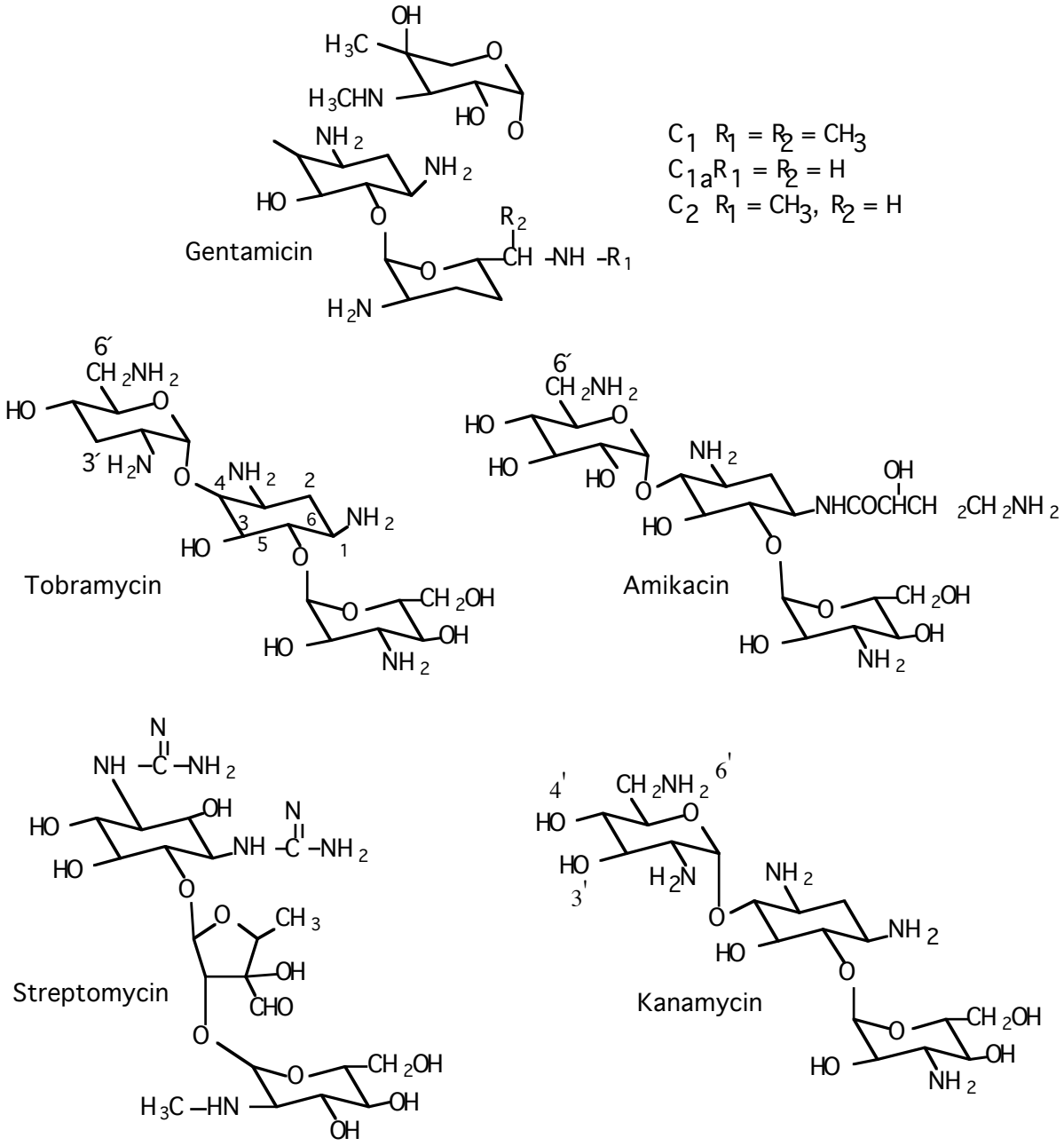
BATERIOCIDAL INHIBITORS OF PROTEIN SYNTHESIS

I. AMINOGLYCOSIDES (all are UW formulary drugs)



1. History and Structural Characteristics

Streptomycin was first isolated by Selman Waksman from Streptomyces griseus in 1943, and this was a breakthrough drug for TB treatment at that time. Waksman received the Nobel prize for this. Kanamycin was isolated in 1957 and was the drug of choice until Gentamicin in 1963. Tobramycin and Netilmicin were developed later as alternatives to gent. Amikacin, a semisynthetic analog, is the most recent and is used when resistance to the others is encountered. All aminoglycosides contain 2 or more sugars linked to an aminocyclitol ring. They are very water soluble and not orally absorbed and are cationic at physiological pH. In streptomycin the aminocyclitol ring is streptidine, whereas in the others it is 2-deoxystreptamine. Gentamicin is not obtained from Streptomyces sp. but rather from Micromonospora purpurea. Hence it is not spelled Gentamycin. Amikacin is obtained by chemical modification of Kanamycin.

2. MOA

AG's bind irreversibly to the 30S ribosomal subunit to decrease initiation and thus inhibit protein synthesis. Unlike other bacterial protein synthesis inhibitors, AG's are bacteriocidal for reasons that are not well understood but in part is due to a misread of protein synthesis.

3. Spectrum

AG's have a broad spectrum against Gram(–) aerobes. Gram (+) activity is limited and usually depends on combination therapy with a cell wall inhibitor (to weaken wall). Gram (+) spectrum may include Staph aureus (including MRSA) and Staph epidermidis. Gram (-) includes aerobic and facultative pathogens. Anaerobes are not generally covered. The AG's diffuse through porin channels in the outer membrane but need active transport to cross the inner membrane. The transport does not occur in anaerobes. A big feature of the AG's is that they are synergistic with beta lactams. Thus the combination results in a powerful antimicrobial effect. The cation pump to cross the inner cell membrane can be a site of resistance to AG's.

4. Use

a) Serious Gram-negative infections due to Enterobacteriaceae, including Enterobacter, Klebsiella, Proteus, Providencia, Morganella, Serratia, and Pseudomonas aeruginosa. Use is being replaced by the less toxic cephalosporins and fluoroquinolones. Two drug regimens (beta lactam + AG) for serious infections are still useful.

b) Enterococcus faecalis and E. faecium (combined with Vancomycin or possibly Pen G or ampicillin); alone have 40-60% resistant

c) Very serious Staphlococcal infections (e.g. MRSA) as an alternate to other antibiotics (combined with vanco). MRSA may be sensitive.

5. Resistance

Since the AG's are being used in serious, life threatening infections, resistance could result the death of the patient. Thus it is critical that resistance patterns be determined and monitored. There are 3 main mechanisms of resistance to the AG's.

a) Resistance due to production of plasmid mediated AG modifying enzymes. This is the most common mechanism and acetylation, adenylation and phosphorylation enzymatic modifications of AG's are well described. The presence of the substituent amide at position 1 with Amikacin confers resistance to enzymatic derivatization at all positions except position 6´. If a pathogen is resistant to amikacin, it is resistant to all other AG's. Amikacin should only be used for resistant pathogens.

b) Resistance due to impaired transport into cell via cation pump in inner membrane. Gm+ and anaerobes have this resistance. Also Pseudomonas aeruginosa.

c) Resistance due to altered ribosomal binding site.

