

## ANTIBIOTIC REVIEW

### ISSUES IN CHOOSING ANTIBIOTICS

**Clinical considerations:** Site of infection; epidemiology; prior antibiotic therapy; clinical status; immune status.

**Antimicrobial factors:** Efficacy (in vitro and in vivo); pharmacology; potential synergy or antagonism; toxicity and drug interactions; specificity; cost (\$); secondary resistance; ease of administration.

### PENICILLINS

**Mechanism of Action:** Decreased bacterial cell wall synthesis by inhibition of terminal cross-linking reaction and probably also other steps. > 7  $\beta$ -lactam binding proteins have been described.

**Mechanisms of Resistance:** Production of  $\beta$ -lactamases (*S. aureus*). Decreased permeability of outer cell membrane to the antibiotic (*P. aeruginosa*). Modification of bacterial penicillin binding proteins (*S. pneumoniae*).

**Pharmacology:** Short serum half lives (30 - 60 minutes). Primarily renal excretion except for nafcillin (biliary).

**Penicillin G:** Active against *Streptococci*, non- $\beta$ -lactamase producing *Staphylococci*, *Haemophilus*, *Spirochetes*, *Pasturella multocida*, *Listeria*, *Neisseria*, and most anaerobes other than *Bacteroides fragilis*. Scant activity against *Enterococci* except in combination with gentamicin. Rare *S. pneumoniae*, *N. gonorrhoeae* and *H. influenzae* express non- $\beta$ -lactamase mediated resistance.

**Penicillin V:** Equal to Pen G except for less activity against *Hemophilus* and *Neisseria*.

**Ampicillin/Amoxicillin:** Spectrum includes that of Pen G plus *E. coli* and *P. mirabilis*.

**Nafcillin, Methicillin, Oxacillin, Dicloxacillin:** Active only against *S. aureus* and *Streptococci* (not *Enterococci*).

**Anti-pseudomonal agents:** Spectrum of activity generally equivalent to ampicillin with the addition of *P. aeruginosa*, *Enterobacter*, indole-positive *Proteus*, *Serratia* species, and other organisms as noted. Penicillin is more active than these agents against  $\beta$ -lactamase (-) gram-positive cocci.

**Carbenicillin** (IV form no longer available in USA): Oral prep. is useful only for Rx of UTI. No activity versus *Enterococci*.

**Ticarcillin:** 5.2 meq sodium per gram. Poor activity versus *Enterococci*.

**Mezlocillin, piperacillin:** Have half as much sodium per gram as ticarcillin and increased activity against *K. pneumoniae* and *Enterobacter*. Adequate activity against *Enterococcus faecalis*.

### Toxicity

**CNS:** seen with massive doses of PCN G, ampicillin and methicillin, especially with renal insufficiency.

**Hemolytic anemia:** positive Coombs test is not uncommon, hemolysis is rare in absence of long-term high dosage.

**Interstitial nephritis:** Uncommon except with prolonged high doses, most frequently seen with PCN G, ampicillin, and methicillin.

**Myelosuppression:** Uncommon except with prolonged high doses, Nafcillin is usual culprit.

**Hepatitis:** Uncommon except with prolonged high doses, oxacillin is usual culprit.

**Platelet dysfunction:** Common with expanded spectrum penicillins.

**Hypokalemia:** secondary to nonresorbable anions of ticarcillin and carbenicillin in distal tubules.

**$\beta$ -LACTAMASE INHIBITORS:** clavulanic acid and sulbactam

**Mechanism of action:** inhibit  $\beta$ -lactamases in *S. aureus*, *Hemophilus*, *Bacteroides* and many *Enterobacteriaceae*. In vitro activity against anaerobes is equivalent to that of metronidazole. No activity against Richmond and Sykes Type I or IV chromosomal  $\beta$ -lactamases in *Enterobacter*, *Serratia*, *Citrobacter*, *Klebsiella* and *Pseudomonas* species. Active against many, but not all, ESBL-containing *E. coli* and *K. pneumoniae*.

**Amoxicillin with clavulanic acid:** Oral combination. Formulated as 250/500 mg amoxicillin + 125 mg clavulanic acid.; dose 1 tab q 8°. Sulbactam is active vs. many *A. baumannii* isolates.

**Ticarcillin with clavulanic acid:** Parenteral combination. 3 grams ticarcillin + 1-200 mg clavulanic acid/dose. (3.1 q 4°-6° for systemic infection. 3.2 q 8° for UTI). Activity against *Enterobacteriaceae* and anaerobes is superior to cefoxitin. Active vs. many *S. maltophilia* isolates.

**Ampicillin with sulbactam:** Parenteral combination. Two to one ratio of ampicillin:sulbactam. Activity against anaerobes is superior and activity against Enterobacteriaceae is similar to that of cefoxitin. Maximum dose is 3 g q 6°.

**Piperacillin with tazobactam:** 8:1 ratio of piperacillin to tazobactam. No advantages for treatment of *P. aeruginosa* infections.

## **CEPHALOSPORINS**

**Mechanism of Action:** Similar to that of the penicillins.

**Mechanisms of Resistance:** Same as for penicillin.

**Toxicity:** similar to that of the penicillins, except for that mediated by methylthiotetrazole side chain. This group is present in cefoperazone, cefamandole, cefotetan, cefmenoxime, and cefmetazole and is responsible for disulfiram reactions and inhibition of vitamin K metabolism.

**First generation:** Cephalothin, Cefazolin, Cephapirin, Cefadroxil, Cephalexin, Cephadrine.

**Activity:** All these agents have good activity against Nafcillin-susceptible gram-positive cocci, and many community-acquired infections due to *E. coli*, *P. mirabilis*, and *K. pneumoniae*. Not active within the CSF.

**Uses:** Patients with delayed penicillin hypersensitivity reaction. Pathogen resistant to less toxic or expensive antibiotics. Surgical prophylaxis.

### **Second Generation**

#### **Active against *H. influenzae***

**Cefuroxime:** Equal to first generation cephalosporins with added activity against  $\beta$ -lactamase (+) *H. influenzae* and *Neisseria* species. Fair activity in CSF.  $t_{1/2} = 1.5^\circ$ .

**Cefuroxime axetil (oral):** Absorption increased with food; crushed tablets are bitter and poorly tolerated by children. Dose 250 - 500 mg bid.

**Cefonocid:**  $t_{1/2} = 4.5^\circ$ . Poor activity versus *Streptococcus viridans* and *S. pneumoniae*.

**Cefamandole:** marginally increased activity against *Haemophilus* and *Enterobacter* species. Has methylthiotetrazole side chain. No longer available in the United States (7-04).

**Cefaclor (oral):** modest improvement in activity against *H. influenzae* including  $\beta$ -lactamase producing strains.

**Cefprozil (oral):** 95% absorption without food effect. Pediatric oral suspension available. Activity against *M. catarrhalis* equals that of cephalexin; slight improvement versus *H. influenzae*.

**Loracarbef (oral):** structurally a carbacephem. Spectrum of activity similar to cefuroxime. 90% absorption.  $t_{1/2} 1^\circ$ . Urinary excretion. Pediatric formulation available. Adult dose 200 - 400 q 12°. Pediatric dose 7.5 - 15 mg/kg q 12°.

#### **Active against anaerobes**

**Cefoxitin:** Less active against gram-positive organisms, slightly better against gram-negative organisms, and much better against anaerobes, especially *B. fragilis*.

**Cefotetan:** Similar to cefoxitin but with longer serum half-life and somewhat less anti-anaerobic activity. Has methylthiotetrazole side chain.

**Cefmetazole:** Similar to cefoxitin but with slightly less anti-anaerobic activity. Has methylthiotetrazole side chain. No longer available in the United States (7-04).

### **Indications**

**Cefuroxime/cefprozil/cefamandole:** option for empiric therapy of community-acquired pneumonia in populations where  $\beta$ -lactamase *H. influenzae* or *M. catarrhalis* are of great concern. Cefamandole is least cost effective.

**Cefoxitin/cefotetan/cefmetazole:** Appropriate for uncomplicated serious mixed aerobic/anaerobic infections, especially in penicillin-allergic patients. Modest utility for surgical prophylaxis of colorectal resections. Cefotetan and cefmetazole have somewhat less anti-anaerobic activity than cefoxitin.

### **Third generation**

**Spectrum of activity:** Excellent against Enterobacteriaceae, (e.g. *E. coli*, *Klebsiella*, *Proteus*, *Serratia*, *Morganella*, *Enterobacter*, *Citrobacter*, and *Provident*), *Haemophilus*, and *Neisseria* species. Modest activity against gram-positive cocci. Variable activity against anaerobes, and *P. aeruginosa*. Good CSF penetration. NOT ACTIVE AGAINST *Enterococci*.

**Cefotaxime/Ceftizoxime/Ceftriaxone:** Adequate activity against *Streptococci*, modest activity against methicillin-susceptible *Staphylococci*, very little activity against *P. aeruginosa*, and slight activity against *B. fragilis*. Cefotaxime and ceftriaxone are best validated third generation cephalosporins for

treatment of meningitis. Ceftriaxone has a very prolonged serum half life and is uniquely associated with biliary pseudolithiasis.

**Ceftazidime/cefoperazone:** active against *P. aeruginosa*. Decreased activity against gram positives and poor activity against anaerobes. Cefoperazone has excellent biliary penetration and methylthiotetrazole side chain. Ceftazidime has better activity against *P. aeruginosa* and some activity vs. *S. maltophilia*.

**Cefepime:** combines aerobic activity of ceftazidime and cefotaxime; poor anaerobic activity. Dose 1 - 2 gm q 12° (0.5 gm w/UTI); q 8° for monoRx for febrile neutropenia ; q 12-24° dosing with CrCl < 60. ↑ activity vs. *Enterobacter* and ± ↑ vs. ESBL isolates. Active vs. PCN-resistant *S. pneumoniae*

**Cefixime (oral):** No activity vs. *S. aureus*, anaerobes, *Pseudomonas*, many *Enterobacter* and *Acinetobacter*. Equals 1<sup>st</sup> gen. cephalosporin against Group A Strep. and *S. pneumoniae* and has good activity versus *Neisseria*, *Hemophilus*, and *Moraxella* (including β-lactamase producing strains) as well as *E. coli*, *Klebsiella*, *Proteus* and *Serratia*. Suspension better absorbed than tablets; latter not recommended for otitis media. Adult dose 400 mg qd, children 200 mg bid.

