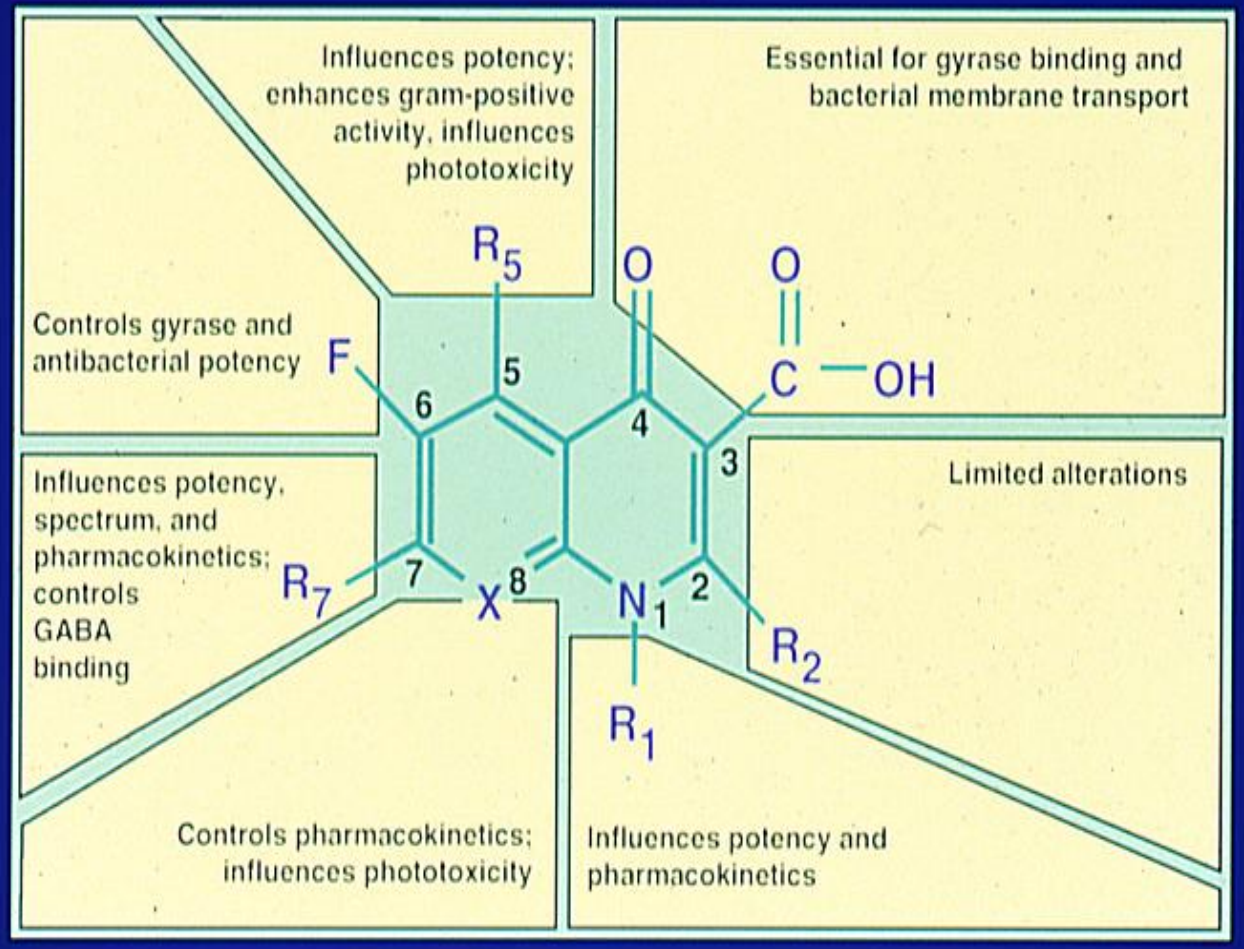
β-Lactams
Adverse Effects

- Cephalosporin-specific: MTT side chain - cefamandole, cefotetan, cefmetazole, cefoperazone, moxalactam
  - Hypoprothrombinemia - due to reduction in vitamin K-producing bacteria in GI tract
  - Ethanol intolerance
- Others: phlebitis, hypokalemia, Na overload

Fluoroquinolones

- Novel group of synthetic antibiotics developed in response to growing resistance
- Agents available today are all structural derivatives of nalidixic acid
- The *fluorinated* quinolones (FQs) represent a major therapeutic advance:
  - Broad spectrum of activity
  - Improved PK properties – excellent bioavailability, tissue penetration, prolonged half-lives
  - Overall safety
- Disadvantages: resistance, expense

Quinolone Antibacterial Structure-Activity Relationships



Domagala JM. *J Antimicrob Chemother.* 1994;33:685-706.

Fluoroquinolones

- Mechanism of Action
  - Unique mechanism of action
  - Inhibit bacterial topoisomerases which are necessary for DNA synthesis
    - *DNA gyrase* – removes excess positive supercoiling in the DNA helix
      - Primary target in gram-negative bacteria
    - *Topoisomerase IV* – essential for separation of interlinked daughter DNA molecules
      - Primary target for many gram-positive bacteria
  - FQs display concentration-dependent bactericidal activity

Fluoroquinolones

- Mechanisms of Resistance
  - Altered target sites – chromosomal mutations in genes that code for DNA gyrase or topoisomerase IV
    - most important and most common
  - Altered cell wall permeability – decreased porin expression
  - Expression of active efflux – transfers FQs out of cell
  - Cross-resistance occurs between FQs

The Available FQs

Older FQs

- Norfloxacin (Noroxin®) - PO
- Ciprofloxacin (Cipro®) – PO, IV

Newer FQs

- Levofloxacin (Levaquin®) – PO, IV
- Gatifloxacin (Tequin®) – PO, IV
- Moxifloxacin (Avelox®) – PO, IV

FQs Spectrum of Activity

Gram-positive – older agents with poor activity; newer FQs with enhanced potency

- Methicillin-susceptible *Staphylococcus aureus*
- *Streptococcus pneumoniae* (including PRSP)
- Group and viridans streptococci – limited activity
- *Enterococcus sp.* – limited activity