6. Disposition, Metabolism, Excretion

AG's are polar bases that have poor oral bioavailability and do not penetrate cell membranes well. They are excreted largely unchanged by glomerular filtration. These agents do not cross the blood brain barrier even when the meninges are inflamed. Because of the high potential for adverse effects, blood levels should be monitored with the goal to keep levels as low as possible and still achieve a therapeutic level. Immunoassays on serum samples are routinely performed at most hospitals. The Pharmacy Department is usually responsible to calculate the dose. These calculations are often based on lean body weight and serum creatinine. These procedures will be covered in other courses. Beta lactam drugs inactivate AG's when mixed together. Administer separately. Post antibiotic effect – concentration dependent killing which argues for less frequent dosing with higher doses. Doug Black will cover this in more detail.

7. Adverse Reactions

See "boxed warning" below from Facts and Comparisons. Other less common effects are neuromuscular blockade due to too rapid IV infusion, hypomagnesemia in some patients on restricted diets, and contact dermatitis with topical use (especially neomycin). Generally keep protocols short (< 5d).

WARNING
Toxicity: Aminoglycosides are associated with significant nephrotoxicity or ototoxicity. These agents are excreted primarily by glomerular filtration; thus, the serum half-life will be prolonged and significant accumulation will occur in patients with impaired renal function. Toxicity may develop even with conventional doses, particularly in patients with prerenal azotemia or impaired renal function. Ototoxicity: (less common but more serious) Neurotoxicity, manifested as both auditory (cochlear) and vestibular ototoxicity, can occur with any of these agents. Auditory changes are irreversible, usually bilateral and may be partial or total. Risk of hearing loss increases with the degree of exposure to either high peak or high trough serum concentrations and continues to progress after drug withdrawal. The risk is greater in patients with renal impairment and with preexisting hearing loss. High frequency deafness usually occurs first and can be detected by audiometric testing. When feasible, obtain serial audiograms. There may be no clinical symptoms to warn of developing cochlear damage. Tinnitus or vertigo may occur, and are evidence of vestibular injury. Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching and convulsions. Total or partial irreversible bilateral deafness may occur after drug discontinuation. Aminoglycoside-induced ototoxicity is usually irreversible. Vestibular toxicity is more predominant with gentamicin and streptomycin; auditory toxicity is more common with kanamycin, and amikacin. Tobramycin affects both functions equally. Relative ototoxicity is: Streptomycin= Kanamycin > Amikacin = Gentamicin = Tobramycin. Kanamycin, amikacin and streptomycin appear in this relative comparison based on high dose (kanamycin, amikacin) and antituberculosis (streptomycin) therapy. Renal toxicity: (5-10% of treated) This may be characterized by decreased creatinine clearance, cells or casts in the urine, decreased urine specific gravity, oliguria, proteinuria or evidence of nitrogen retention (increasing BUN, nonprotein nitrogen [NPN]or serum creatinine). Renal damage is usually reversible. The relative nephrotoxicity of these agents is estimated to be: Kanamycin = Amikacin = Gentamicin > Tobramycin> Streptomycin. Monitoring: Closely observe all patients treated with aminoglycosides. Monitoring renal and eighth cranial nerve function at onset of therapy is essential for patients with known or suspected renal impairment and also in those whose renal function is initially normal, but who develop signs of renal dysfunction. Evidence of renal impairment or ototoxicity requires drug discontinuation or appropriate dosage adjustments. When feasible, monitor drug serum concentrations. Avoid concomitant use with other ototoxic, neurotoxic or nephrotoxic drugs. Other factors which may increase risk of toxicity are dehydration and advanced age.

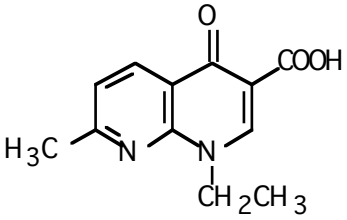
8. Products

   a) Parenteral drugs. Tobramycin is more potent against Pseudomonas then gent. Amikacin should be reserved for infection resistant to gent. and tobra. Kanamycin is usually used for topical therapy of gut infections. Usually try to keep peak serum levels of gentamicin at 4-8 mcg/ml. Amikacin peak should be 16-32 but not >35. Streptomycin is used for TB.

   b) Oral agents. Note this is for "topical" GI effects only. Kanamycin, neomycin, and paromomycin. The latter is used for intestinal amoebiasis.

J. FLUOROQUINOLONES

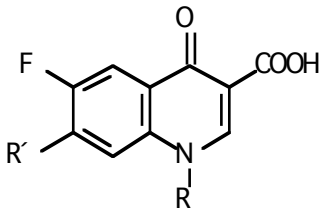
1. Older nonfluorenated - been around since 1960



Nalidixic Acid NegGram ® Sanofi Winthrop
Cinoxacin generics - similar drug

These agents have a short half life and poor tissue levels so are now only used for UTI caused by gram-negative bacteria.

2. Fluoroquinolones - since 1985



These agents have much better pharmacokinetic properties, an excellent spectrum of activity against aerobic gram-negative infections and are relatively free of adverse effects. Newer agents have a good gram-positive spectrum as well. They are generally bacteriocidal.

a) Mechanism of action -
inhibit DNA gyrase (topoisomerase II and IV), topoisomerase II negatively supercoils bacterial DNA and repairs nicks in single stranded DNA. These agents are bacteriocidal and have a relatively broad spectrum if they can get inside the cell.

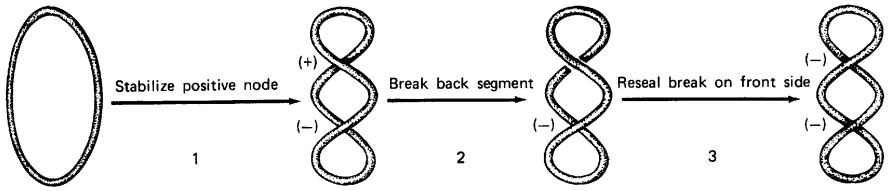


Figure 10–2. Model of the formation of negative DNA supercoils by DNA gyrase. The model presented here is the "sign inversion" model where the enzyme binds to two segments of DNA (1), creating a node of positive (+) superhelix. The enzyme then introduces a double-strand break in the DNA and passes the front segment through the break (2). The break is then resealed (3), creating a negative (−) supercoil. Nalidixic acid inhibits both the nicking and closing activity of the gyrase. (From Cozzarelli.[15])

b) Resistance
Becoming a problem especially with Neisseria gonorrheae, Pseudomonas and Staph. Due to altered DNA gyrase. Also multidrug resistant efflux systems (efflux pumps) to remove drug. Also changes in porin channel size can lead to resistance.