**Ceftibuten (oral):** similar to cefixime. No activity vs. *S. aureus* and poor to modest activity vs. *S. pneumoniae* (not PRSP). Less effective than other agents vs. *Moraxella*. Dose 400 mg qd (adults).

**Cefpodoxime proxetil (oral):** Similar to cefixime except for presence of some activity vs. *S. aureus* and less activity versus *Serratia*, and many *Enterobacter*. Adult dose 400 mg BID (soft tissue), 200 mg BID (LTRI) or 100 mg BID (UTI).

**Moxalactam** (no longer available in USA): NO activity against gram-positives, high rate of coagulation and platelet abnormalities. Has methylthiotetrazole side chain.

#### Indications:

Gram-negative meningitis due to a susceptible organism. Cefotaxime, Ceftriaxone, Ceftizoxime, Ceftazidime.

Neutropenic host: (ceftazidime + amikacin).

Renal insufficiency: Infection likely to be due to highly-resistant *Enterobacteriaceae* in patient with compromised renal function. Monotherapy with a β-lactam is not likely to be adequate for life-threatening infections due to *Enterobacter* or *Pseudomonas spp.*

Surgical prophylaxis: No data support the use of 3rd gen. cephalosporin for surgical prophylaxis.

**MONOBACTAMS:** Aztreonam is only agent. Aztreonam structure is similar to ceftazidime.

**Mechanism of action:** Binds to PBP3. Very resistant to cleavage by β-lactamases.

**Activity:** Good vs. *Enterobacteriaceae*, *Pseudomonas*, *Acinetobacter*, *Haemophilus*, *Neisseria*, *Aeromonas*. NULL against anaerobes or Gram-positives.

**Pharmacology:** T 1/2 = 1 - 2°. ~ 9:1 renal : biliary excretion.

## CARBAPENEMS

### Resistance:

- In vitro, doripenem selects less frequently for resistant mutations than meropenem and imipenem.
- Loss of carbapenem-specific OprD (that causes reduced permeability) impacts imipenem resistance to *P. aeruginosa* greater than doripenem and meropenem.
  - High-level resistance imipenem usually requires OprD mutation and AmpC β-lactamases.
  - High-level resistance to doripenem and meropenem usually requires the combination of efflux pumps (i.e., MexAB-OprM) and OprD mutation in *P. aeruginosa*; this occurs less frequently than the combination of OprD mutation and AmpC β-lactamases).
- Organisms harboring carbapenemases will result in cross-resistance to all carbapenems.
  - Emergence of carbapenemase-resistant *Enterobacteriaceae* is of increasing concern.
  - Presence of this mechanism of resistance should be suspected whenever ertapenem-resistant *Enterobacteriaceae* are detected. Regardless of whether susceptibility to other β-lactams is reported, these isolates are clinically resistant to all β-lactams including the carbapenems.

### Imipenem (Thienamycin)

**Mechanism of action:** Structurally a carbapenem. Binding to PBP 2 results in rapid bacterial lysis. Induces β-lactamase production, may therefore antagonize β-lactam combinations.

**Pharmacology:** t 1/2 = 1°. Good CSF penetration. Administered with cilastin (an agent which inhibits dihydropeptidases in the renal tubule brush border) in order to increase urine levels and decrease nephrotoxicity. 50% renal excretion; removed by hemodialysis.

**Toxicity:** may lower seizure threshold

## Activity

GPC: Strep, Staph, some Enterococci (static), Listeria (static)

Enterobacteriaceae: Similar to 3rd gen. cephalosporins.

Haemophilus, Neisseria: good, but < 3rd gen. ceph.

P. aeruginosa: good but resistance develops with monotherapy; marginal vs. *P. cepacia*, poor vs.

*Stenotrophomonas maltophilia*.

Anaerobes: including *B. fragilis* but not *C. difficile*

Acinetobacter: good

Synergy: with aminoglycosides against *S. faecalis*, *S. aureus*; but less so against *P. aeruginosa*.

**Meropenem**: unlike imipenem not cleaved by renal dihydropeptidases. Does not require cilastin.

**Activity**: like imipenem but has slightly increased activity vs. GNR and decreased activity vs. GPC.

Targets PBP 2,3. Poor inducer of type 1  $\beta$ lactamases.

**Indications**: Therapeutically equivalent to imipenem; used successfully to treat pneumonia, meningitis, intra-abdominal infections, bacteremia, urinary tract infections, and febrile episodes in neutropenic patients.

**Pharmacology**:  $t_{1/2}$  1°; 70% urine excretion. Good CSF penetration (has meningitis indication). Dose 0.5 - 1.0 gram q 6-8°; decreased for CrCl < 50. Little protein binding.

**Toxicity**: apparently less neurotoxicity than with imipenem.

**Doripenem**: not cleaved by renal dihydropeptidases. Does not require cilastin.

**Activity**: like imipenem but has slightly increased activity vs. GNR and decreased activity vs. GPC.

Targets PBP 2,3. Poor inducer of type 1  $\beta$ lactamases.

**Indications**: FDA-approved for complicated intra-abdominal infections and complicated urinary tract infections

**Pharmacology**:  $t_{1/2}$  1°; 70% urine excretion. Dose 500 mg IV q 8°; decreased for CrCl < 50, no dosing recommendations for severe renal dysfunction (CrCl < 50) including hemodialysis.

**Toxicity**: apparently less neurotoxicity than with imipenem. Most common adverse reactions occurring in  $\geq 5\%$  of patients include headache, phlebitis, nausea, diarrhea, and rash. Drug-drug interactions with valproic acid.

## Ertapenem:

**Activity**: similar to imipenem but lacks activity against *P. aeruginosa* or *Acinetobacter spp.*

**Pharmacology**: Standard dose = 1 gram qd IV  $\Rightarrow$  1  $\mu$ g/mL at 24 hours; 4 hours  $t_{1/2}$ . 80% renal elimination.  $\downarrow$  dose to 0.5 g/d with CrCl < 30

**Toxicity**: similar to meropenem.

## QUINOLONES

**Mechanism of Action**: Inhibits DNA gyrase activity and thereby blocks DNA replication and transcription. This results in rapid bactericidal activity due to inhibition of protein synthesis.

**Mechanisms of Resistance**: Mutation. Change in bacterial permeability. No plasmid mediated resistance known.

**Pharmacology**: Substantial renal clearance. Good penetration of prostate. Absorption impaired by magnesium-, calcium- and aluminum-containing antacids, ferrous sulfate, zinc containing vitamins, sucralfate, and dairy products. 14-30% serum-protein binding.

**Spectrum of Activity**: *S. aureus*, *Enterobacteriaceae*, *Neisseria*, *Moraxella*, *H. influenzae*, *Aeromonas*, *Campylobacter*, and *Vibrios*. Variable activity versus *P. aeruginosa*, *S. pneumoniae*, anaerobes, *Legionella*, *Mycobacteria*, and *Chlamydia*.

MIC <sub>90</sub>	Ciprofloxacin	Levofloxacin	Moxifloxacin	Gatifloxacin
<i>S. aureus</i> (MSSA)	1.0	0.25	0.06	0.12
MRSA	> 2	16	4	> 4
<i>S. pneumoniae</i>	2.0	1.0	0.25	1.0
GAS	0.5	2.0	0.25	0.5
<i>P. aeruginosa</i>	0.5 – 2.0	32	32	32
<i>K. pneumoniae</i>	0.015	0.12	0.12	0.5
Protein binding (%)	20-40	30	45	20
Oral dose	500-750 bid	500 qd	500 qd	500 qd
Peak []	2.4-4.3	6.5	5.5	4.2
$t_{1/2}$	4°	6°	12°	7°

**Resistance:** cross-resistance occurs between all quinolones; they all act against the same enzyme.

**Toxicity**

**Drug interactions:** Enoxacin (most potent), ciprofloxacin, inhibit CYP1A2 => ↑ theophylline levels. (and caffeine) excretion and displace warfarin from albumin. Theophylline excretion is not affected by norfloxacin, (lev)ofloxacin, lomefloxacin.

**CNS:** Enoxacin, norfloxacin, and ciprofloxacin lower seizure threshold; may be additive with theophylline and NSAID.

**Cartilage toxicity:** demonstrated in some animals, thus the drugs are not recommended in patients with incomplete skeletal development.

**Other:** anaphylactoid reactions, photosensitivity (sparfloxacin), hepatotoxicity (trovafloxacin), torsades de pointes/↑QTc (grepafloxacin ~ sparfloxacin > moxifloxacin > gatifloxacin ~ levofloxacin/ofloxacin, ciprofloxacin, clarithromycin), serum sickness (temafloxacin– removed from market), interstitial nephritis reported with cipro.

**Ciprofloxacin**

**Pharmacology:**  $t_{1/2}$  = 3-4°.  $C_{max}$  4 µg/ml. Cleared by filtration and renal tubular secretion. Adequate serum levels with 750 mg po. IV dose 200-400 q 12°.

**Indications:** Similar to norfloxacin plus role in chronic therapy of highly resistant infections such as gram-negative osteomyelitis and invasive otitis externa.

**Levofloxacin:** active racemic isomer of ofloxacin.

**Pharmacology:** 95% orally bioavailable.  $t_{1/2}$  5°. Dosage 500 mg PO/IV qd. Peak after 500 mg dose =  $C_{max}$  6.5 µg/ml. 90% CSF penetration. 70% renal excretion. Does not affect theophylline excretion.

**Moxifloxacin:** 8-methoxy-fluoroquinolone. 400 mg QD oral or IV dosing. Active vs. *S. pneumoniae*, *S. aureus*, *H. influenzae*, *M. catarrhalis*, *Neisseria*, *C. pneumoniae*, *M. pneumoniae*, and *L. pneumophila*. Activity vs. enteric GNR is similar to levofloxacin, but lack activity vs. *P. aeruginosa*. Modest anaerobic activity.