FQs Spectrum of Activity

Gram-Negative – all FQs have excellent activity (cipro=levo>gati>moxi)

- *Enterobacteriaceae* – including *E. coli, Klebsiella sp, Enterobacter sp, Proteus sp, Salmonella, Shigella, Serratia marcescens, etc.*
- *H. influenzae, M. catarrhalis, Neisseria sp.*
- *Pseudomonas aeruginosa* – significant resistance has emerged; ciprofloxacin and levofloxacin with best activity

FQs Spectrum of Activity

Anaerobes – only trovafloxacin has adequate activity against *Bacteroides sp.*

Atypical Bacteria – all FQs have excellent activity against atypical bacteria including:

- *Legionella pneumophila* - DOC
- *Chlamydia sp.*
- *Mycoplasma sp.*
- *Ureaplasma urealyticum*

Other Bacteria – *Mycobacterium tuberculosis*, *Bacillus anthracis*

Fluoroquinolones
Pharmacology

- Concentration-dependent bacterial killing – AUC/MIC (AUIC) correlates with efficacy
- Absorption
  - Most FQs have good bioavailability after oral administration
  - Cmax within 1 to 2 hours; coadministration with food delays the peak concentration
- Distribution
  - Extensive tissue distribution – prostate; liver; lung; skin/soft tissue and bone; urinary tract
  - Minimal CSF penetration
- Elimination – renal and hepatic; not removed by HD

Fluoroquinolones
Adverse Effects

- Gastrointestinal – 5 %
  - Nausea, vomiting, diarrhea, dyspepsia
- Central Nervous System
  - Headache, agitation, insomnia, dizziness, rarely, hallucinations and seizures (elderly)
- Hepatotoxicity
  - LFT elevation (led to withdrawal of trovafloxacin)
- Phototoxicity (uncommon with current FQs)
  - More common with older FQs (halogen at position 8)
- Cardiac
  - Variable prolongation in QTc interval
  - Led to withdrawal of grepafloxacin, sparfloxacin

Fluoroquinolones
Adverse Effects

- Articular Damage
  - Arthopathy including articular cartilage damage, arthralgias, and joint swelling
  - Observed in toxicology studies in immature dogs
  - Led to contraindication in pediatric patients and pregnant or breastfeeding women
  - Risk versus benefit
- Other adverse reactions: tendon rupture, dysglycemias, hypersensitivity

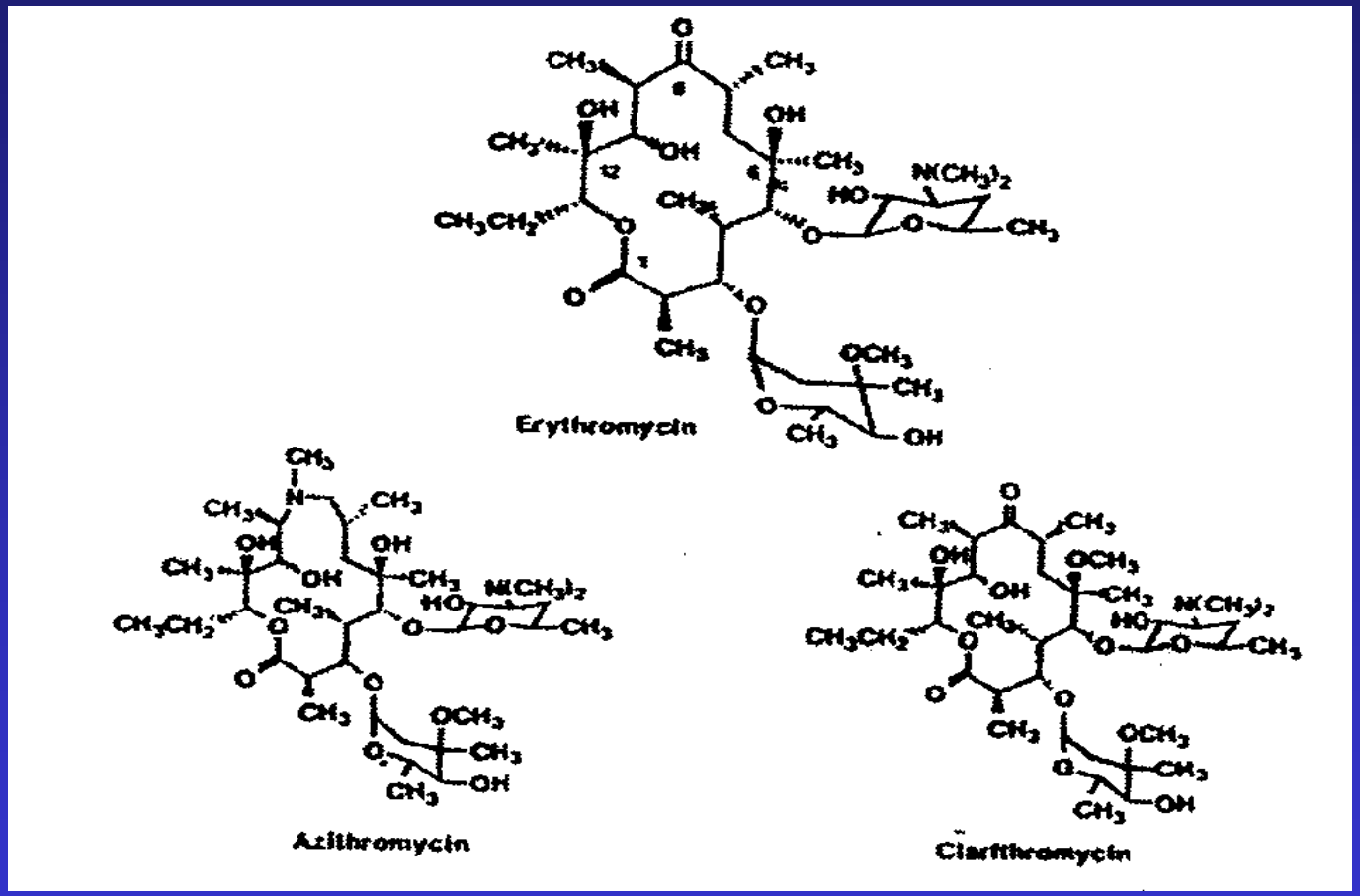
Fluoroquinolones
Drug Interactions

- Divalent and trivalent cations – ALL FQs
  - Zinc, Iron, Calcium, Aluminum, Magnesium
  - Antacids, Sucralfate, ddI, enteral feedings
  - Impair oral absorption of orally-administered FQs – may lead to CLINICAL FAILURE
  - Administer doses 2 to 4 hours apart; FQ first
- Theophylline and Cyclosporine - cipro
  - inhibition of metabolism, ↑ levels, ↑ toxicity
- Warfarin – idiosyncratic, all FQs