c) Spectrum

1) broad Gram-negative activity against most aerobes even some Pseudomonas strains. Excellent against Enterobacteriaceae.
2) Gram-positive organisms vary in sensitivity. The newer agents have good Gram (+) activity, including Strep. as well as PRSP but not MRSA
3) Anaerobes - only moxifloxacin
4) Syphilis - not very effective.
5) Other - Chlamydia, Mycobacterium tuberculosis, MAC and certain other Mycobacteria are sensitive and these fluoroquinolones may be very useful.
6) Mycoplasma – newer drugs
7) Enterococcus - no

d) Pharmacokinetics

T 1/2 = 4-12h and therefore BID or even qd dosing is possible; they have excellent tissue penetration and some penetration into CNS (but not usually indicated for CNS infections). Excellent for intracellular infections like Chlamydia, MAC and TB. Mainly eliminated via kidney; some in bile; Cipro and newer agents have excellent bioavailability

e) Uses

1) UTI - especially for complicated infections involving Klebsiella, Providencia, Pseudomonas, Proteus. Excellent agents for UTI as they cover most potential pathogens including some Pseudomonas (UTI).
2) gut infections - good (e.g. Salmonella, Shigella E. coli) and normal anaerobic flora is not extensively perturbed; are excreted in the bile and reach high gut concentrations. Are preferred drugs for traveler's diarrhea.
3) respiratory infections in cystic fibrosis - often Pseudomonas. Newer agents have indications for community acquired pneumonia (Strep. pneumo, H. flu, M. cat) including penicillin resistant Streptococcus pneumoniae and anaerobic bacteria.
4) osteomyetitis with Gram-negative bacteria - good bone penetration.
5) Prostatitis
6) complicated and mixed infections due to aerobic gram-negative bacteria resistant to beta lactams.
7) Can also be used for:
   a. acute exacerbations of chronic bronchitis - H. flu, Moraxella catarrhalis
   b. pneumonias, including community acquired pneumonia using the new agents
8) STD - cover N. gonorrhea (but resistance is increasing) and many have a STAT dose indication for uncomplicated gonorrhea. A 7-day regimen is needed for Chlamydia, however, so Azithromycin STAT is preferred. A fluoroquinolone plus Azithro given STAT will cover both gonorrhea and chlamydia. Not effective for syphilis.
9) Skin and skin structure – may work; have some activity against staph (usually not MRSA) and strep, especially the newer agents.
10) bioterrorism: Bacillus antracis

f) Adverse Effects

1) good safety profile with most but there have been problems

Fluoroquinolones have been approved for marketing by the FDA based on good safety profiles in the clinical trials only to discover serious adverse effects when in actual use in larger populations.

- e.g. temoflaxacin – withdrawn in 1992, six months after introduction due to renal toxicity, hemolysis, and hepatic toxicity seen in 1/5000 patients.
- e.g. trovafloxacin – approved in 1997 with great promise due to impressive potency and spectrum. Now withdrawn due to hepatotoxicity.
- e.g. grepafloxacin and moxifloxacin – prolonged QT interval effects causes worry. Grepafloxacin has been removed from the US market. All fluoroquinolines can do this. Clinical significance?

2) GI problems - 5%

3) CNS - < 1% (headache, seizures, dizziness, confusion) but not to be given to patients at risk for seizures.

4) children - not recommended for those < 18 years old due to risk of bone/joint/cartilage erosion problems (seen in animal studies) unless benefit outweighs the risk (e.g. cystic fibrosis, complicated pyelonephritis).

5) adult cartilage weakening?

6) pregnancy, lactation – no (see #4)

7) phototoxicity – especially those with a fluorine in position 8 e.g. sparfloxacin; this is now off the market

g) Drug Interactions

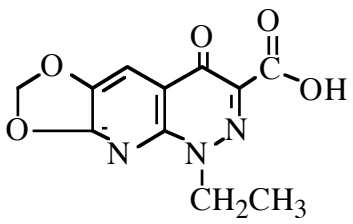
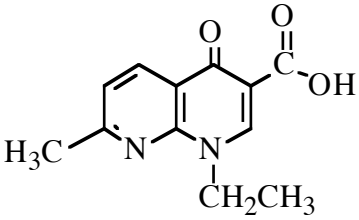
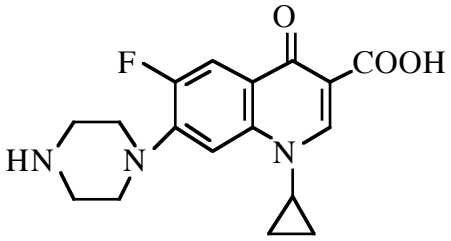
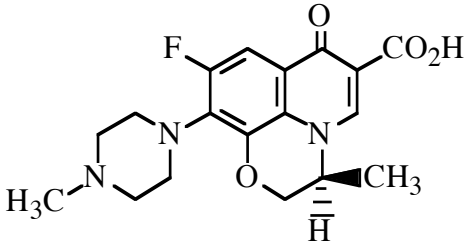
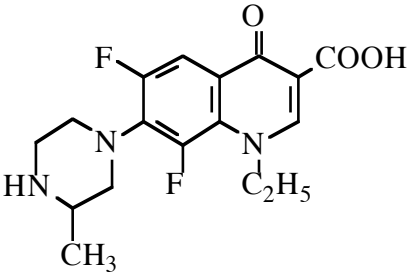
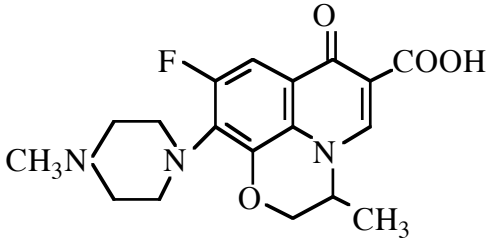
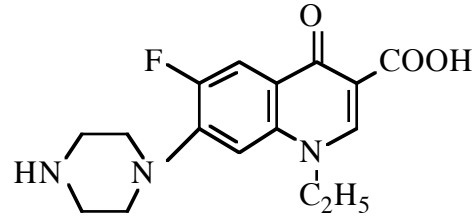
- Ciprofloxacin is a CYP1A2 inhibitor and has been reported to increase blood levels of theophylline and caffeine. Newer agents are weaker inhibitors.
- Polyvalent cations form chelates that have reduced absorption, e.g. antacids, multivitamin/mineral combinations, iron products, calcium products, dairy products. Allow a 4-6h interval.