**Pharmacology:**  $t_{1/2}$  12°.  $C_{max}$  5.5 µg/ml, 45% protein-bound. No metabolism by or interference with cytochrome P450 system. No dose adjustment with renal failure. Avoid with moderate-severe hepatic failure.

**Toxicity:** QT prolongation. **Contra-indicated** in setting of hypokalemia or use of Class IA (e.g. quinidine, procaineamide), or Class III (e.g., amiodarone, sotalol) anti-arrhythmics). Caution with use of cisapride, erythromycin, anti-psychotics, tricyclic anti-depressants. No photosensitivity reactions.

**Indications:** Acute exacerbations of chronic bronchitis, community-acquired pneumonia, acute sinusitis.

**Gemifloxacin.** Active vs. *S. pneumoniae*, *S. aureus*, *H. influenzae*, *M. catarrhalis*, *Neisseria*, *C. pneumoniae*, *M. pneumoniae*, *L. pneumophila*, and some strains of *K. pneumoniae*. Favorable AUC/MIC ratio for *S. pneumoniae*.

**Pharmacology:** 320 mg QD oral dosing; 70% oral bioavailability. No effect of food. 36% urinary excretion. Not affected by and does not affect cytochrome P450 system. Dose adjustment with CrCl <40 to 160 mg qd (same dose in dialysis patients). No dose adjustment with hepatic impairment.

**Toxicity:** Rash about 3% overall. Usually occurs between day 8 and 10 of Rx. Up to 30% in women <40 who received 10 days of Rx. Low rate of sensitization to other fluoroquinolones (~15%). No reports of Stevens-Johnson Syndrome; rare photosensitivity. No reports of dysglycemia. Less QTc prolongation than with levofloxacin.

**Other quinolones**

**Removed from market**

*Sparfloxacin:* QD oral dosing. Active vs. *S. pneumoniae*. Taken off market in US due to photosensitivity reactions and prolongation of QT interval.

*Grepafloxacin:* oral dosing. Active vs. *S. pneumoniae*. Taken off market in US due to prolongation of QT interval.

*Gatifloxacin:* oral dosing. Active vs. *S. pneumoniae*. Taken off market in US due to frequent hypoglycemic and hyperglycemic episodes.

**Norfloxacin:** Dosage: Normal GFR: 400 mg po q 12°. GFR < 30: 400 mg po q 24°. Active only in GI and GU tract. Activity largely limited to GNR

**Ofloxacin:** 95% orally bioavailable.  $t_{1/2}$  5°. Peak after 400 mg dose = 4.0 µg/ml. 90% CSF penetration. 70% renal excretion. Does not affect theophylline excretion. Dosage: 200 - 400 mg po q 12°; 400 mg x 1 dose for GC. Adjust for creatinine clearance < 50. Has indication for *C. trachomatis*

**Enoxacin:** Primary renal excretion. Absorption decreased by food and by lowered gastric acidity.  
Indications: UTI, gonorrhea. Dosage: 400 qd: uncomplicated cystitis. Activity largely limited to GNR;  $\pm$  vs. *S. aureus*.

**Lomefloxacin:**  $t_{1/2}$  7°-8°. 400 mg yields peak of 3.4  $\mu\text{g/ml}$ . 68% urine excretion. Adjust for CrCl < 30.  
Does not affect theophylline pharmacokinetics. Activity largely limited to GNR;  $\pm$  vs. *S. aureus*.  
Indications: UTI. Dosage: 400 mg qd.

## AMINOGLYCOSIDES

**Mechanism of action:** Binding to ribosomes yields misreading of mRNA codons. Uptake is dependent on oxygen, therefore no activity against anaerobes and poor activity within abscesses. Low pH also decreases activity.

**Mechanisms of resistance:** Plasmid mediated modifying enzymes. Decreased cellular permeability. Chromosomal mutants with altered ribosomal binding site.

### Spectrum of activity

#### *Enterobacteriaceae*

#### *Pseudomonas aeruginosa*

#### *Aeromonas, Vibrios, Campylobacter*

**Synergy:** with penicillin/ampicillin against *Streptococci* (including *Enterococci*), and with nafcillin/methicillin against *S. aureus*. No activity when used alone against these bacteria.

**Dosing:** Once daily dosing wherein the full daily dose is given as a single infusion has been shown to be equally effective and no more toxic in most patients who require aminoglycoside therapy. Once daily dosing is not, however, recommended during pregnancy or infancy, or in patients with renal failure requiring dialysis, anasarca, *Enterococcal* endocarditis, cystic fibrosis, mycobacterial infections, or burns involving  $\geq 20\%$  of body surface area.

### Individual agents

**Streptomycin:** tuberculocidal.

**Kanamycin:** rarely used, tuberculocidal.

**Gentamicin:** best for synergy against gram-positives.

**Tobramycin:** excellent against *P. aeruginosa*.

**Netilmicin:** decreased ototoxicity (?).

**Amikacin:** broadest activity against *Enterobacteriaceae*; tuberculocidal.

### Toxicity

**Ototoxicity:** Irreversible.

**Cochlear damage:** Initial symptom is usually tinnitus.

**Vestibular damage:** Initial symptoms are dizziness, vertigo with movement, and nystagmus.

**Nephrotoxicity:** Generally reversible. The nephrotoxicity of all of the aminoglycosides is clinically equivalent (~2 - 10%). Tubular dysfunction may result in electrolyte abnormalities (decreases in serum potassium, magnesium, calcium, and pH) and/or decreased glomerular filtration rate.

**Risk factors for ototoxicity and nephrotoxicity:** High peak serum levels, high fevers, bacteremia, dehydration, shock, old age, renal or hepatic dysfunction, and long duration of therapy.

**Aminoglycoside levels:** Peak levels for systemic or deep tissue infections should be 5 - 10  $\mu\text{g/ml}$  for gentamicin, netilmicin, or tobramycin, and 20 - 30  $\mu\text{g/ml}$  for amikacin. When used to treat urinary tract infections or in combination with penicillin against *Streptococci*, *Enterococci* or *Staphylococci* peaks of 3 - 5  $\mu\text{g/ml}$  of gentamicin/tobramycin and of 20  $\mu\text{g/ml}$  of streptomycin are acceptable. Trough levels should be < 2  $\mu\text{g/ml}$  for gentamicin, netilmicin, or tobramycin, and < 10  $\mu\text{g/ml}$  for amikacin.

## COLISTIN/POLYMYXIN

**Mechanism:** Colistin is a multi-component polypeptide antibiotic with colistin A (polymyxin E<sub>1</sub>) and colistin B (polymyxin E<sub>2</sub>) being the two major components. Rapid bactericidal activity with a detergent-like mechanism. Concentration-dependent killing. Polymyxins A - E are cationic branched cyclic decapeptides that destroy bacterial membranes with a surface detergent-like mechanism by interacting with membrane phospholipids and increasing cellular permeability

**Resistance:** Rare, develops slowly.

**Pharmacology:** Two different forms of colistin are available commercially, colistin sulfate ( $t_{1/2}$  4 hours) for oral and topical use, and sodium colistin methanesulphonate ( $t_{1/2}$  2 hours; technically a not a salt; all antimicrobial activity is due to conversion to colistin) for parenteral and aerosol use. Compared

with colistin, the in vitro antibacterial potency of colistin methanesulphonate is considerably reduced, as are the toxic and undesirable side effects. In vivo colistin methanesulphonate is hydrolyzed to colistin.

**Dose:** 2.5-5 mg **colistin base**/kg/day divided into 2-4 doses (US preparation=Coly-Mycin), max 300 mg/d. This is equivalent to 6 – 12 mg/kg colistimethate; max dose 720 mg/d

<u>Dosing vs serum creatinine:</u>	≤1.5	1.6 – 2.5	>2.5	Dialysis
Colistin base (60 kg pt)	150 mg q 12h	150 mg q 24h	150 mg q 36h	75 mg p dialysis

**Activity:** GNR only; lacks activity vs *Proteus*, *Providentia*, *Serratia*, *Burkholderia*

**Toxicity:** nephrotoxicity (acute tubular necrosis) and neurotoxicity (dizziness, weakness, paresthesias, vertigo, visual disturbances, confusion, and neuromuscular blockade).

## VANCOMYCIN

**Mechanism:** Inhibition of bacterial cell wall synthesis

**Resistance:** Rare among usually susceptible bacteria.

**Pharmacology:** Entirely renally excreted. Marginal CSF penetration.

**Activity:** Enterococci, methicillin-resistant *S. aureus* and *S. epidermidis*, *C. difficile*, various highly resistant *Corynebacteria* species and all bacteria which are sensitive to methicillin. Bactericidal against all but Enterococci.

**Toxicity:**

**Nephrotoxicity:** ~5% of patients; increases in patients receiving concurrent aminoglycoside therapy. Nephro- and ototoxicity common occurs with peak levels > 80 µg/ml; rare with peaks of 40 µg/ml. Peak levels should be from 20 to 40 µg/ml and trough levels from 5 to 15 µg/ml.

**Other:** neutropenia, fever, and rash. Infusion over less than 30 minutes causes hypotension + a diffuse erythematous rash related to depressed cardiac output and decreased peripheral vascular resistance.

## NEW GRAM-POSITIVE TREATMENT STRATEGIES

**Quinupristin/dalfopristin** (Synercid®): Two semisynthetic pristinamycin derivatives in a 30:70 ratio.

Inhibits peptide synthesis. Dalfopristin – group A streptogramin; quinupristin is in group B)

**Mechanism:** Type A streptogramins (i.e., dalfopristin) bind to the free arms of the peptidyl transferase in the 50S ribosomal subunit, blocking the addition of new amino acids to the growing peptide chain. Quinupristin (a streptogramin B compound), like macrolides, works at a later phase of protein synthesis, preventing further peptide elongation and causing release of incomplete peptide chains. In the absence of specific resistance mechanisms, the affinity of quinupristin for the 50S ribosomal subunit is

**Activity:** *S. aureus* and CNS (including methicillin-resistant isolates and GISA), *S. pneumoniae* (including penicillin- and macrolide-resistant isolates), Group A Streptococci, VS/VR *E. faecium* (not active vs. *E. faecalis*). Also *N. meningitidis*, *N. gonorrhoeae*, *M. catarrhalis*, *L. pneumophila*, *M. pneumoniae*, *Listeria*, *Corynebacterium jeikeium*, viridans Streptococci. Synergistic with doxycycline vs. VR *E. faecium*.