Macrolides

- Erythromycin is a naturally-occurring macrolide derived from *Streptomyces erythreus* – problems with acid lability, narrow spectrum, poor GI intolerance, short elimination half-life
- Structural derivatives include clarithromycin and azithromycin:
  - Broader spectrum of activity
  - Improved PK properties – better bioavailability, better tissue penetration, prolonged half-lives
  - Improved tolerability

Macrolide Structure



Macrolides

Mechanism of Action

- Inhibits protein synthesis by reversibly binding to the 50S ribosomal subunit
  - Suppression of RNA-dependent protein synthesis
- Macrolides typically display bacteriostatic activity, but may be bactericidal when present at high concentrations against very susceptible organisms
- Time-dependent activity

Macrolides

Mechanisms of Resistance

- Active efflux (accounts for 80% in US) – *mef* gene encodes for an efflux pump which pumps the macrolide out of the cell away from the ribosome; confers *low level* resistance to macrolides
- Altered target sites (primary resistance mechanism in Europe) – encoded by the erm gene which alters the macrolide binding site on the ribosome; confers *high level* resistance to all macrolides, clindamycin and Synercid
- Cross-resistance occurs between all macrolides

Macrolide Spectrum of Activity

Gram-Positive Aerobes – erythromycin and clarithromycin display the best activity

(Clarithro>Erythro>Azithro)

- Methicillin-susceptible *Staphylococcus aureus*
- *Streptococcus pneumoniae* (only PSSP) – resistance is developing
- Group and viridans streptococci
- *Bacillus sp., Corynebacterium sp.*

Macrolide Spectrum of Activity

Gram-Negative Aerobes – newer macrolides with enhanced activity

(Azithro>Clarithro>Erythro)

- *H. influenzae* (not erythro), *M. catarrhalis, Neisseria sp.*
- Do NOT have activity against any *Enterobacteriaceae*

Macrolide Spectrum of Activity

Anaerobes – activity against upper airway anaerobes

Atypical Bacteria – all macrolides have excellent activity against atypical bacteria including:

- *Legionella pneumophila* - DOC
- *Chlamydia sp.*
- *Mycoplasma sp.*
- *Ureaplasma urealyticum*

Other Bacteria – *Mycobacterium avium complex* (MAC – only A and C), *Treponema pallidum, Campylobacter, Borrelia, Bordetella, Brucella. Pasteurella*

Macrolides
Pharmacology

Absorption

- Erythromycin – variable absorption (F = 15-45%); food may decrease the absorption
  - Base: destroyed by gastric acid; enteric coated
  - Esters and ester salts: more acid stable
- Clarithromycin – acid stable and well-absorbed (F = 55%) regardless of presence of food
- Azithromycin –acid stable; F = 38%; food decreases absorption of capsules

Macrolides
Pharmacology

Distribution

- Extensive tissue and cellular distribution – clarithromycin and azithromycin with extensive penetration
- Minimal CSF penetration

Elimination

- Clarithromycin is the only macrolide partially eliminated by the kidney (18% of parent and all metabolites); requires dose adjustment when CrCl < 30 ml/min
- Hepatically eliminated: ALL
- NONE of the macrolides are removed during hemodialysis!
- Variable elimination half-lives (1.4 hours for erythro; 3 to 7 hours for clarithro; 68 hours for azithro)

Macrolides
Adverse Effects

- Gastrointestinal – up to 33 %
  - Nausea, vomiting, diarrhea, dyspepsia
  - Most common with erythro; less with new agents
- Cholestatic hepatitis - rare
  - > 1 to 2 weeks of erythromycin estolate
- Thrombophlebitis – IV Erythro and Azithro
  - Dilution of dose; slow administration
- Other: ototoxicity (high dose erythro in patients with RI); QTc prolongation; allergy

Macrolides
Drug Interactions

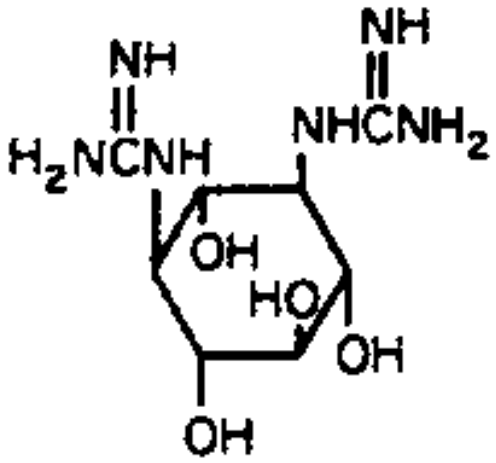
Erythromycin and Clarithromycin ONLY– are ***inhibitors*** of cytochrome p450 system in the liver; may increase concentrations of:

Theophylline	Digoxin, Disopyramide
Carbamazepine	Valproic acid
Cyclosporine	Terfenadine, Astemizole
Phenytoin	Cisapride
Warfarin	Ergot alkaloids