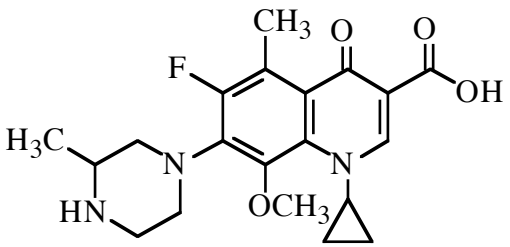
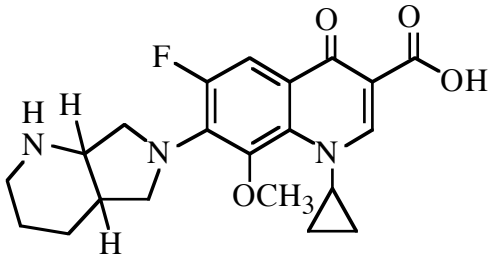
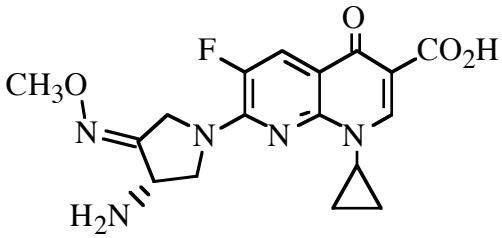
h) Summary - excellent, well tolerated but expensive oral drugs for serious infections; less expensive than IV drugs, much more expensive than narrow spectrum oral agents.

i) Agents available now

Table - Available Quinolones and Fluoroquinolones

Generation	Name	Use	Comment	Structure

First	cinoxacin (Cinobac®)	UTI	rarely used	
(quinolones)	nalidixic acid (Neg Gram®)	UTI	rarely used	
Second	ciprofloxacin (Cipro®)	general	best Gm(–) now generic	
	levofloxacin (Levaquin®)	general	some Gm(+) coverage	
	lomefloxacin (Maxaquin®)	general	photosensitivity (8-F)	
	ofloxacin (Floxin®)	general		
	norfloxacin (Noroxin®)	UTI	was the first FQ	

Third	gatifloxacin (Tequin®)	Now only an ophthalmic drop product		
	moxifloxacin (Avelox®)	general		
	gemifloxacin (Factive®)	general		

j) UW Formulary Agents

*Ciprofloxacin Cipro ® Bayer and now generic
oral and IV

Excellent Gm(-) activity but limited Gm (+) activity
Indications:
- Acute sinusitis
- LRI
- Nosocomial pneumoniae (IV)
- Skin or skin structure
- Bone/joint
- UTI
- Uncomplicated cystitis
- Chronic bacterial prostatitis
- Infectious diarrhea
- Gonorrhea (500 mg stat)
- AND inhalation anthrax
- resistance is on the increase

*Levofloxacin Levaquin ® Ortho-McNeil
oral and IV

l-isomer of ofloxacin
more potent compared to ofloxacin
Gram (+) activity as well as reasonable Gram (-)
numerous approved indications:
- acute sinusitis
- acute exacerbation of chronic bronchitis
- nosocomial pneumonia
- community acquired pneumonia
- complicated and uncomplicated skin and skin structure
- complicated and uncomplicated UTI

acute pyelonephitis
prostatitis
UTI
available as 250 mg, 500 mg, and 750 mg tablets and for IV use
dose: 500-750 mg q d x 10-14

*Moxifloxacin Avelox ® Bayer

- approved Jan. '00
- broad spectrum agent but best Gm(+) coverage of all
- binds to topo II and topo IV
- no p450 effects but small prolonged QT interval has
- been reported
- q d dosing

indications for acute sinusitis
chronic bronchitis
CAP
uncomplicated skins/skin structure infections
some antianaerobe activity
has better Gm(+) activity than levofloxacin but diminished Gm(–) activity. Some evidence that development of resistance may be slower than other fluoroquinolones. It is not eliminated exclusively via the kidney so is not a good UTI drug. Best used for respiratory infections due to Gm(+) pathogens.

k) Patient counseling

1) avoid antacids within 8h before and within 2h after dosing. Best to avoid dairy and multivitamin/multimineral and calcium products within this window also. (With qd dosing this is not a huge burden).

2) inform if experiencing tendon pain

3) inform if experiencing severe or prolonged diarrhea

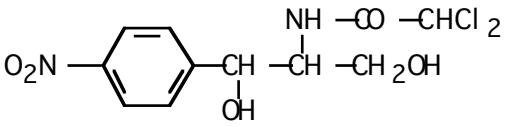
4) inform if have history of cardiac arrhythmia

5) be careful with caffeine if taking cipro

6) use sunscreen if taking lomefloxacin

7) usually not to be given to children <18

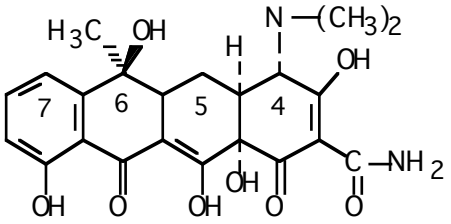
K. CHLORAMPHENICOL



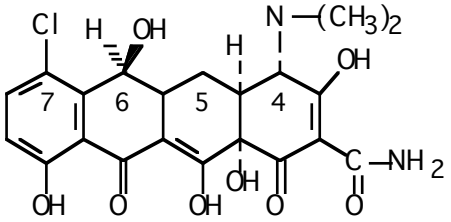
This potent broad spectrum antibiotic is reserved for use in serious infections where other less dangerous agents have not worked. It penetrates into the CNS well and can be used for meningitis.

The danger relates to the risk of serious and fatal blood dyscrasias (aplastic anemia, thrombocytopenia, granulocytopenia). It occurs in ~ 1:40,000 courses of treatment. The rare aplasic anemia which is irreversible is the most feared because close monitoring may not prevent. A reversible bone marrow suppression due to inhibition of bone marrow cell mitochondrial protein synthesis is more common. It is available and widely used OTC in some developing countries! Must monitor blood picture frequently during therapy. Infants don't form the glucuronide metabolite efficiently and may develop the "grey baby syndrome," probably due to inhibition of mitochondrial respiration.

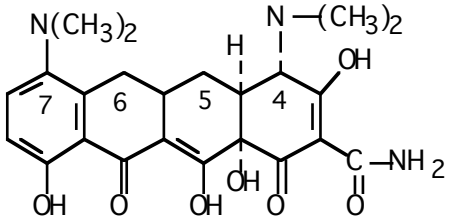
Bacteriostatic Inhibitors of Protein Symthesis
L. TETRACYCLINES



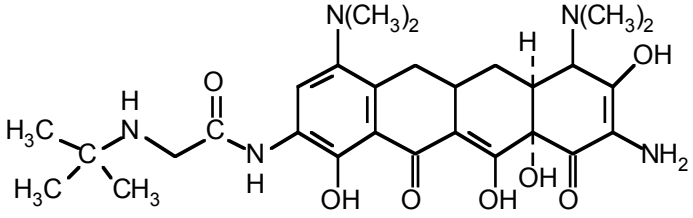
Tetracycline



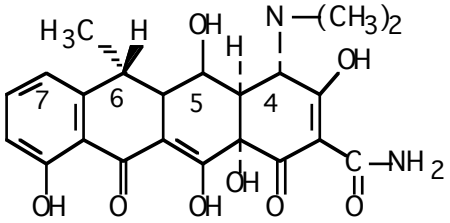
Demeclocycline



Minocycline



Tigecycline



Doxycycline

(All are on UW formulary.)