**Resistance:** Inducible resistance (iMLS<sub>B</sub>) to macrolides, lincosamides, and streptogramin B => erythro-R, clinda-S, quinu-S. Single subsequent mutation => constitutive resistance (cMLS<sub>B</sub>) and clind-R, quinu-R, but Dalfo-S, Q/D-S and ↓ bactericidal activity vs. VRE and MRSA (uncommon in VSE, MSSA). cMLS<sub>B</sub> isolates may require tid dosing to maintain activity. Enzymatic inactivation and active reflux are rare.

**Pharmacology:** 7.5 mg/kg q8° IV for VRE q 12° for complicated skin/soft tissue infections. Non-enzymatic metabolism; biliary excretion. Not cleared by hemodialysis. 90X ↑ intracellular concentration in macrophages. Inhibits CYP3A4 => ↑ nifedipine, midazolam, cyclosporin, terfenadine. Contraindicated with cisapride. Expect ↑ [ ] astemizole, NNRTIs, PIs.

**Toxicity:** 75% phlebitis at infusion site if given through a peripheral IV; recommend 1° infusion through central line. ~ 10% arthralgias and myalgias (may be severe). 3% ↑ conjugated bilirubin. < 5% nausea, rash, diarrhea, headache

**Cost:** >\$3,000 for 10 day course in 65 kg patient.

**Linezolid** (Zyvox™). Oxazolidinone class of antimicrobial. Ribosomal inhibitor.

**Activity:** *S. aureus* and CNS (including methicillin-resistant isolates and GISA ), *S. pneumoniae* (including penicillin- and macrolide-resistant isolates), Group A/B Streptococci, VS/VR *E. faecium* and *E. faecalis*, *P. multocida*. Binds to 23S ribosomal RNA on 50S subunit – prevents formation of

functional 70S initiation complex. Bacteriostatic vs enterococci and staphylococci; usually bactericidal for streptococci. MIC 90 for Enterococci and *S. aureus* ~ 4 µg/ml.

**Pharmacology:** 600 mg q 12° PO (+/- food) and IV. 400 mg bid for skin/soft tissue. ~100% bioavailability. 30% protein bound. 70% CSF penetration. Oxidatively metabolized. No P450 interactions. 30% renal excretion. No dose adjustment with renal failure (significance of metabolite accumulation is unknown). 30% clearance by hemodialysis. No dose adjustment with mild/moderate hepatic insufficiency; no data with Childs Class C.  $T_{min} = 3 - 6 \mu\text{g/ml}$  (400 – 600 mg q 12h). Activity predicted by time over MIC (> 40 – 60% of dosing interval).

**Indications (FDA):** VRE, nosocomial or community-acquired pneumonia, skin/soft tissue infections.

**Resistance:** Gram-positive have 4 – 6 copies of 23S rRNA; mutations in  $\geq 2$  copies => ↓ susceptibility. Resistance may emerge during treatment of enterococcal or staphylococcal infections. No documented antagonism with rifampin, aminoglycosides or βlactams.

**Toxicity:** Diarrhea, nausea, vomiting; thrombocytopenia (~3%); rare pan-cytopenias; occasional peripheral neuropathy.. Weak. Non-selective, reversible non-selective **MAO inhibitor** (interacts with adrenergic and serotonergic agents). Enhances responses to pseudoephedrine or phenylpropanolamine. Rare reports of serotonin syndrome in patients receiving SSRIs, Few data in patients with uncontrolled HTN, pheochromocytoma, carcinoid syndrome or untreated hyperthyroidism. No data with > 28 days of use.

**Daptomycin:** novel lipopeptide

**Activity:** *S. aureus* and CNS (including methicillin-,linezolid- and vancomycin-resistant isolates), Group A/B Streptococci, VS/VR *E. faecium* and *E. faecalis*, *C. jeikeium*. Calcium dependent insertion into bacterial cell membrane and subsequent calcium-dependent oligomerization leads to intracellular potassium loss and subsequent membrane depolarization and bacterial death. Concentration-dependent bactericidal activity.

**Pharmacology:** complicated skin/soft tissue infections 4 mg/kg/ q 24°; *S. aureus* bacteremia/endocarditis 6 mg/kg q 24°. No significant drug-drug interactions. 92% protein bound (reversible). Renal excretion; ↓ dose to 4 mg/kg/ q 48° if CrCl < 30. Give dose post dialysis or CAPD.

**Indications (FDA):** complicated skin/soft tissue infections, *S. aureus* bacteremia including right-sided endocarditis caused by MRSA and MSSA. **Does not penetrate alveolar fluid. Not active versus pneumonia (failures in human phase III studies).** Limited data in bacteremic patients.

**Resistance:** Resistant *S. aureus* and *E faecalis* have been identified. Mechanism of resistance not known.

**Toxicity:** Myopathy with higher doses or multiple daily doses; with 4 mg/kg/d myopathy rates 2.8% with daptomycin vs 1.8% with control regimens. In limited data, no evidence of increased rate of myopathy with daptomycin in patients with baseline CPK > 500 or in patients taking concomitant simvastatin. Monitor CPK; strongly consider halting statin while on daptomycin. D/c with signs and symptoms of myopathy plus CPK >1000. Possible peripheral neuropathy.

**Telavancin (Vibativ):** lipoglycopeptide antibiotic produced through chemical modification of vancomycin.

Dual mechanism of action: inhibition of peptidoglycan synthesis and disruption of the cell membrane

- inhibits cell wall synthesis by binding to late-stage peptidoglycan precursors, including lipid II, in a manner similar to vancomycin
- Membrane effects depend on binding to lipid II and are observed at concentrations that are higher than the telavancin MIC, but well below clinically achievable plasma levels.

**Activity;** concentration-dependent, bactericidal activity against Gram-positive organisms

**Pharmacology:** telavancin dose of 10 mg/kg IV over 60 minute continuous infusion q 24 hr, renal impairment CrCl 30-50, 7.5 mg. kg q 24 h, CrCl 10 – 30: 10 mg/kg q 48 hr.  $t_{1/2}$  8 hours. 75% renal excretion; no metabolic products. The mean binding is approximately 90%.

Dose Adjustment for Patients with Renal Impairment

CrCl (mL/min)	Telavancin Dosage
30-50	7.5 mg/kg q 24 hr
< 30	10 mg/kg q 48 hr

- insufficient information to make recommendations for patients with end-stage renal disease (CrCl <10 mL/min), including patients receiving hemodialysis
- Accumulation of the solubilizer hydroxypropyl-beta cyclodextrin can occur in patients with renal dysfunction

- Patients with creatinine clearance  $\leq 50$  mL/min also had lower clinical 294 cure rates.

**Indications:** adult patients with complicated skin and skin structure infections (cSSSI) caused by susceptible Gram-positive bacteria

**Interactions:** binds to artificial phospholipid surfaces resulting in interference with many PT, PTT and INR assays.

**Resistance:** Mediated by *VanA* (as for VRSA), but clinical significance not determined. No known cross-resistance with other classes of antibiotics.

**Activity vs VISA, VRSA:** Among 653 US MRSA, the telavancin MIC<sub>range</sub> was 0.06 - 1  $\mu$ g/mL with a MIC<sub>90</sub> of 0.5  $\mu$ g/mL while the vancomycin MIC<sub>range</sub> was 0.25 - 2  $\mu$ g/mL with a MIC<sub>90</sub> of 1  $\mu$ g/mL. Against isolates of VISA, telavancin MICs ranged from 0.12 - 4  $\mu$ g/mL. Against isolates described as hVISA (n = 44), the telavancin MIC<sub>90</sub> value was 1.0  $\mu$ g/mL (MIC<sub>range</sub> = 0.12 - 2  $\mu$ g/mL). Against three isolates defined as VRSA, telavancin demonstrated *in vitro* activity at therapeutically achievable concentrations. In early investigations, no heteroresistance to telavancin has been observed in *S. aureus* populations. Company data suggest that telavancin has superior *in vitro* activity against hVISA compared with vancomycin. *There is no meaningful clinical information regarding effectiveness in the treatment of VISA or VRSA infections.*

**Toxicity:** also causes foamy urine; nausea

- **Multi-species teratogen:** adverse developmental outcomes observed in 3 animal species at clinically relevant doses raise concerns about potential adverse developmental outcomes in humans
- Dysgeusia or altered taste (33.5%); nausea (26.8%)
- $\downarrow$  efficacy with moderate/severe baseline renal impairment.
- Increases in serum creatinine to 1.5 times baseline occurred more frequently among telavancin-treated patients with normal baseline serum creatinine (15%) compared with vancomycin-treated patients with normal baseline serum creatinine (7%).
- Administer over at least 60 minutes to minimize infusion-related reactions.
- QTc prolongation: Avoid use in patients at risk (congenital long QT syndrome, known prolongation of the QTc interval, uncompensated heart failure, or severe left ventricular hypertrophy; these patients were not included in clinical trials).
- New onset or worsening renal impairment has occurred. Monitor renal function in all patients

## TRIMETHOPRIM/SULFAMETHOXAZOLE

**Activity:** Bactericidal activity against *Staphylococci* (including some methicillin-resistant *S. aureus*) and *Streptococci* (not *Enterococci*), *H. influenzae* and most Enterobacteriaceae. No activity against anaerobes or *P. aeruginosa*.

**Pharmacology:** Excellent po absorption; peak levels at 2 - 4 hours. Excellent lipid solubility.

### Indications

UTI, chronic prostatitis; effective even with severe decreases in GFR.

Acute exacerbation of chronic bronchitis

*Pneumocystis carinii* pneumonia

*Salmonella* and *Shigella* infections

*L. monocytogenes* meningitis in penicillin allergic patients.

**Toxicity:** Sulfa rash, hemolytic anemia (G6PD), falsely increased serum creatinine (interference with colorimetric assay), bone marrow suppression. Ataxia and other CNS toxicity accompany high serum concentrations of trimethoprim (> 8  $\mu$ g/ml).

## NITROFURANTOIN

**Mechanism:** poorly understood, appears to require enzymatic reduction yielding reduced derivatives that bind to ribosomal proteins and block protein synthesis. May also inhibit bacterial respiration and pyruvate metabolism.