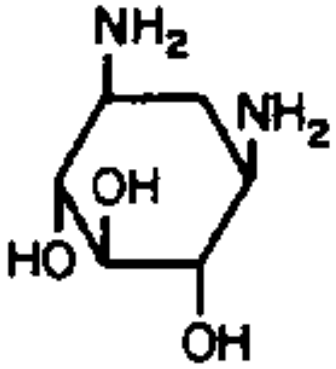
Aminoglycosides

- Initial discovery in the late 1940s, with streptomycin being the first used; gentamicin, tobramycin and amikacin are most commonly used aminoglycosides in the US
- All derived from an actinomycete or are semisynthetic derivatives
- Consist of 2 or more amino sugars linked to an aminocyclitol ring by glycosidic bonds = aminoglycoside
- Are polar compounds which are poly-cationic, water soluble, and incapable of crossing lipid-containing cell membranes

Aminoglycoside Structure



streptidine



2-deoxystreptamine

Aminoglycosides
Mechanism of Action

- Multifactorial, but ultimately involves inhibition of protein synthesis
- Irreversibly bind to 30S ribosomes
  - must bind to and diffuse through outer membrane and cytoplasmic membrane and bind to the ribosome
  - disrupt the initiation of protein synthesis, decreases overall protein synthesis, and produces misreading of mRNA
- Are bactericidal

Aminoglycosides
Mechanism of Resistance

- Alteration in aminoglycoside uptake
  - decreased penetration of aminoglycoside
- Synthesis of aminoglycoside-modifying enzymes
  - plasmid-mediated; modifies the structure of the aminoglycoside which leads to poor binding to ribosomes
- Alteration in ribosomal binding sites

Aminoglycosides
Spectrum of Activity

Gram-Positive Aerobes

most *S. aureus* and coagulase-negative staph

viridans streptococci

Enterococcus sp.

Gram-Negative Aerobes (not streptomycin)

E. coli, K. pneumoniae, Proteus sp.

Acinetobacter, Citrobacter, Enterobacter sp.

Morganella, Providencia, Serratia, Salmonella, Shigella

Pseudomonas aeruginosa (amik>tobra>gent)

Mycobacteria

- tuberculosis - streptomycin
- atypical - streptomycin or amikacin

Aminoglycosides
Pharmacology

- Absorption - poorly absorbed from gi tract
- Distribution
  - primarily in extracellular fluid volume; are widely distributed into body fluids but NOT the CSF
  - distribute poorly into adipose tissue, use LBW for dosing
- Elimination
  - eliminated unchanged by the kidney via glomerular filtration; 85-95% of dose
  - elimination half-life dependent on renal fxn
    - normal renal function - 2.5 to 4 hours
    - impaired renal function - prolonged

Aminoglycosides
Adverse Effects

Nephrotoxicity

- nonoliguric azotemia due to proximal tubule damage; increase in BUN and serum Cr; reversible if caught early
- risk factors: prolonged high troughs, long duration of therapy (> 2 weeks), underlying renal dysfunction, elderly, other nephrotoxins

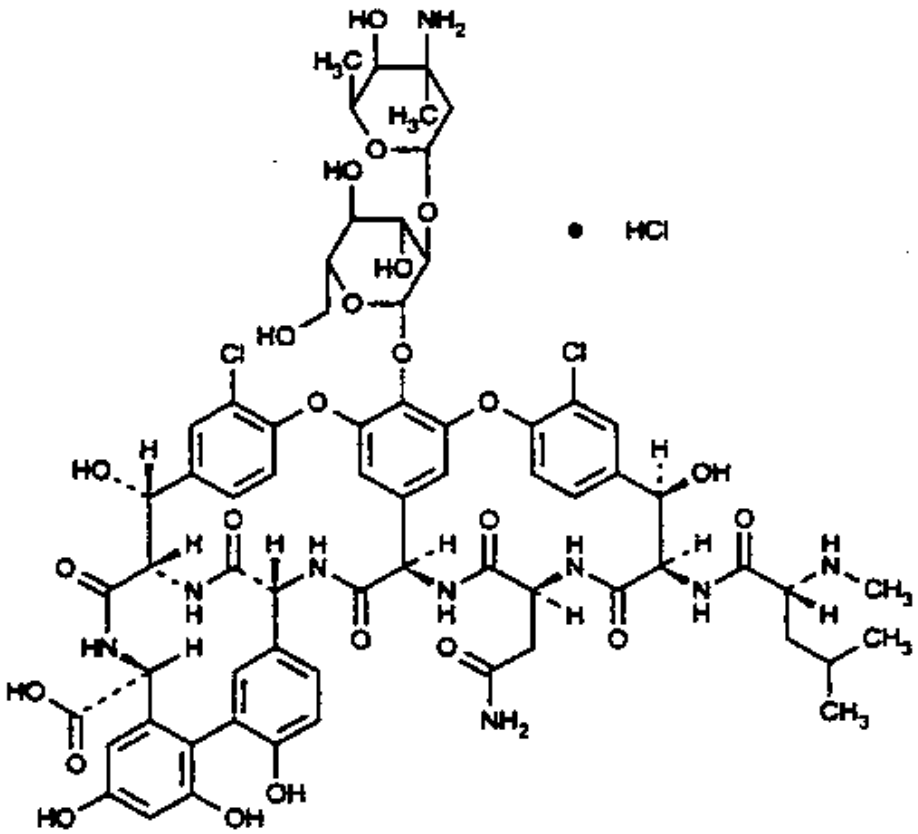
Ototoxicity

- 8th cranial nerve damage - vestibular and auditory toxicity; irreversible
- vestibular: dizziness, vertigo, ataxia – S, G, T
- auditory: tinnitus, decreased hearing – A, N, G
- risk factors: same as for nephrotoxicity

Vancomycin

- Complex tricyclic glycopeptide produced by *Nocardia orientalis*, MW = 1500 Da
- Commercially-available since 1956
- Current product has been extensively purified - decreased adverse effects
- Clinical use decreased with introduction of antistaphylococcal penicillins
- Today, use increasing due to emergence of resistant bacteria (MRSA)

Vancomycin Structure



Vancomycin
Mechanism of Action

- Inhibits bacterial cell wall synthesis at a site different than beta-lactams
- Inhibits synthesis and assembly of the second stage of peptidoglycan polymers
- Binds firmly to D-alanyl-D-alanine portion of cell wall precursors
- Bactericidal (except for Enterococcus)