1. Chemistry - History

   Tetracyclines consist of 4 fused rings with substitutions on positions 5, 6, and 7. They have different pharmacokinetic properties but the same spectra. Tigecycline is new. It is less prone to pathogen resistance. They are sometimes grouped into short acting (tetracycline), intermediate acting (demeclocycline) and long acting (doxycycline, minocycline). The first, chlortetracycline, was isolated in 1949 from *Streptomyces aureus* found in soil. Doxycycline and Minocycline were introduced in the 1960's. Tigecycline was approved in 2005.

2. MOA

Tetracyclines are taken up by bacteria by an active process. They bind to the 30S ribosomal subunit and block binding of the aminoacyl-t-RNA to affect protein synthesis. These drugs are bacteriostatic.

3. Spectrum

   a) General comment: These are broad spectrum antibiotics with activity against Gram-positive and Gram-negative bacteria, against rickettsia, Mycoplasma, Chlamydia, and some amoeba but resistance is widespread thus limiting the usefulness of the tetracyclines. These drugs are still valuable for certain infections, however. Resistance has developed due to overuse (especially in

developing countries) and because of use in animal feeds. Resistance is usually due to efflux or 30S ribosomal modifications. Tetracycline resistance genes (Tet) are encoded on plasmids, transposons and integrons and are therefore mobile. The glycylcyclines are not subject to the activity of the present efflux pumps and bind tightly to the 30S ribosome, even if modified. Overuse of glycylcyclines will certainly result in resistance, however. The only commercially available glycylcycline is tigecycline. It is discussed in more detail in a separate monograph.

b) Gram-positive: If sensitive, Strep and Staph can be treated but resistance is common. Strep. pneumoniae may be sensitive to doxycycline. Community acquired MRSA may be sensitive also.

c) Gram-negative: Many are now resistant

d) Other unusual pathogens are sensitive. For example: Rickettsia (Rocky Mountain Spotted Fever, typhus), Chlamydia trachomatis, Mycoplasma species, Borellia burgdorferi (Lyme disease), Brucella, Francisella, Pasturella multocida, Treponema pallidum, and actinomyces.

4. Use

a) Doxycycline, 100 mg BID or tetracycline 500 mg QID x 7d for Chlamydia trachomatis urithritis, cervicitis, conjunctivitis, proctitis and lymphogranuloma venerium. This is the number 1 STD in the USA. Azithromycin is now preferred (stat dose). Neisseria gonorrhea resistance is too prevalent now in most parts of the country for effective use. Therefore the recommendation is to use Ceftriaxone 250 mg 1M stat or Vantin® po stat to cover the gonococcus.

b) Lyme disease - Borellia burgdorferi

c) Other miscellaneous pathogens: Brucella, Vibrio cholerae, Mycoplasma pneumoniae (walking pneumonia)

d) Acne: systemic and topical; lower doses work well with fewer adverse effects, e.g. 250 mg/d

e) Doxycycline 100 mg q d to prevent Traveller's diarrhea (but ciprofloxacin is better)

f) Malaria prophylaxis (short term) an approved indication for doxycycline is for malaria prophylaxis for trips < 4 mos.

g) Helicobacter pylori - with Metronidazole and bismuth

h) anthrax – *Bacillus anthracis* – doxy 100mg q 12h for 3 months if exposed

5. Disposition, Excretion, Absorption

a) Widely distributed including CSF (20-30% of plasma conc.)

b) Accumulates in growing bone and teeth. Excreted in breast milk

c) Excreted in bile, urine, and feces

d) Note: divalent cations (Mg, Ca, Al, Zn, Bi) will form a chelate which is poorly absorbed. Definite interaction. Avoid concurrent use with dairy products or antacids or iron products. (Doxycycline is okay with dairy products because it does not bind so well to calcium.)

e) avoid taking with meals but doxycycline is okay with meals.

6. Adverse Effects

a) Permanent discoloration of the teeth if used during dentation period in children. Not rec. for children under 8 or during pregnancy.

b) GI upset. Common.

c) Can cause hepatotoxicity and renal toxicity

d) Photosensitivity

e) Vertigo with minocycline

e) Don't use outdated products (↑ renal toxicity)

g) Irritating when given IM or IV and can cause gastric distress

h) Superinfection due to broad spectrum and impact on normal intestinal and vaginal flora. Candida overgrowth is common.

7. Products

a) Caps, tabs, suspension, and powder for inj. available; generic products avail.

b) There are some differences between the various tetracyclines. For example, minocycline has an indication for asymptomatic Neisseria meningitis carriers. Doxycycline has an indication for anthrax including inhalation anthrax. Minocycle has better Gram pos. activity and may be better for MRSA and PRSP.

8. Tigecycline Tygacil® (Wyeth)

a) is the first marketed glycylcycline

b) poor oral bioavailability so IV use only

c) is much less susceptible to efflux pump resistant mechanisms and 30S ribosomal modifications

d) is approved (for now) for only complicated skin and skin structure infections, e.g. MRSA and complicated intrabdominal infections e.g. Bacteriodes

e) the UW has it on the formulary in “restricted for treatment of multidrug resistant infections”