**Activity:** Good activity against *E. coli*, *Citrobacter*, *S. saprophyticus*, Enterococci, Group B Streptococci. Poor against *Enterobacter*, *Klebsiella*, *Proteus*, *Providencia*, *Morganella*, *Serratia*, *Acinetobacter*, and *Pseudomonas*,

**Pharmacology:** active only against cystitis. Not effective for treatment of pyelonephritis, prostatitis. In patients with renal failure, nitrofurantoin excretion is decreased in proportion to decreases in creatinine clearance, and urinary drug concentrations become subtherapeutic. Thus, nitrofurantoin<sup>Rx</sup> should not be used in patients with renal insufficiency (creatinine clearance of <40 mL/min).

**Toxicity:** gastrointestinal (less with macrocrystalline forms), rash (1%). Pulmonary reactions (acute, subacute, and chronic forms) occur at a frequency of one or fewer cases per 100,000 courses of treatment. Pulmonary fibrosis occurs with chronic therapy only. May be used during pregnancy except near term.

**FOSFOMYCIN:** available orally in the US as fosfomycin tromethamine (*Monurol* - Forest) for single-dose oral treatment of uncomplicated urinary tract infections in women. Intravenous formulations available elsewhere.

**Mechanism:** organic phosphonate, inhibits UDP-N-actylglucosamine enolpyruvyl transferase (MurA) and thus the first step in bacterial cell wall synthesis.

**Activity:** moderately active *in vitro* against *Escherichia coli* and many other common pathogens in uncomplicated urinary tract infections, including some strains of *Staphylococcus saprophyticus* and most strains of enterococci. In multiple-dose use, resistance to fosfomycin emerges rapidly

**Pharmacology:** active only against cystitis. Not effective for treatment of pyelonephritis, prostatitis. In patients with renal failure, nitrofurantoin excretion is decreased in proportion to decreases in creatinine clearance, and urinary drug concentrations become subtherapeutic. Thus, nitrofurantoin<sup>Rx</sup> should not be used in patients with renal insufficiency (creatinine clearance of <40 mL/min).

**Toxicity:** diarrhea (9%).

## **METRONIDAZOLE**

**Activity:** Excellent bactericidal activity against virtually all obligate anaerobes. Poor activity against microaerophilic organisms and no activity against aerobes.

**Pharmacology:** Excellent CSF penetration. Hepatic metabolism.

**Toxicity:** Disulfiram (antabuse) like reactions, bone marrow suppression, ataxia, peripheral neuropathy (increased risk at > 50 g/month), and abnormal LFTs. Contraindicated during pregnancy.

## **CLINDAMYCIN**

**Mechanism:** 50s ribosome - binding inhibits protein synthesis.

**Activity:** Bacteriostatic activity against most anaerobes (including *B. fragilis*) except some *Clostridia*. Adequate activity against *Staphylococci* and most *Streptococci* (except *Enterococci*).

**Resistance:** in the United States, most macrolide-resistant *S. pneumoniae* and *S. pyogenes* strains are of the M phenotype, which does not show cross-resistance to clindamycin.

**Pharmacology:** No CSF penetration. Metabolized by the liver.

**Toxicity**

**Allergic:** rare rash, erythema multiforme, fever

**Pseudomembranous colitis** < 20%

**Hepatotoxicity:** minor increases in SGOT, SGPT

**Occasional bone marrow suppression**

**Neuromuscular blockade**

## **MACROLIDES**

**Mechanism:** 23S ribosome-binding inhibits protein synthesis.

**Resistance:**

Macrolide resistance results mainly from methylase gene expression (*erm*<sup>+</sup>) which results in methylation of ribosomal adenine residue [A2058] in 23S ribosomal RNA. This blocks macrolide binding to rRNA domain II.

### **Erythromycin**

**Activity:** Most *Staphylococci*, *Streptococci*, *Neisseria*, *Moraxella catarrhalis*, *T. pallidum*, *Legionella species*, *Mycoplasma* and *Ureaplasma*, *C. trachomatis*, *B. pertussis* and *C. diphtheriae*. Borderline activity against *H. influenzae*.

**Pharmacology:** Poor CSF penetration; excellent penetration of PMNL and macrophages; 10 - 15% excreted in the urine.

### **Individual agents**

**Base:** Acid-labile, peak levels in 1°-4°, delayed by food.

**Stearate:** Enteric-coating reduces acid-lability. Absorption is delayed and decreased by food.

**Ethylsuccinate:** Acid stable, absorption not delayed by food. 400 mg = action of 250 mg of other preparations.

**Estolate:** Not acid-labile, peak levels 2° after oral dose. Absorption not delayed by food. Absorbed as ester (inactive) and base.

Toxicity:

GI: GI intolerance, rare cholestatic jaundice (especially with estolate or ethylsuccinate) or hepatocellular toxicity, occasional pancreatitis.

Ototoxicity: at 4 gms/d incidence may be 20% and occur after 3-7 days of therapy. Correlates with peak > 12µg/ml. Increased risk with renal disease and high serum levels.

Cardiac: High dose IV therapy associated with prolonged QT intervals and torsades de pointes.

Drug interactions: Impairs theophylline, cyclosporin and disopyramide metabolism.

**Clarithromycin**

**Activity:** better than erythromycin versus *H. influenzae*, *M. avium* complex. Spectrum otherwise similar to erythromycin. Cross-resistance with erythromycin.

**Indications:** Upper/lower respiratory tract, skin, soft tissue infections.

**Pharmacology:** long  $t_{1/2}$ , well absorbed  $\pm$  food, acid-stable, otherwise similar to erythromycin.

**Dosage:** 250-500 bid; higher dose for *H. influenzae* and sinusitis.

**Toxicity:**

GI: less distress than with erythromycin

Pregnancy: do not use; Class C.

Children: safety not established.

Drug interactions: Impairs theophylline, cyclosporin and carbamazepine metabolism.

**Azithromycin** (PO and IV)

**Activity:** spectrum similar to erythromycin.

**Indications:** Upper/lower respiratory tract, skin, soft tissue infections, STD.

**Pharmacology:** Absorption decreased by food, acid-stable, long  $t_{1/2}$ , otherwise like erythromycin.

**Dosage:** NGU: 1 gm po single dose. MAC prophylaxis: 1200 mg q week. LRTI (IV): 500 mg qd.

Other: 500 mg load, then 250 mg qd x 4.

**Toxicity:**

Pregnancy: caution; Class B.

Children: safety not established.

Drug interactions: effect on theophylline not known.

**KETOLIDES:** Related to macrolides

**Telithromycin:**

**Mechanism:** inhibits 50S ribosomal subunit protein synthesis (Binds to 23S rRNA domains II and V).

When compared with erythromycin telithromycin's ketone- and methoxy-group substitutions make it more acid stable, and both less susceptible to drug export pumps and to displacement by ribosomal methylation thereby increasing ribosomal binding affinity and overcoming the most frequent mechanisms of bacterial resistance to macrolides.

Does not induce the *erm* gene.

**Activity:** *S. aureus* (MSSA only), *S. pneumoniae* (including PRSP), *H. influenzae*, *M. catarrhalis*, Group A. Streptococci, *C. pneumoniae*, *M. pneumoniae*, *L. pneumoniae*, *S. aureus*.

Active vs erythromycin-inducibly resistant *S. aureus*, and GAS, but not against *S. aureus*, and GAS bacteria with constitutive MLS<sub>B</sub> expression.

*S. pneumoniae* with high-level MLS<sub>B</sub> expression reported to be telithromycin resistant in Taiwan.

**Indications:** community-acquired pneumonia, acute bacterial exacerbations of chronic bronchitis, acute bacterial sinusitis.

**Pharmacology:** 800 mg po qd. Oral only.  $t_{1/2}$  7 – 9 hours. 57% absorption. 50% metabolized by CYP 3A4. Substrate and inhibitor of CYP3A4.

Dose: 800 mg qd x 5 days (bronchitis, sinusitis) or 10 days (CAP).

**Toxicity:** visual disturbance ( $\downarrow$  ability to accommodate or release accommodation) in 1 – 2%; most common 1 – 3° after 1<sup>st</sup> or 2<sup>nd</sup> dose and in women under age 40 (2%); increased frequency when taken with CYP3A4 inhibitor. Diarrhea 10%, nausea 7%. QT prolongation has not been observed in clinical trials; there are no reports of torsades de pointes or other ventricular arrhythmias. *Avoid* in setting of hypokalemia or use of Class IA (e.g. quinidine, procaineamide), or Class III (e.g., amiodarone, sotalol) anti-arrhythmics). Rare, fatal hepatotoxicity. Exacerbations of myasthenia gravis.

**Contraindications** include cisapride, pimozide, simvastatin, lovastatin, atorvastatin, midazolam; myasthenia gravis.

**Warnings** include simvastatin, midazolam, digoxin, rifampin

## TETRACYCLINES

**Mechanism:** 30s ribosome-binding blocks protein synthesis. Plasmid-mediated resistance is due to decreased bacterial uptake.

**Resistance:** efflux pump or ribosomal protection, rare enzymatic inactivation. Efflux pumps confer resistance to the earlier tetracyclines but not to doxycycline and minocycline

**Pharmacology:** All except doxycycline are primarily excreted by the kidneys. Doxycycline and minocycline offer the best absorption.

**Activity:** *Rickettsia*, *Spirochetes*, *Chlamydia*, *Ureaplasma*, *Mycoplasma*, *Neisseria*, and the agents of brucellosis, tularemia, and plague. 2 - 5% of *S. pneumoniae*, 10 - 15% of Group A *Streptococci*, and many gram-negative rods are resistant.

### Individual advantages

**Doxycycline:** no accumulation in renal failure

**Minocycline:** useful for *N. meningitidis* prophylaxis.

### Toxicity

**Fanconi syndrome:** due to outdated tetracycline

**Nephrogenic diabetes insipidus:** especially with demeclocycline

**Minocycline:** vestibular

**Demeclocycline:** phototoxicity

**Hepatotoxicity:** use during pregnancy or with severe renal disease.

**Tooth discoloration:** from 4th month of pregnancy to age 12.

**Increased BUN:** antianabolic effect in persons with renal disease.

**GLYCYLGLYCINES:** Tetracycline derivatives, active vs. VR *E. faecium* and *E. faecalis*.

**Tigecycline** (Tygacil™): available only for intravenous administration

**Mechanism:** binds to 30S ribosomal unit.; binds to more biosomal sites than do tetracyclines Not affected by major tetracycline resistance mechanisms (ribosomal protection and efflux).