Vancomycin
Mechanism of Resistance

- Prolonged or indiscriminate use may lead to the emergence of resistant bacteria
- Resistance due to modification of D-alanyl-D-alanine binding site of peptidoglycan
  - terminal D-alanine replaced by D-lactate
  - loss of binding and antibacterial activity
- 3 phenotypes - vanA, vanB, vanC

Vancomycin
Spectrum of Activity

Gram-positive bacteria

- Methicillin-Susceptible AND Methicillin-Resistant *S. aureus* and coagulase-negative staphylococci
- *Streptococcus pneumoniae* (including PRSP), viridans streptococcus, Group streptococcus
- *Enterococcus* sp.
- *Corynebacterium, Bacillus. Listeria, Actinomyces*
- *Clostridium* sp. (including *C. difficile*), *Peptococcus, Peptostreptococcus*

No activity against gram-negative aerobes or anaerobes

Vancomycin
Pharmacology

- Absorption
  - absorption from gi tract is negligible after oral administration except in patients with intense colitis
  - Use IV therapy for treatment of systemic infection
- Distribution
  - widely distributed into body tissues and fluids, including adipose tissue; use TBW for dosing
  - inconsistent penetration into CSF, even with inflamed meninges
- Elimination
  - primarily eliminated unchanged by the kidney via glomerular filtration
  - elimination half-life depends on renal function

Vancomycin
Clinical Uses

- Infections due to methicillin-resistant staph including bacteremia, empyema, endocarditis, peritonitis, pneumonia, skin and soft tissue infections, osteomyelitis
- Serious gram-positive infections in β-lactam allergic patients
- Infections caused by multidrug resistant bacteria
- Endocarditis or surgical prophylaxis in select cases
- Oral vancomycin for refractory *C. difficile* colitis

Vancomycin
Adverse Effects

Red-Man Syndrome

- flushing, pruritus, erythematous rash on face and upper torso
- related to RATE of intravenous infusion; should be infused over at least 60 minutes
- resolves spontaneously after discontinuation
- may lengthen infusion (over 2 to 3 hours) or pretreat with antihistamines in some cases

Vancomycin
Adverse Effects

- Nephrotoxicity and Ototoxicity
  - rare with monotherapy, more common when administered with other nephro- or ototoxins
  - risk factors include renal impairment, prolonged therapy, high doses, ? high serum concentrations, other toxic meds
- Dermatologic - rash
- Hematologic - neutropenia and thrombocytopenia with prolonged therapy
- Thrombophlebitis

Streptogramins

- Synercid® is the first available agent which received FDA approval in September 1999
- Developed in response to need for agents with activity against resistant gram-positives (VRE)
- Synercid® is a combination of two semi-synthetic pristinamycin derivatives in a 30:70 w/w ratio:

Quinupristin:Dalfopristin

Synercid® Structure

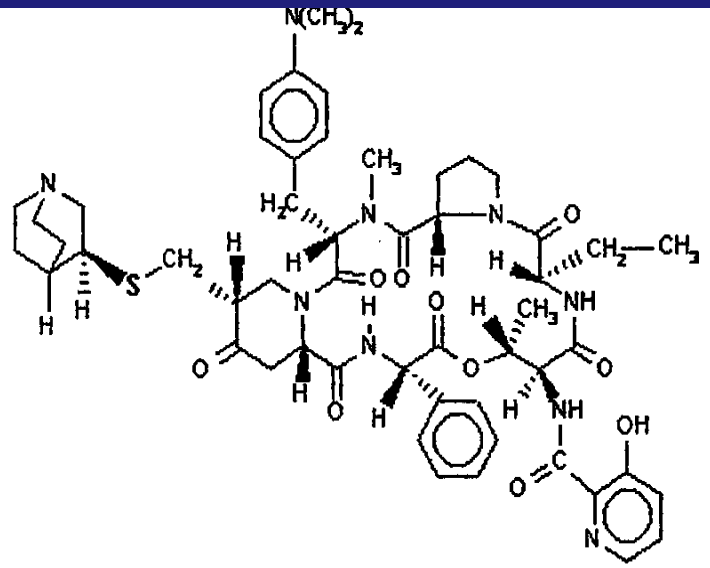


Figure . Structural formula of the main component of quinupristin.

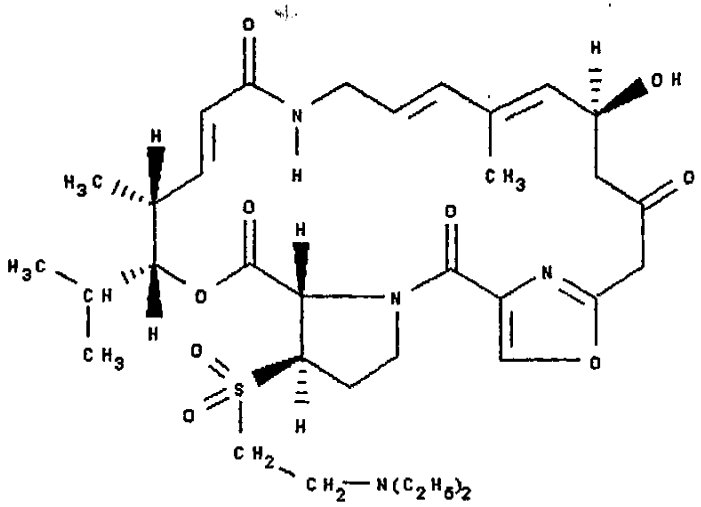


Figure . Structural formula of dalfopristin.