9. Patient counseling

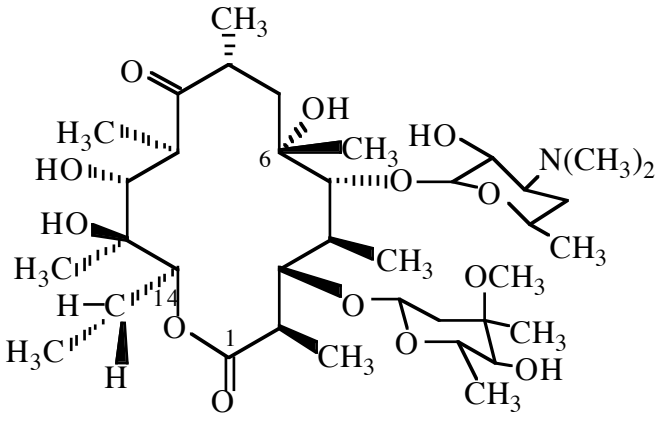
a) take on an empty stomach

b) avoid concurrent dairy, antacids, or iron; wait ~ 2h

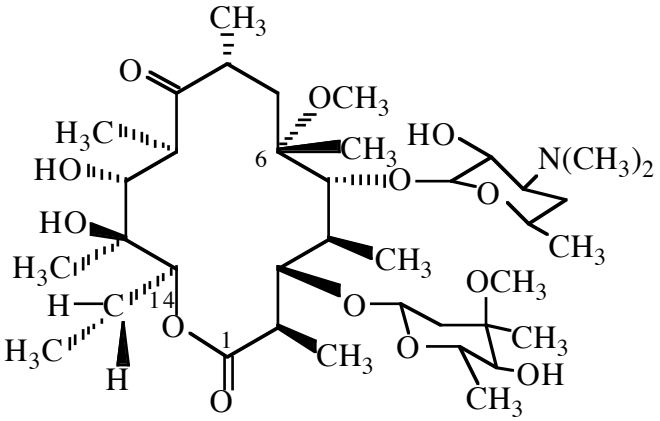
c) use sunscreen

d) discard any left

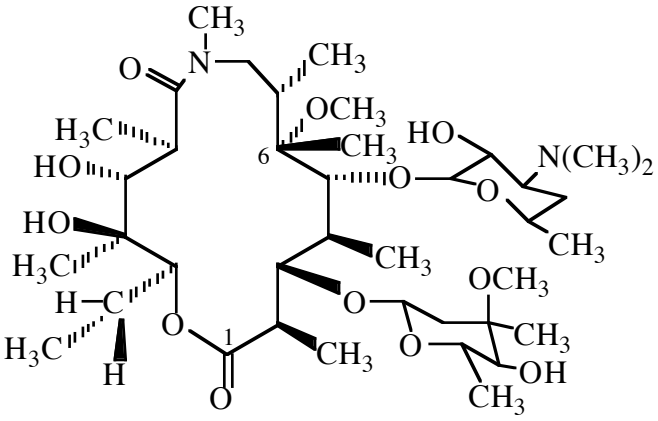
M. MACROLIDES



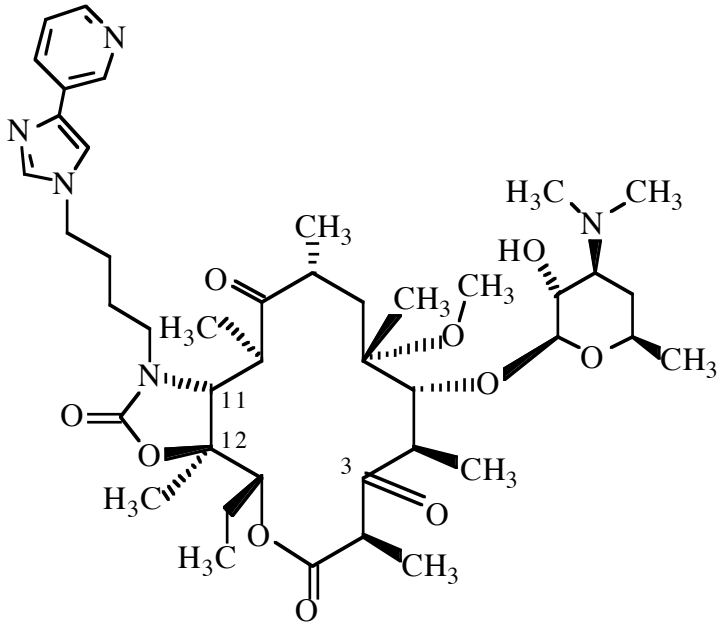
Erythromycin



Clarithromycin



Azithromycin



Telithromycin (Ketek ®)

1. History and Chemistry

The prototype drug is erythromycin which was isolated in 1952 from a Phillipine soil microbe, Streptomyces erythreus. All the macrolides have a large macrocytic lactone ring attached to 2 sugars. Clarithromycin is 6-methoxy erythromycin. Azithromycin has an extra nitrogen in the lactone ring to give a 15 membered ring.

2. MOA

Bind to the 50s ribosomal subunit to block transpeptidation/translocation reactions. Similar to chloramphenicol and clindamycin. Bacteriostatic but 'cidal in high doses.

3. Spectrum

These antibiotics are noted for excellent tissue penetration, especially azithromycin and clarithromycin.

Erythromycin: good activity against Gram-positive bacteria and Gram-negative cocci. Also Mycoplasma and Chlamydia. Clarithromycin is 2-4 times more potent than erythro. and includes some pathogens not hit by erythro. Azithromycin is somewhat less potent than erythro against staph and strep but has much better activity against many Gram-negative pathogens including H. influenzae. Clarithro and Azithro have some antianaerobe activity. Note: no useful activities for Enterobacteriaceae; in these bacteria the macrolides are weak bases and do not penetrate the outer cell membrane. Under alkaline pH conditions (uncharged) they do have some activity. Enterobacteriaceae also elaborate esterases which may hydrolyze macrolides.

4. Uses

a) Upper and lower respiratory infections due to Strep, Moraxella catarrhalis, H. influenzae. For the Moraxella and H. influ., Clarithro and Azithro will be more potent. Many Staph strains are resistant.

b) Mycoplasma pneumonia "walking pneumonia"

c) Legionaire's disease - Legionella sp.

d) Chlamydia pneumoniae, especially azithromycin

e) As alternative drug in penicillin allergic patient unable to take sulfas for infections due to Staph, Strep, H. influenzae but fluoroquinolones may take over some of this use. Erythro. is inexpensive.

f) otitis media - the combination of Erythro and sulfisoxazole (Pediazole ®) is popular. Azithromycin covers the common pathogens and is available as a suspension.

g) Helicobacter pylori

h) STD - Azithromycin. Approved as a 1 g stat dose for Chlamydia trachomatis cervicitis and urethritis. Compliance better than the 7d tetracycline protocol but cost may be a consideration. Give in combination with an antigonoccal drug (e.g. Ceftriaxone stat IM or cefixime stat po) because the infection may have both pathogens present. Azithromycin is not highly effective against N. gonorrhea.

i) Mycobacterium avium complex "MAC" - clarithromycin and azithromycin

5. Resistance

Alteration of a single 50S ribosomal protein by methylation (erm A, B, C genes) results in resistance to the macrolides and clindamycin. Decreased permeability also. Also cleavage of the lactone by esterases from some Enterobacteriaceae. Also efflux pump action. The erm is inducible.

6. Disposition, Metabolism, Excretion

a) Absorption -- erythromycin is unstable in stomach acid and the breakdown products are inactive. The bioavailability is about 25%. Ester derivatives or enteric coatings are used to protect the drug. Clarithro and Azithro are more stable (50% bioavail) and can be taken without regard to meals.

b) Distribution. The macrolides have excellent tissue penetration but do not cross the blood brain barrier into the CNS well. Azithromycin concentrates in cells with tissue:blood ratios of 10-100! Tissue T1/2 of 2-4d.

c) Metabolism. Erythromycin is demethylated by cytochrome P450 3A4 to inactive metabolites. It is a strong inhibitor of this enzyme as is telithromycin. Clarithro is a somewhat weaker 3A4 inhibitor and azithro inhibition is minimal. Erythromycin also weakly inhibits CYP1A2. Clarithro is metabolized to an active metabolite (14-OH).

d) Elimination. All are excreted in bile (found in feces) and urine. Erythromycin is extensively metabolized (N-demethylation). Azithro is slowly eliminated unmetabolized, clarithro is metabolized to a 14-hydroxy active metabolite.

e) Pharmacokinetic properties: the macrolides are characterized by good tissue penetration and intercellular levels. This is especially true for azithromycin. Azithro is excellent for intracellular infections like Chlamydia.