**Activity:** Generally bacteriostatic. Clinical activity demonstrated vs. MSSA/MRSA, VSE, *S. agalactiae*, *S. intermedius*, *S. constellatus*, *S. pyogenes*, *Enterobacteriaceae*, *B. fragilis*, *C. perfringens*, *C. difficile*, *P. micros*. Active but clinical relevance not known for *S. pneumoniae*, VRE, *Listeria*, *Acinetobacter*, *Aeromonas*, *Pasteurella*, *S. maltophilia*. **Not active** vs. *Morganella*, *Proteus*, *Providencia* or *P. aeruginosa*

**Indications:** complicated skin/soft tissue infections, complicated intra-abdominal infections and community-acquired pneumonia. Did not satisfy approval criteria for hospital-acquired pneumonia; results were unfavorable in patients with ventilator-associated pneumonia.

**Pharmacology:**  $t_{1/2}$  27+ hours. ~80% protein bound. Not extensively metabolized. 60% biliary excretion.

**Dosage:** 100 mg loading dose then 50 mg q 12°. No dose adjustment with ↓ GFR or hemodialysis. ↓ dose in Child-Pugh Class C (100 mg loading dose, 25 mg q 12° maintenance).

**Toxicity:** similar to tetracycline. ?? ↑ mortality c/w comparators in patients presenting with sepsis/septic shock (may be due to ↑ baseline severity of disease, per FDA).

**GI:** ↑ N/V (~ 2x) compared with comparator agents; rates of 20 – 30% reported.

**Pregnancy:** **Class D.**

**Children:** avoid in children under the age of 8 (tooth discoloration) .

**Drug interactions:** No known or expected significant drug-drug interactions.

## CHLORAMPHENICOL

**Mechanism:** 50S ribosome - binding blocks protein synthesis. Resistance develops due to decreased bacterial permeability and acetylation of the drug, the latter is plasmid-mediated.

**Pharmacology:** Hepatic metabolism. Excellent CSF penetration.

**Activity:** *Rickettsia*, anaerobes, *S. pneumoniae*, *S. viridans*, *N. meningitidis*, *S. typhi*, and β-lactamase producing *H. influenzae*.

### Toxicity

#### **Bone marrow suppression**

Common, reversible, acute, dose-related; associated with poor bone marrow iron utilization.

Rare, irreversible, delayed, not dose-related; aplastic.

**Gray baby syndrome:** Lactic acidosis secondary to high serum levels; associated with immature hepatic metabolism.

## Optic neuritis

**G6PD hemolytic anemia:** in Mediterranean form only.

## Rare psychiatric disturbances

**Drug interactions:** Inhibits p450 metabolism of tolbutamide, chlorpropamide, phenytoin and coumadin.

## PENTAMIDINE

**Mechanism:** uncertain.

**Pharmacology:** No correlation of clinical response with serum levels. Rapidly bound to tissues; slowly excreted in urine. Not dialyzable, with GFR < 10 give full dose q 48°.

**Toxicity:** hypotension with rapid iv infusion, leukopenia, rash, renal toxicity, hypoglycemia with rebound hyperglycemia, pancreatitis, cardiac (torsade de pointes).

## ANTIFUNGAL AGENTS

**Amphotericin B:** Inevitable decrease in GFR; also causes RTA. Correction of hypokalemia, acidosis, and hypovolemia may improve renal function. GOLD STANDARD ANTI-FUNGAL AGENT. Several different preparations now available: New formulations offer advantage of decreased nephrotoxicity but are much more expensive.

**Resistance:** most often demonstrated by *C. lusitanae*, occasional *C. glabrata* and *C. krusei*

**Conventional amphotericin B:** formulated in dexoycholate. Usual dosage 0.5 – 1.0 mg/kg/d.

Highest doses reserved for aspergillosis and mucor infections, or *C. glabrata* and *C. krusei* in immunocompromised patients.

**Alternative preparations:** Reserved for immunocompromised patients treated for invasive non-*Candida* infections who have a significant ↓ of renal function despite adequate trial of salt loading and alteration of amphotericin B dosing schedule (reduced qod)

**Amphotericin B cholesteryl sulfate complex (Amphotec®)**, amphotericin B colloidal dispersion ABCD). Usual dose = 3-4mg/kg/d (range 3-6). Minimum 2 hour infusion time. FDA indication for invasive aspergillosis refractory invasive fungal infections and for patients intolerant of standard amphotericin. \$525/day at 5 mg/kg/d for a 70 kg pt.

**Amphotericin B lipid complex (ABLC, Abelcet®):** Usual dose = 5 mg/kg/d administered at 2.5 mg/kg/hour. FDA indication for refractory invasive fungal infections and in patients intolerant of standard amphotericin. \$675/d at 5 mg/kg/d for 70 kg pt.

**Liposomal amphotericin (AmBisome®):** Usual dose = 3 – 5 mg/kg/qd; 2 hour IV infusion. FDA indication for empiric Rx of febrile neutropenic pts with presumed fungal infection, refractory invasive fungal infections and in patients intolerant of standard amphotericin, and for visceral leishmaniasis. AWP => \$790/day at 3 mg/kg/d for a 70 kg pt. Can be infused over 30 – 60 minutes.

Rankings:

Nephrotoxicity:	AmB dexoycholate > ABCD > ABLC > L-AMB
Infusion tox	AmB dexoycholate = ABCD > ABLC > L-AMB
Cost:	AmB dexoycholate << ABCD < ABLC < L-AMB

**Flucytosine** (5-fluoro-cytosine, 5FC; oral): => frequent diarrhea, BM suppression, and hepatitis, any of which may be life-threatening. Check levels.

## Azoles

**Mechanism:** block cytochrome P450 demethylase thus blocking synthesis of fungal ergosterol.

## Drug interactions:

**Drugs that reduce azole levels:** INH, rifampin, cimetidine, phenobarbital, phenytoin, carbamazepine. Effect greatest with ketoconazole > itraconazole > fluconazole.

**Drugs whose metabolism is impaired by azoles:** phenytoin, warfarin, cyclosporin, sulfonyleureas, terfenadine (ventricular arrhythmias).

**Activity:** Miconazole and ketoconazole are not adequate for treatment of any life-threatening fungal infection or for any infection caused by aspergillus, rhizopus, or mucor agents.

**Miconazole:** Rapid administration of 1<sup>st</sup> dose may => cardiovascular collapse. Withdrawn from US.

**Ketoconazole:** decreases testosterone and cortisol synthesis when given in high doses; secondary buildup of deoxycorticosterone has mineralocorticoid effects leading to hypertension and hyponatremia. Absorption impaired by gastric alkalization, sucralfate.

**Fluconazole:** compared with ketoconazole less inhibition of mammalian sterol synthesis.

Dose: Candidemia: *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. lusitaniae* 400 mg/d (6 mg/kg/d); *C. glabrata* 12 mg/kg/d (prefer initial therapy with voriconazole or AmB).

Renal dose adjustment: decrease dose by 50% in persons with creatinine clearance < 50.

Drug-drug interactions: multiple drug-drug interactions. Contraindicated with terfenadine, cisapride. Other important interactions occur with oral hypoglycemic, coumadin, phenytoin, cyclosporine, rifampin, theophylline, astemizole, rifabutin, tacrolimus, short-acting benzodiazepines.

Pharmacology: Absorption unaffected by food. 75% urine excretion; 30 hour half-life; 94% bioavailable orally; 60-70% CSF penetration.

Indications: Mucosal and disseminated candidiasis, cryptococcosis, coccidioidomycosis (especially meningitis). Poor choice for histoplasmosis.

Toxicity includes hepatitis, nausea, diarrhea, headache, rash. Potential QT prolongation. Potentially associated with multiple congenital abnormalities with prolonged use of high doses during pregnancy.

Resistance: *C. krusei* (always). Occasional resistance of *C. glabrata* and rare resistance of *C. albicans* (primarily in multiply treated HIV+ patients) has also reported.

### **Itraconazole:**

Dose: PO max dose 200 mg bid (↑ absorption with use of cyclodextrin solution); IV 200 mg bid x 4 days then 200 mg qd. Oral use requires loading with 800 mg for 3 days or 600 mg for 4 days to more rapidly reach steady state.

Pharmacology: decreased absorption with increased gastric pH. Capsules have increased bioavailability with food but solution is best absorbed on an empty stomach.  $T_{1/2}$  21°. No more than 200 mg can be absorbed at once. 99% protein bound; lipophilic. No CSF penetration. 3-18% fecal excretion. 0.03% renal excretion of active drug. Increased absorption of liquid formulation.

Renal insufficiency: PO: no dose alteration with renal insufficiency. IV: contraindicated with CrCl < 30/min (concerns with solubilizing agent).

Indications: Histoplasmosis, blastomycosis, sporotrichosis; allergic bronchopulmonary aspergillosis

Toxicity: severe hypokalemia, hypertension, adrenal insufficiency and rhabdomyolysis have occurred with 400 - 600 mg po daily doses. Also CHF.

Contraindications: astemizole, cisapride, oral midazolam, triazolam, pimozide, quinidine, lovastatin, simvastatin. Not recommended with nevirapine

**Voriconazole:** 60% protein bound. Absorption not affected by gastric pH.

### Dose:

Candidemia and hematogenously disseminated candidiasis: 300 mg (4 mg/kg) twice per day for 2 doses, then 200 mg (3 mg/kg) twice per day IV or po

Aspergillosis, Scedosporiosis and Fusariosis: Loading dose 400 mg (6 mg/kg) q12h for 2 doses. Maintenance 300 mg (4 mg/kg) IV. Maintenance 20 – 300 mg q 12h.

Hepatic dose adjustment: Decrease maintenance dose by 50% in patients with Child-Pugh Class A or B cirrhosis. Not studied in Child-Pugh Class C.