Synercid®

Mechanism of Action

- Each agent acts on 50S ribosomal subunits to inhibit early and late stages of protein synthesis
- Bacteriostatic (cidal against some bacteria)

Mechanism of Resistance

- Alterations in ribosomal binding sites
- Enzymatic inactivation

Synercid®
Spectrum of Activity

Gram-Positive Bacteria

- Methicillin-Susceptible and Methicillin-Resistant *Staph aureus* and coagulase-negative staphylococci
- *Streptococcus pneumoniae* (including PRSP), viridans streptococcus, Group streptococcus
- *Enterococcus faecium* (ONLY)
- *Corynebacterium, Bacillus. Listeria, Actinomyces*
- *Clostridium* sp. (except *C. difficile*), *Peptococcus, Peptostreptococcus*

Gram-Negative Aerobes

- Limited activity against *Neisseria sp.* and *Moraxella*

Atypical Bacteria

- *Mycoplasma, Legionella*

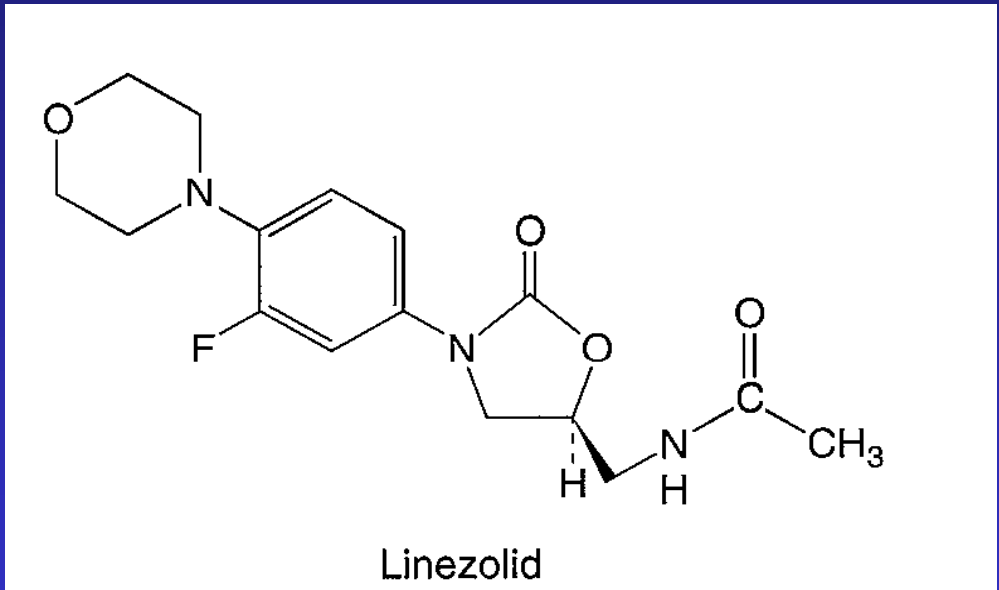
Synercid®
Adverse Effects

- Venous irritation – especially when administered in peripheral vein
- Gastrointestinal – nausea, vomiting, diarrhea
- Myalgias, arthralgias – 2%
- Rash
- ↑ total and unconjugated bilirubin

Oxazolidinones

- Linezolid (Zyvox®) is the first available agent which received FDA approval in April 2000; available PO and IV
- Developed in response to need for agents with activity against resistant gram-positives (MRSA, GISA, VRE)
- Linezolid is a semisynthetic oxazolidinone which is a structural derivative of earlier agents in this class

Linezolid Structure



Linezolid

Linezolid

Mechanism of Action

- Binds to the 50S ribosomal subunit near to surface interface of 30S subunit – causes inhibition of 70S initiation complex which inhibits protein synthesis
- Bacteriostatic (cidal against some bacteria)

Mechanism of Resistance

- Alterations in ribosomal binding sites (RARE)
- Cross-resistance with other protein synthesis inhibitors is unlikely

Linezolid
Spectrum of Activity

Gram-Positive Bacteria

- Methicillin-Susceptible, Methicillin-Resistant AND Vancomycin-Resistant *Staph aureus* and coagulase-negative staphylococci
- *Streptococcus pneumoniae* (including PRSP), viridans streptococcus, Group streptococcus
- *Enterococcus faecium AND faecalis* (including VRE)
- *Bacillus. Listeria, Clostridium* sp. (except *C. difficile*), *Peptostreptococcus, P. acnes*

Gram-Negative Aerobes – relatively inactive

Atypical Bacteria

- *Mycoplasma, Chlamydia., Legionella*

Linezolid
Pharmacology

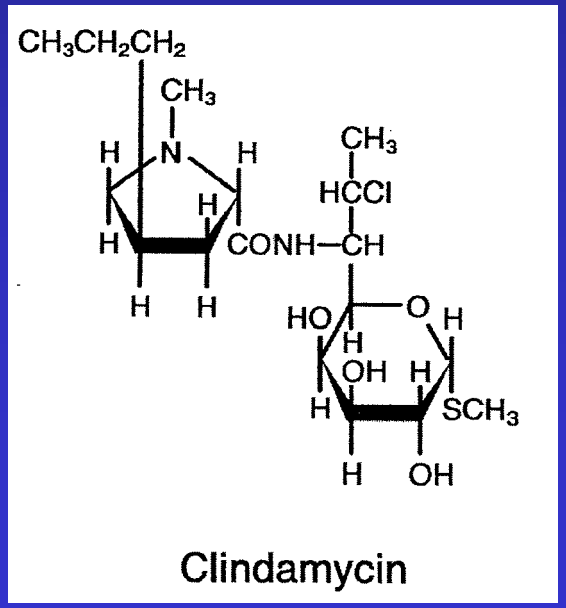
- Concentration-independent bactericidal activity
- PAE exists for Gram-Positive Bacteria
  - 3 to 4 hours for *S. aureus* and *S. pneumoniae*
  - 0.8 hours for Enterococcus
- Absorption – 100% bioavailable
- Distribution – readily distributes into well-perfused tissue; CSF penetration ≈ 30%
- Elimination – both renally and nonrenally, but primarily metabolized; t½ is 4.4 to 5.4 hours; no adjustment for RI; not removed by HD

Linezolid
Adverse Effects

- Gastrointestinal – nausea, vomiting, diarrhea (6 to 8 %)
- Headache – 6.5%
- Thrombocytopenia – 2 to 4%
  - Most often with treatment durations of > 2 weeks
  - Therapy should be discontinued – platelet counts will return to normal