7. Drug Interactions

Erythromycin and telithromycin (and to a somewhat lesser extent clarithromycin) have the potential to inhibit the metabolism of any other drug taken concurrently that is metabolized by CYP3A4. A few documented interactions with erythro include cyclosporin (CYP3A4), carbamazepine (CYP3A4), and digoxin. Digoxin is a special case. It is pumped out of cells by "p-glycoprotein" which is inhibited by erythromycin. This is a drug interaction not mediated by P450. Deaths due to cardio-vascular toxicity have been reported with patients taking erythromycin and astemizole (Hismanal ®) or terfenadine (Seldane ®). These drugs are absolutely contraindicated with erythromycin. They have now been removed from the market in the USA. Clarithromycin is a weaker inhibitor but the potential still exists for significant drug interactions. Dirithromycin and azithromycin seems to not be a problem, but caution is advised. Erythro and clarithro also inhibit CYP1A2 and can inhibit the metabolism of theophylline.

8. Adverse Effects

a) Erythromycin is a very safe drug, however about 20% of patients discontinue because of annoying GI effects. Clarithro and Azithro are better tolerated.

b) Diarrhea and GI irritation. 13-32% with erythro, 3-5% with clarihro, 3% with azithro. It has been shown that erythromycin results in high amplitude contractions from stomach to intestine are similar to that observed with motilin, a GI polypeptide hormone. It is a motilin agonist. Erythro has actually been successfully used in cases of GI atrophy!

c) Hepatotoxicity. There have been deaths due to liver failure with telithromycin. FDA now requires label warnings. Elevated liver transaminases (1-2% with azithro). Erythro has been associated with rare cholestatic hepatitis, usually with the estolate salt in adults. This is reversible.

d) PMC - the usual risk

e) Pregnancy. Clarithromycin and dirithromycin have been associated with adverse effects on pregnancy in animals. Do not use in pregnancy unless

there are no other reasonable options. Use caution with azithromycin and erythromycin in pregnancy.

f) Breastfeeding. Erythromycin is okay, for the others there is no information.

g) myasthenia gravis. Fatal respirator failure seen in some patients taking telithromycin. This is a "boxed warning" now with telithromycin.

9. Products (*indicates UW formulary drug)

a) *Erythromycin base. 250 mg, 333 mg, 500 mg tabs or caps. (also as enteric coated tabs or delayed release capsules). The usual dose is 250 mg QID x 7-10d.

b) Erythromycin estolate - tabs, caps, suspension; use for pediatric patients only (why use this form as it can be hepatotoxic!).

c) Erythromycin stearate - tabs

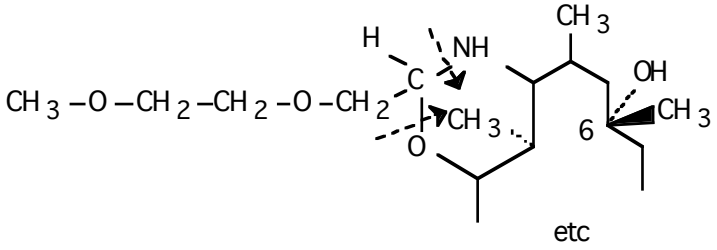
d) *Erythromycin ethylsuccinate - tabs, caps, powder, granules

e) *Erythromycin lactobionate - powder for injection.

f) *Clarithromycin - Biaxin ® (Abbott) 250 mg and 500 mg film coated tabs. Usual dose is 1 BID x 7d. Metallic taste is bad. Oral suspension available; $70/20 tables (250 mg). Biaxin XR 500 mg is now available It is now available generically.

g) *Azithromycin - Zithromax ® (Pfizer) 250 mg tablets. Usual dose is 2 on day 1, then 1 qd x 4. Suspension for oral use is available as is a 1g single dose packet. Zithromax is a top selling antibiotic. It is now available generically.

h) Dirithromycin Dynabac ® (Muro)



- this is a prodrug that is hydrolyzed upon absorption to erythromycylamine
- eliminated in bile and feces unchanged
- indications:
  - acute exacerbations of chronic bronchitis: H. flu, M. cat. or S. pneumoniae
  - secondary infections of acute bronchitis: M. cat. or S. pneumoniae
  - community acquired pneumonia: Legionella, Mycoplasma pneumoniae, S. pneumoniae
  - pharyngitis, tonsillitis: S. pyogenes
  - skin: S. aureus (not MRS) and S. pyogenes
- take with food
- available as enteric coated 250 mg tablets. Take one qd x 7 - 10d.
- worth the extra cost?? (cost ~ $60/14 tablets)

i) Telithromycin Ketek ® Aventis approved April 2004

- long T1/2 (~9h)
- 1 daily dose for 5 or 7 d
- binds to 2 sites on the 50S ribosomal subunit and does not induce erm
- PRSP is mutated at one site so that drug can still work
- indications – like azithro except PRSP is included. Not MRSA or erythromycin resistant Strep. pyogenes
- indications: bronchitis, sinusitis, CAP
- adverse: vision, prolonged QT interval, muscle weakness, hepatitis, exacerbation of myasthenia gravis
- interactions: is CYP 3A4 inhibitor
- pregnancy: class 3; not recommended
- pediatrics: not enough data; not recommended
- place in therapy?

10. Approved indications for formulary macrolides

a) Erythromycin
- URI - mild to moderate
- LRI - mild to moderate
- Respiratory tract - Mycoplasma pneumoniae
- skin - mild to moderate due to Strep pyogenes and Staph
- diphtheria
- amebiasis
- PID - N. gonorrheae in penicillin allergic
- Legionnaire's disease - Legionella pneumophilia

b) Clarithromycin
- pharyngitis/tonsilitis
- acute maxillary sinusitis
- acute exacerbation of chronic bronchitis
- CAP
- skin
- MAC
- H. pylori
- otitis media

note: pregnancy category C and safety in kids < 6 months not established
note: clarithromycin is more potent than erythromycin

c) Azithromycin
- COPD
- CAP
- STD for chlamydia
- pharyngitis/tonsilitis
- skin
- MAC
- otitis media

note: azithromycin has less Gram(+) and more Gram(–) activity than clarithromycin