Renal dose adjustment: beware accumulation of intravenous vehicle (sulfobutyl ether beta-cyclodextrin sodium – SBECD) for solubilization in persons with creatinine clearance < 50.

Drug-drug interactions: multiple severe interactions: Metabolized via CYP2C9, CYP3A4, CYP2C19. Inhibits the metabolic activity of the cytochrome P450 enzymes CYP2C19, CYP2C9, and CYP3A4.

- Decreased voriconazole levels (all contra-indicated): carbamazepine, long-acting barbiturates, rifampin, rifabutin
- Increased by voriconazole: cisapride, ergot, quinidine, sirolimus (all contraindicated).

### Activity:

Invasive aspergillosis: ↑ survival at 12 weeks compared with ampho B.

*Candida:* more active than fluconazole vs. *C. glabrata*, *C. krusei*, *C. albicans*, *C. dubliniensis*, *C. guilliermondii* and *C. lusitaniae*.

*Coccidioides*

Other: Active vs. *Blastomyces*, *Histoplasma*, *Scedosporium apiospermum* (the asexual form of *Pseudallescheria boydii*), *Fusarium spp*, *Paecilomyces*, *Bipolaris*, *Alternaria*. Not active against zygomycetes

Neutropenic fever: ↓ fever breakthrough, ↓ ntox, ↓ infusion reaction, = hepatotox c/w ampho B

Indications: Invasive aspergillosis, *Candida* infections (candidemia, disseminated candidiasis and esophageal candidiasis), serious infections caused by *Scedosporium apiospermum*

Toxicity: hepatotoxicity, teratogenic, potential QT prolongation, rash & photosensitivity.

Visual disturbances: 30% photopsia (abnormal vision, color vision change and/or photophobia) during infusion. If treatment continues beyond 28 days, visual function including visual acuity, visual field and color perception should be monitored.

**Posaconazole:** >98% protein bound

Dose: available as oral suspension **give with food**. Absorption not affected by gastric acidity. ↓ absorption with dose greater than 400 mg at one time. 200 mg tid for GVH or AML anti-fungal prophylaxis.

Drug-drug interactions: inhibits CYP3A4

40 – 50% ↓ posaconazole serum levels with rifabutin (p-glycoprotein induction), phenytoin (p-glycoprotein induction) and cimetidine; no effect seen with other antacids, H2RAs or PPIs. ↑ serum levels of cyclosporine, tacrolimus, rifabutin, midazolam, phenytoin

Activity: *A. fumigatus*, *Candida* including *glabrata* (somewhat less effective than voriconazole) and *krusei*, many (but not all *Zygomycetes*), and *Histoplasma*, *Blastomyces*, *Coccidioides* and *Cryptococcus*.

Indications: prophylaxis of invasive *Aspergillus* and *Candida* infections in high risk patients (hematopoietic stem cell with GVH, or neutropenia post cytotoxic chemotherapy)

Pharmacology: steady state conc achieved after 7-10 days after which  $t_{1/2} = 35$  hours. 70% fecal excretion, primarily as parent drug; glucuronidated; no oxidative metabolites. Substrate for p-glycoprotein efflux. Substantial inter-patient variances in steady state concentration are unexplained.

Toxicity: hepatotoxicity, ↑ QTc

Contraindicated with: terfenadine, astemizole, cisapride, pimozide, halofantrine or quinidine

## **Echinocandins**

### **Caspofungin**

Activity: Inhibitor of synthesis of  $\beta$  (1,3)-D-glucan. Active vs *Candida* (fungicidal), *Aspergillus*, *Pneumocystis jiroveci*. Marginal activity vs *Coccidioides*, *Histoplasma*, *Blastomyces*, *Scedosporium*, *Paecilomyces*. Not active vs *Cryptococcus*, *Zygomycetes*,

Pharmacology: Little renal excretion of active drug. No interactions with any enzyme in cytochrome P450 system.

Dose: 70 mg loading dose followed by 50 mg qd. No adjustment for renal failure, hemodialysis or mild hepatic insufficiency (Child-Pugh score 5 – 6), ↓ dose to 35 mg qd with moderate hepatic insufficiency (Child-Pugh score 7 – 9), no data for patients with severe hepatic insufficiency.

Caspofungin concentrations not affected by concomitant itraconazole, amphotericin, mycophenolate, nelfinavir or tacrolimus. 30% ↓ caspofungin with concomitant rifampin (↑ caspofungin dose to 70 mg qd). ↑ dose to 70 mg qd with concomitant efavirenz, nevirapine, phenytoin, dexamethasone, or carbamazepine

Caspofungin has no effect of PK of itraconazole, amphotericin, or active metabolite of mycophenolate

Caspofungin ⇒ 20% ↓ tacrolimus AUC, 35% ↑ cyclosporin AUC

Warnings: Do not administer with cyclosporin (possible increased hepatotoxicity). Embryotoxic in rats and rabbits

Toxicity: histamine release, little or no nephrotoxicity or hepatotoxicity; more fever, abdominal pain, hypokalemia and pyuria than with fluconazole

### **Micafungin (Mycamine™)**

Activity: Inhibitor of synthesis of  $\beta$  (1,3)-D-glucan. Active in vitro vs *Candida* (fungicidal),

Pharmacology: Little renal excretion of active drug. Substrate for (but very little metabolism by) and weak inhibitor of CYP3A. Do not interact with P-glycoprotein.

Dose: 150 mg qd for esophageal candidiasis; 50 mg qd for prophylaxis on *Candida* infections in patients undergoing hematopoietic stem cell transplantation. 100 mg for Candidemia. No adjustment for renal failure, hemodialysis or mild-to-moderate hepatic insufficiency (Child-Pugh score 5 – 9), no data for patients with severe hepatic insufficiency.

No drug interactions with mycophenolate, cyclosporine, tacrolimus, prednisone or fluconazole.

Mild increase of sirolimus and nifedipine AUC.

Indications: esophageal candidiasis, prophylaxis on *Candida* infections in patients undergoing hematopoietic stem cell transplantation.

Warnings: Pregnancy class C

Toxicity: histamine release, little or no nephrotoxicity or hepatotoxicity; rare acute intravascular hemolysis

### **Anidulafungin (Eraxis™)**

Activity: Inhibitor of synthesis of  $\beta$  (1,3)-D-glucan. Active in vitro vs *Candida* (fungicidal),

Pharmacology: Little renal excretion of active drug. Not a substrate, inducer or inhibitor of CYP450 isoenzymes. Undergoes slow non-enzymatic chemic degradation.

Dose: 100 mg loading dose than 50 mg qd for esophageal candidiasis. 200 mg loading dose than 100 mg qd for candidemia. No adjustment for renal failure, hemodialysis or Child-Pugh A, B and C. No interaction with voriconazole, tacrolimus, cyclosporin or rifampin. Reconstituted with alcohol/ 100 mg dose ~ 1/2 jigger of alcohol.

Indications: esophageal candidiasis, candidemia and candidiasis. In vitro activity vs. *Aspergillus*

Warnings: Pregnancy class C

Toxicity: little or no nephrotoxicity or hepatotoxicity

### **Other**

#### **Terbinafine (Lamisil):**

Dose: 250 mg qd x 6 wks for fingernail onychomycosis; 12 weeks for toenails. Not recommended with CrCl < 50.

Pharmacology: Inhibits CYP2D6 metabolism, may  $\uparrow$  effect of tricyclic antidepressants,  $\beta$ blockers, SSRIs, and monoamine oxidase inhibitors.

Indications: treatment of onychomycosis. Active against *Trichophyton spp.* In vitro activity against *C. albicans*.

Toxicity: Rare cases of hepatic failure. Not recommended for patients with chronic or active liver disease.

### **ANTIVIRAL AGENTS**

**Amantadine, Rimantadine** (oral): both suppress influenza A by inhibiting ion-channel function of virus protein M2 and thereby preventing fusion function of hemagglutinin and blocking viral penetration of host cells. Both inactive vs. influenza B. Both need to be started within 48<sup>o</sup> of symptom onset. Toxicities include light-headedness, dizziness (amantadine > rimantadine). Amantadine has been associated with  $\uparrow$  seizures in persons with an underlying seizure disorder.

**Neuraminidase inhibitors:** zanamavir (inhaled powder) and oseltamivir (pill).

**Zanamivir** (Relenza®): inhaled influenza neuraminidase inhibitor.

Activity: influenza A and B. Inadequate data regarding outcomes in patients with underlying chronic pulmonary disease to draw conclusions regarding efficacy. No head-to-head comparisons with amantadine or rimantadine.

Indications: Treatment of influenza

Pharmacology: ~10% absorption of inhaled dose. No dose adjustment for renal failure.

Toxicity: Asthmatics should have fast-acting bronchodilator available prior to using Disk-haler inhalation device (delivers dry powder).

Resistance: No evidence of resistance in clinical trials thus far.

**Oseltamivir** (Tamiflu™): oral influenza neuraminidase inhibitor.

Activity: influenza A and B.

Indications: Treatment (and prophylaxis) of influenza

Pharmacology: Dose 75 mg bid x 5 days; adjust for CrCl < 30.

Resistance: demonstrated during in vitro passages of influenza A. 1-3% of post-treatment isolates show emergence of resistance.

**Vidarabine** (Ara-A, Adenine arabinoside; iv): decreases viral and host DNA polymerase activity.

Therapy of Herpes simplex encephalitis is complicated by large amounts of fluid necessary to deliver the drug. Poor clinical activity against acyclovir-resistant HSV and HZV.

**Acyclovir** (po, iv, topical): Inhibits viral thymidine kinase and acts as DNA chain terminator. Rapid IV dose yields renal dysfunction 2<sup>o</sup> to crystalluria; occasional encephalopathy or tremor. Somewhat more effective than vidarabine for therapy of *Herpes simplex* encephalitis. Intracellular T $\frac{1}{2}$  1-2<sup>o</sup>. Resistance via mutation of viral thymidine kinase.

**Famciclovir (oral):** Deacylated to form penciclovir in the GI tract. Intracellular  $T_{1/2}$  10-20°. Similar mechanism of action as acyclovir. Indicated for HZV. Dosage 500 mg tid x 7 days.