Clindamycin

Clindamycin is a semisynthetic derivative of lincomycin which was isolated from *Streptomyces lincolnesis* in 1962; clinda is absorbed better with a broader spectrum



Clindamycin

Clindamycin

Mechanism of Action

- Inhibits protein synthesis by binding exclusively to the 50S ribosomal subunit
  - Binds in close proximity to macrolides – competitive inhibition
- Clindamycin typically displays bacteriostatic activity, but may be bactericidal when present at high concentrations against very susceptible organisms

Clindamycin

Mechanisms of Resistance

- Altered target sites – encoded by the erm gene which alters the clindamycin binding site on the ribosome; confers *high level* resistance to all macrolides, clindamycin and Synercid
- Active efflux – *mef* gene encodes for an efflux pump which pumps the macrolide out of the cell but NOT clindamycin; confers *low level* resistance to macrolides, but clindamycin still active

Clindamycin
Spectrum of Activity

Gram-Positive Aerobes

- Methicillin-susceptible *Staphylococcus aureus (MSSA only)*
- *Streptococcus pneumoniae* (only PSSP) – resistance is developing
- Group and viridans streptococci

Clindamycin
Spectrum of Activity

Anaerobes – activity against Above the Diaphragm Anaerobes (ADA)

Peptostreptococcus
Actinomyces
Propionibacterium
Clostridium sp. (not *C. difficile*)
some *Bacteroides sp*
Prevotella sp.
Fusobacterium

Other Bacteria – *Pneumocystis carinii, Toxoplasmosis gondii,* Malaria

Clindamycin
Pharmacology

Absorption – available IV and PO

- Rapidly and completely absorbed (F = 90%); food with minimal effect on absorption

Distribution

- Good serum concentrations with PO or IV
- Good tissue penetration including bone; minimal CSF penetration

Elimination

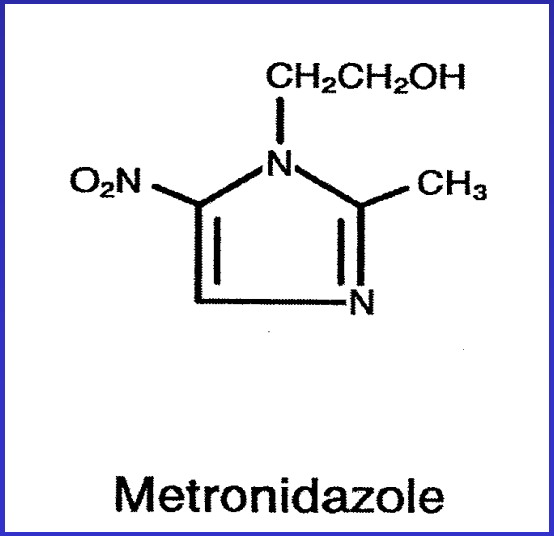
- Clindamycin primarily metabolized by the liver; half-life is 2.5 to 3 hours
- Clindamycin is NOT removed during hemodialysis

Clindamycin
Adverse Effects

- Gastrointestinal – 3 to 4 %
  - Nausea, vomiting, diarrhea, dyspepsia
- *C. difficile* colitis – one of worst offenders
  - Mild to severe diarrhea
  - Requires treatment with metronidazole
- Hepatotoxicity - rare
  - Elevated transaminases
- Allergy - rare

Metronidazole

Metronidazole is a synthetic nitroimidazole antibiotic derived from azomycin. First found to be active against protozoa, and then against anaerobes where it is still extremely useful.



Metronidazole

Mechanism of Action

- Ultimately inhibits DNA synthesis
  - Prodrug which is activated by a reductive process
  - Selective toxicity against anaerobic and microaerophilic bacteria due to the presence of ferredoxins within these bacteria
  - Ferredoxins donate electrons to form highly reactive nitro anion which damage bacterial DNA and cause cell death
- Metronidazole displays concentration-dependent bactericidal activity

Metronidazole

Mechanisms of Resistance – well documented but relatively uncommon

- Impaired oxygen scavenging ability – higher local oxygen concentrations which decreases activation of metronidazole
- Altered ferredoxin levels – reduced transcription of the ferredoxin gene; less activation of metronidazole

Metronidazole
Spectrum of Activity

Anaerobic Bacteria (BDA)

Bacteroides sp. (ALL)
Fusobacterium
Prevotella sp.
Clostridium sp. (ALL)
Helicobacter pylori

Anaerobic Protozoa

Trichomonas vaginalis
Entamoeba histolytica
Giardia lamblia
Gardnerella vaginalis

Metronidazole
Pharmacology

Absorption – available IV and PO

- Rapidly and completely absorbed (F > 90%); food with minimal effect on absorption

Distribution

- Good serum concentrations with PO or IV
- Well absorbed into body tissues and fluids; DOES penetrate the CSF

Elimination

- Metronidazole is primarily metabolized by the liver (metabolites excreted in urine); half-life is 6 to 8 hours
- Metronidazole IS removed during hemodialysis

Metronidazole
Adverse Effects

- Gastrointestinal
  - Nausea, vomiting, stomatitis, metallic taste
- CNS – most serious
  - Peripheral neuropathy, seizures, encephalopathy
  - Use with caution in patients with preexisting CNS disorders
  - Requires discontinuation of metronidazole
- Mutagenicity, carcinogenicity
  - Avoid during pregnancy and breastfeeding

Metronidazole Drug Interactions

Drug	Interaction
Warfarin*	↑ anticoagulant effect
Alcohol*	Disulfiram reaction
Phenytoin	↑ phenytoin concentrations
Lithium	↑ lithium concentrations
Phenobarbital	↓ metronidazole concentrations
Rifampin	↓ metronidazole concentrations

Antifungal Agents

- Polyenes - amphotericin B
  - *standard* of therapy for most invasive or life-threatening fungal infections
  - MOA: binds to ergosterol in cell wall and alters its integrity leading to cell lysis
  - conventional ampho B - significant toxicity and administration problems
    - infusion-related reactions and nephrotoxicity
    - use of test dose, proper infusion time, dose escalation, use of premedications
  - dose/duration of conventional AmB - depends on patient and type of infection