11. Patient counseling

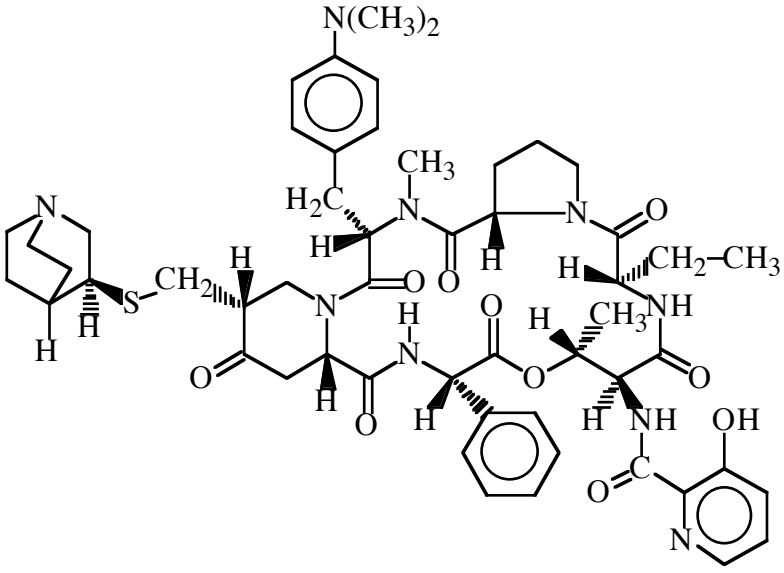
a) erythro – do not take with food

b) azithro – avoid concurrent use of antacids (small decrease in Cmax)

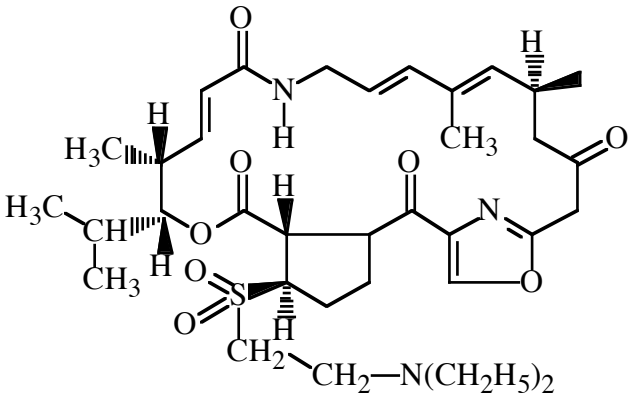
N. SYNERCID® Aventis

1. Streptogramins – synergistic mixture of the cyclic peptides quinupristin (group B Streptogramin) and dalfoprisitin (group A Streptogramin) (30:70)

quinupristin



dalfopristin



2. Approved 1999 on a "fast track"

3. Uses
   a) Vancomycin resistant E. faecium infections
   b) Complicated skin and skin structure infections including MRSA
   c) Note: not active against E. faecalis

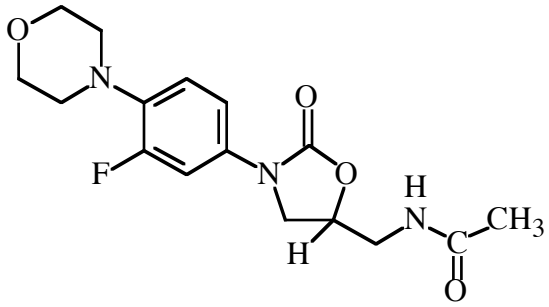
4. MOA
   a) bind to separate site 23S on 50S ribosomal subunit to block initiation
   b) dalfopristin – peptidyl transferase similar to erythromycin
   c) quinupristin – addition of t-RNA-aa to peptide
   d) 'cidal for Strep
   e) 'static for Enterococcus and Staph

5. Adverse effects: arthralgias, venous irritation

6. Drug interactions: is a P450 3A4 inhibitor

7. UW formulary restricts use to prior approval by ID service

O. OXAZOLIDINONES



1. Linezolid Zyvox® Pharmacia (now Pfizer)
   approved in April 2000
   a) ~100% bioavail.; available PO & IV
   b) activity against Gram (+) aerobes including resistant Staph, Strep, and Enterococci
   c) inhibits initiation of protein synthesis
   d) no cross resistance
   e) synthetic
   f) gram (+) not gram (-)
   g) 'cidal but 'static for Enterococcus
   h) indications
      1) vanco res. Enterococcus faecium
      2) nosocomial pneumonia with Staph or Strep including MRSA
      3) skin infections with Staph or Strep
      4) community acquired pneumonia – Gm+ MRSA
   i) interactions: no P450 effects but is a MAO inhibitor therefore avoid foods with high tyramine content, e.g. cheese, fermented foods, beer and wine. Also avoid adrenergic drugs and serotonergic drugs (SSRI)
   j) metabolism: metabolized to two inactive metabolites; no dose adjustment needed in renal failure
   k) adverse: some cases of thrombocytopenia have been noted
   l) UW formulary restricts use to vancomycin resistant enterococcal infections when ampicillin is unlikely to be effective

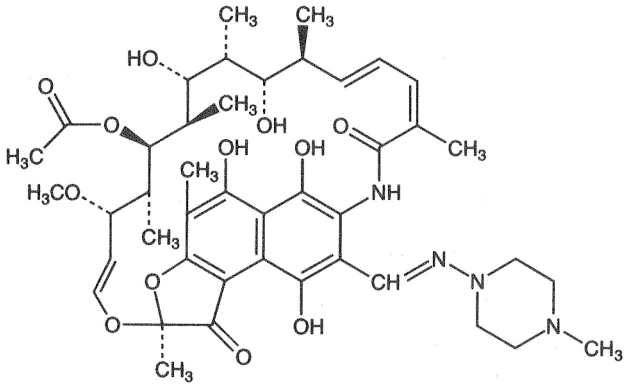
MEMBRANE POISON

P. Daptomycin Cubicin ® (Cubist)

a) cyclic lipopeptide from Streptomyces roseosporus
b) binds to Gm+ cytoplasmic membrane to affect lethal depolarization
c) spectrum: MRSA, Streptococcal infections including PRSP, Enterococcus faecalis and faecium
d) indications: complicated skin and skin structure due to Staph (including MRSA), Strep and Enterococci
e) adverse: myopathy is possible
f) UW restricted to ID service approved
g) IV drug

DNA Dependent RNA Polymerase Inhibitors- rifamycin derivatives

Q. Rifampin



a) semisynthetic derivative of rifamycin B produced by Streptomyces mediterranei. It is a large nonpolar molecule.
b) inhibits DNA dependent RNA synthesis
c) bacteriocidal against Gram positive cocci and Mycobacterium tuberculosis. It is too big and nonpolar to get in to Gram neg.
d) resistance develops fast due to point mutations on target enzyme. Rarely used alone.
e) used as part of a drug regimen for TB, resistant Staph (MRSA) and Strep. Used alone in the prophylaxis against Neiserria meningitidis.
f) drug interactions are huge as the drug is a strong CYP3A4 inducer
g) well tolerated drug. It does color urine and tears orange.

R. Rifabutin

a) structurally similar to rifampin
b) prophylaxix of MAC

S. Rifaximin Xifaxan® (Salix)

a) structurally similar to rifampin but not orally absorbed
b) used for travelor's diarrhea due to noninvasive E. coli.
c) off label use for C. difficile.