**Valacyclovir (oral):** Prodrug of acyclovir. 3-5 x ↑ oral bioavailability compared with acyclovir.

**Ganciclovir (GCV):**

**Activity** - Inhibits DNA polymerase of CMV, HSV and HZV. Inactive against acyclovir-resistant HSV and HZV isolates. Unlike acyclovir is not a DNA chain terminator

**Toxicity** - neutropenia and thrombocytopenia are the principal dose-limiting toxicities.

**Resistance:**

**CMV:** Low-level resistance occurs through mutations in CMV UL97 (phosphotransferase) gene). High-level resistance occurs through mutation in CMV UL97 and UL54 (DNA polymerase) genes. Mutations in UL54 ⇒ resistance to cidofovir and foscarnet. High-level GCV resistance often ⇒ cidofovir resistance and sometimes foscarnet-resistance

**Pharmacology** - Entirely renally excreted. 5 - 9% absorption of oral GCV (increased with meals). Intracellular  $T_{1/2}$  12°. Oral formulation largely irrelevant with availability of oral val-GCV (exception for liver transplant patients).

**Dosage** - 5 mg/kg over 1° q 12° for 14-21 day induction therapy, then 5 mg/kg/d or 6 mg/kg/d (5 days/wk) for maintenance; up to 10 mg/kg/d given for relapses. Infusion pump is not required. 500 mg may be infused in 10 ml volume.

**Ganciclovir implants (Vitraser™):** polymer-based, drug-delivery platform. Surgically placed in the posterior segment of the eye. 2.5 mm diameter by 1 mm thickness tablet. Release 1 µg/hour of GCV for 7-8 months yielding intravitreal concentration of 4 µg/ml as opposed to 1 µg/ml for IV GCV

**Valganciclovir (oral):** Oral prodrug of ganciclovir.

**Indication:**

**HIV:** oral valganciclovir (900mg twice daily for 3 weeks then 900 mg once daily) and intravenous ganciclovir (5 mg/kg twice daily for 3 weeks then 5 mg/kg once daily) equally effective in the treatment of newly diagnosed CMV retinitis in 160 patients with AIDS.

**Transplant:** At least as effective for prophylaxis of CMV disease as oral ganciclovir for kidney, heart and kidney/pancreas transplants. But **less effective** than oral ganciclovir in liver transplant patients.

**Pharmacology:** Oral valganciclovir 900 mg provides a daily exposure of ganciclovir comparable to that of intravenous ganciclovir 5 mg/kg. Dose adjust for creatinine clearance, 40 – 59, half dose; 25 – 39, quarter dose; 10 – 24, 1/8 dose.

**Toxicity:** neutropenia, anemia, thrombocytopenia, gastrointestinal (including diarrhea, nausea, vomiting and abdominal pain), fever, headache, insomnia, peripheral neuropathy, paresthesia and retinal detachment.

**Resistance:** same as for GCV.

**Ribavirin:** guanosine analogue.

**Activity:** Lassa fever, hantavirus, HCV, RSV, parainfluenza, measles

**Drug interactions:** inhibits ZDV and d4T phosphorylation and anti-HIV activity; increases activity of ddl (↑ ddA phosphorylation).

**Mechanism:** uncertain; ribavirin triphosphate inhibits guanyl transferase thereby blocking necessary 5' capping and elongation of viral mRNA by methylated guanosine residues.

**Pharmacology:** 45% bioavailable. 35° plasma  $t_{1/2}$ . 67% CSF penetration. Renal clearance.

**Toxicity:** hemolytic anemia, mild lymphopenia, hyperuricemia, itching, rash, cough and nasal stuffiness.

**Foscarnet (iv):**

**Activity** - HSV, HZV, and CMV.

**Toxicity** - nephrotoxicity, hypocalcemia (total may be normal in face of severely diminished ionized calcium), hypomagnesemia, hyper- and hypophosphatemia, hypokalemia, hypertension, seizures, diabetes insipidus, fatal arrhythmias, hypotension and genital ulcers. Vigorous fluid loading diminishes nephrotoxicity. IV pentamidine may potentiate foscarnet-mediated hypocalcemia.

**Pharmacology** - Renally excreted.

**Dosage** - Induction at 60 mg/kg over 1° q 8° for two weeks then maintenance at 90 - 120 mg/kg iv qd given over 2°; infusion pump is mandatory. Given by central vein at dilution of 24 mg/ml, by peripheral vein at 12 mg/ml (must be diluted to avoid phlebitis). Administer at a maximum rate of 1 mg/kg/min to minimize acute metabolic abnormalities.

**Resistance:**

CMV: Occurs through mutation in CMV UL54 (DNA polymerase) gene.

**Cidofovir** (HPMPC; Vistide™):

**Toxicity** - Nephrotoxicity is the major dose-limiting toxicity. Also 20% neutropenia, and probenecid toxicity (fever, nausea/vomiting, rash). Occasional uveitis/iritis; rare hearing loss.

**Contraindications:** Because of irreversible nephrotoxicity, use of cidofovir is contra-indicated in patients with a serum creatinine > 1.5 mg/dL, a creatinine clearance < 55 ml/min, urine protein ≥ 100 mg/dL (≥ 2+) or who have received any nephrotoxic drugs (e.g., foscarnet, amphotericin B, aminoglycosides, NSAID, IV/IM pentamidine) within 7 days.

**Administration:** Use of cidofovir requires careful attention to intravenous hydration and the mandatory concomitant use of high-dose probenecid. All infusions of cidofovir must be given under direct medical supervision. Advantages include the infrequent dosage and thus the avoidance of semi-permanent intravenous catheters. *Decrease dosage* to 3 mg/kg if creatinine increases to 0.3 - 0.4 mg/dL above baseline. *Indications for discontinuance* if creatinine increases to ≥ 0.5 mg/dL above baseline or 3+ proteinuria develops.

**Indications:** CMV, ? utility with smallpox (JID 2000;181:10).

**Resistance:**

CMV: Occurs through mutation in CMV UL54 (DNA polymerase) gene.

**Entecavir** (Baraclude): deoxyguanosine analog.

**Activity:** Reverse transcriptase inhibitor active against HBV. No activity against HIV.

**Resistance:** 8- to 30-fold ↓ activity with 3TC-resistant HBV. >70-fold ↓ activity with primary 3TC resistance mutations (rtL180M and/or rtM204V/I) plus mutations at rtT184, rtS202, or rtM250, or ± rtI169 substitution.

**Pharmacology:** 0.5 mg qd; increase to 1 mg qd for patients with HBV viremia while on 3TC or known 3TC-resistance. Dosage adjustment of for patients with a creatinine clearance <50 mL/min.

**Telbivudine** (Tyzeka™): synthetic thymidine nucleoside analogue

**Activity:** Reverse transcriptase inhibitor active against HBV; chain terminator. No activity against HIV.

**Resistance:** ↓ activity with 3TC-resistant HBV harboring rtM204I mutation or rtL180M/rtM204V double mutation; maintains activity in presence of rtM204V single mutation. Cross-resistance with adefovir rtA181V mutation but not the rtN236T mutation

**Pharmacology:** 600 mg qd. Dosage adjustment of for patients with a creatinine clearance <50 mL/min. No drug-drug interactions with other nucleos(t)ide agents

## SPECIAL FEATURES OF ANTIBIOTICS

**Potential of G6PD mediated hemolytic anemia:** sulfonamides, dapsone, nitrofurantoin, furazolidine, diaminophenylfulfone, chloramphenicol, nalidixic acid, primaquin, niridazole

**Altered effect of oral hypoglycemics:**

**Increased action:** sulfamonomides, chloramphenicol

**Decreased action:** rifampin

**Decreased theophylline excretion:** Norflaxacin, ciprofloxacin, perfloxacin, enoxacin, erythromycin.

**Neurotoxicity**

**Post-operative respiratory depression:** clindamycin, colistin, aminoglycosides, bacitracin

**Potential or induction of myasthenia gravis:** colistin, polymyxin B, aminoglycosides, tetracyclines.

**Seizures:** megadosage of penicillin or imipenem, especially in renal failure. Quinolones may reduce seizure threshold.

**Usable during pregnancy:** Penicillins and cephalosporins (except agents associated with platelet dysfunction near delivery), erythromycin (except for estolate preparation), INH, ethambutol, clindamycin, nitrofurantoin (avoid in last trimester), sulfa (except third trimester), spectinomycin (last trimester only), rifampin (avoid if possible).

**Avoid in pregnancy**

**Aminoglycosides:** potential cochlear, vestibular and renal dysfunction.

**Chloramphenicol:** avoid near term (gray-baby syndrome)

**Pyrimethamine:** megaloblastic anemia, if use is mandatory give with leucovorin

**Quinolones:** cartilage toxicity (avoid before puberty).

**Tetracyclines:** avoid before puberty

**Other:** Clarithromycin, metronidazole, mebendazole, ethionamide, griseofulvin, primaquine, vancomycin (ototoxic).

**Platelet dysfunction** (inhibition of aggregation)

Expanded-spectrum penicillins and moxalactam

**Potential of warfarin:** Sulfa, chloramphenicol, quinolones, metronidazole, and broad spectrum antibiotics which suppress the gut flora.

**Inhibition of vitamin K metabolism:** Methylthiotetrazole ring-containing cephalosporins (cefamandole, cefotetan, moxalactam, cefoperazone, cefmetazole).

**Disulfiram reactions:** Metronidazole and methylthiotetrazole ring-containing cephalosporins

**Nephrotoxicity**

**Hypersensitivity glomerular damage (rare):** penicillins, sulfa

**Fanconi syndrome:** tetracycline degradation products

**Tubular toxicity:** aminoglycosides, polymyxin, cephaloridine, vancomycin

**Interstitial nephritis:** beta-lactam antibiotics

**Tubular obstruction:** sulfa

**Ototoxicity:** aminoglycosides, vancomycin, high-dose erythromycin

**Cerebrospinal fluid penetration**

**Good:** sulfa, chloramphenicol, isoniazid, rifampin, minocycline, metronidazole

**Fair:** penicillins (nafcillin > methicillin), 3rd generation cephalosporins, vancomycin.

**Effective treatment for chronic prostatitis:** Trimethoprim, doxycycline, quinolones.