Antifungal Agents

- Polyenes - amphotericin B
  - lipid-based ampho B - advantages
    - increased daily doses can be given (up to 10x)
    - high tissue concentrations
    - decreased infusion-related reactions, less pre-meds administered
    - marked decrease in nephrotoxicity
  - disadvantages include: COST and lack of clinical trials
  - primarily used in patients with renal insufficiency (Cr > 2.5, CrCl < 25), who develop renal insufficiency, or who are on other nephrotoxins

Antifungal Agents

- Pyrimidines - 5-Flucytosine (5-FC)
  - MOA: interferes with protein and RNA/DNA synthesis
  - limited SOA; typically used in combination
  - SE: bone marrow toxicity, rash, nausea
  - only available orally
  - dose adjust in renal dysfunction

Antifungal Agents

- Azoles - alternative to AmB
  - ketoconazole, fluconazole, itraconazole
  - MOA: inhibit ergosterol synthesis
  - SOA: broad; only itra covers *Aspergillus*
  - ketoconazole and itraconazole - lipid soluble, not into CSF, primarily metabolized, inhibit cp450
  - fluconazole - water soluble, into CSF, renal elimination, doesn't inhibit cp450
  - IV itraconazole - new

Antifungal Agents
Spectrum of Activity

Spectrum of Activity of Select Antifungal Agents

Organism	Ampho B	5-FC	Ketoconazole	Fluconazole	Itraconazole
Candida albicans	S	S	S	S	S
Candida, non albicans	S	S	S/V	S/V	S/V
Candida krusei	S		R	R	V/R
Blastomyces dermatitidis	S	R	S	S	S
Histoplasma capsulatum	S	R	S	S	S
Coccidioides immitis	S	R	S	S	S
Cryptococcus neoformans	S	S	S	S	S
Aspergillus spp.	S	V	R	R	S
Fusarium spp.	S/V	R	R	R	R
Zygomycetes (Mucor)	S	V	R	R	R
Sporothrix schenckii	V	R	V	V	S

Antifungal Agents

Properties of Antifungal Agents

	Ampho B	5-FC	Ketoconazole	Fluconazole	Itraconazole
Oral Bioavailability (%)	< 5	> 80	75	90	> 70 (po soln, empty stomach)
Absorption ↓ by H-2 blockers or antacids		No	Yes	No	Probably
Protein Binding (%)	91-95	4	99	11	99
Half-life (hours)	15 days	3-4	7-10	17-30	24-42
Route of Excretion	unknown	Renal (adjust dose with RI)	hepatic	renal (adjust dose with RI)	hepatic
Unchanged Drug in Urine (%)	3	> 75	2-4	> 80	< 1
CSF:Plasma Concs. (%)	2-4	> 75	< 10	> 70	< 1
Dosage Form	Intravenous	Oral	Oral	Oral, Intravenous	Oral, Intravenous
Dose	0.3-1.5 mg/kg/day	100-150 mg/kg/day	200-800mg QD	100- 800mg QD	100-≥400mgQD
Adverse Effects	N/V, chills, fever during infusion; ↓ K, ↓ Mg; phlebitis; nephrotoxicity	Leukopenia, ↓ plts, N/V, diarrhea, rash, ↑ LFTs	N/V, abd pain, hepatotoxicity, gynecomastia, ↓ cortisol/testost., rash	N/V, rash, hepatotoxicity	N/V, headache, hepatotoxicity, rash
Monitoring Parameters	BUN, SCr, K, Mg, CBC	CBC with diff, SCr, LFTs	LFTs	SCr, LFTs	LFTs

Azole Drug Interactions

Drug Interactions of Antifungal Agents

Antifungal	Interacting Drug	Manifestation of Interaction
Ketoconazole and Itraconazole	drugs ↑ gastric pH	↓ azole absorption
	rifampin	↑ azole metabolism
	warfarin	increase in PT
	cyclosporine	↑ cyclosporine levels
	terfenadine/ astemizole / cisapride	prolongation of QT interval
Fluconazole	Warfarin	increases in PT
	cyclosporine/ phenytoin	↑ cyclosporine and phenytoin levels
	rifampin	↑ fluconazole clearance

Antifungal Agents

- Echinocandins - Caspofungin (Cancidas)
  - approved January 2001; new class
  - MOA: inhibits glucan synthesis which is necessary for fungal cell wall
  - SOA: broad, includes azole- and AmB-resistant strains
  - SE: fever, thrombophlebitis, headache, ↑ LFTs, rash, flushing
  - for patients with *Aspergillus* who do not respond or cannot tolerate AmB
  - only available IV - very expensive

Availability and Cost

Availability and Cost of Antifungal Agents

Antifungal	Brand Name	Dosage Form	Strength	AWP Cost per Unit ($)
Ampho B	Fungizone	Powder for inj.	50mg vial	17.85
Liposomal Amphotericin	AmBisome		50mg vial	188.40
AmB Lipid Complex (ABLC)	Abelcet		50mg vial 100mg vial	134.66 230.00
AmB Colloidal Dispersion (ABCD)	Amphotec		100mg/50ml	160.00
Flucytosine	Ancobon	Capsules	250mg 500mg	3.51 6.98
Ketoconazole	Nizoral	Tablets	200mg	3.68
Fluconazole	Diflucan	Soln for inj Tablets Oral suspension	2 mg/ml 50mg 100mg 150mg 200mg 50 mg or 200mg/ 5mL	88.90 (100mg) 4.78 7.52 11.97 12.31 30.96 (35ml) 111.75 (35 ml)
Itraconazole	Sporanox	Capsules Oral suspension IV solution	100mg 10 mg/ml 10 mg/ml amp	7.41 116.58 (150ml) 176.23 (25 ml)
Terbinafine	Lamisil	Tablets	250mg	8.35
Caspofungin	Cancidas	IV Solution	50mg vial 70mg vial	360.00 463.75