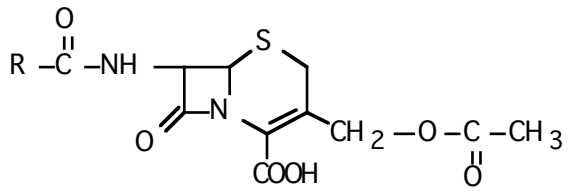
B. CEPHALOSPORINS



1. Development

2. Properties

   a) broad spectrum
   b) low toxicity
   c) methicillin sensitive staph is usually sensitive to cephs but they are not agent of choice for Staph. MRSA is usually resistant
   d) Generations
      1st - better Gm(+) than Gm(–) activity, susceptible to most Gm(–) beta lactamases; now are generic
      2nd - more resistant to Gm(–) beta lactamases some are generic now
      3rd - increased potency and penetration and resistance to Gm(–) beta lactamses; some have activity against Pseudomonas
      4th - even more than 3rd, often active against Pseudomonas
   e) cleared renally (except cefoperazone)
   f) Probenecide ↓ elimination rate but rarely used
   g) distribution – similar to Pen G except that only cefuroxime and some 3rd and 4th generation penetrate CNS
   h) metabolism 5-30%
   i) toxicity – like the penicillins, is generally low

      i. renal – low but significant in patients with impaired renal function
      ii. GI overgrowth, colitis
      iii. bleeding – those cephalosporins with the methyl tetrazole ring (cefamandol, cefotetan, cefmetazole, cefoperazone) have some risk of bleeding. Mechanisms involve (1) decreasing gut flora and therefore vitamin K, (2) direct interaction with prothrombin, and (3) platelet dysfunction. The phenomenon is best associated with Moxalactam (2-3% with fatalities reported) (no longer on the market) but is possible for any cephalosporin with the methyl tetrazole ring.
      iv. disulfuram like reaction – cephalosporins with the methyl tetrazole ring have the potential to inhibit aldehyde dehydrogenase resulting in a sick feeling when alcohol is taken with these drugs or up to 72 h after
      v. *C. difficile* overgrowth is possible → diarrhea, colitis, pseudomembranous colitis

3. Absorption – some orally absorbed; others IM or IV

4. Allergy – 5-10% cross reactivity with penicillin allergy

5. Cephalosporin spectrum

   a) Gram-positive – including penicillinase producers (older 1st generation better here)

      i. Staph – but penicillinase resistant penicillins are agents of choice; MRSA=no
      ii. Strep but not *Enterococcus faecalis* or *E. faecium* or PRSP
      iii. otherwise similar to Pen G except less potent

b) Gram-negative (2nd, 3rd, 4th generations are better)
   i. *E. coli* - usually sens.
   ii. *Proteus*; 2nd and 3rd generation also active against *Morganella, Providencia,* and *Serratia*.
   iii. *Salmonella*
   iv. *Shigella* – usually sen.
   v. *Neisseria meningititis* – useful if ceph. will enter CSF
   vi. *Neisseria gonorrhoeae* – OK, particularly ceftriaxone, cefixime, and cefpodoxime which are agents of choice
   vii. *H. influenza* – 2nd, 3rd and 4th generations are better
   viii. *Klebsiella – K. pneumonia* – usually sen., and is important use of Cephs.
   ix. *Enterobacter and Pseudomonas* – only 3rd and 4th generations; sensitivity varies
   x. Anaerobes – Cefoxitin, cefmetazole, cefotetan and some 3rd generation only

6. Use

   a) respiratory infections – gram-positive and gram-negative, Klebsiella
   b) sepsis – especially mixed infections using 3rd or 4th generations
   c) surgical prophylaxis – first or 2nd generations
   d) meningitis – some will penetrate CSF and cover *E. coli, Klebsiella pneumoneae, Serratia*, and *Neisseria meningitidis*
   e) UTI – very high renal conc.
   f) alternate drug for penicillin allergic patient, for penicillinase resistant penicillins, for staph infections

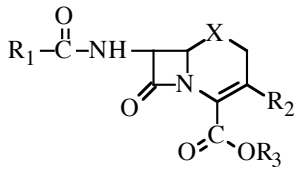
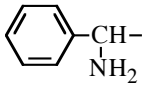
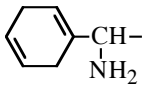
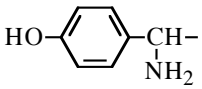
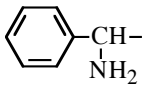
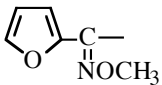
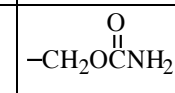
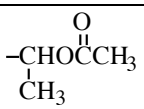
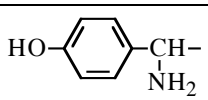
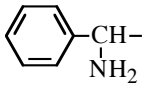
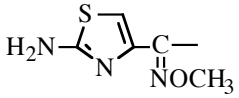
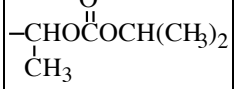
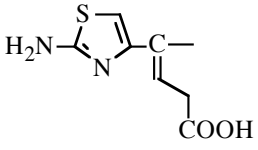
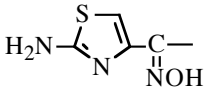
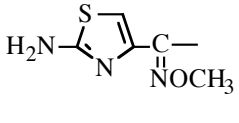
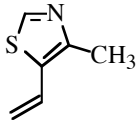
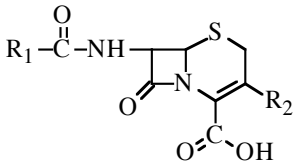


Table - Oral Cephalosporins

generation	name	brand name	structure				dose
			R_1	R_2	R_3	X	
1	cephalexin	generic		$-CH_3$	—H	—S—	QID
1	cephradine	generic		$-CH_3$	—H	—S—	BID
1	cefadroxil	generic		$-CH_3$	—H	—S—	BID
2	cefaclor	generic		—Cl	—H	—S—	TID
2	cefuroxime axetil	generic				—S—	BID
2	cefprozil	Cefzil®		$-CH=CHCH_3$	—H	—S—	BID

2	loracarbef	Lorabid®		–Cl	—H	–CH_2–	BID
3	cefpodoxime proxetil	Vantin®		–CH_2OCH_3		–CH_2–	BID
3	ceftibutin	Cedex®			—H	—S—	qd
3	cefdinir	Omnicef®		–CH=CH_2	—H	—S—	BID
3	cefditoren pivoxil	Spectracef®			–$CH_2OCOC(CH_3)_3$	—S—	BID



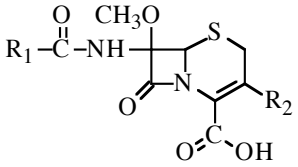
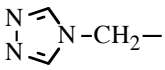
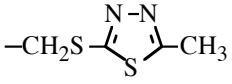
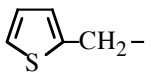
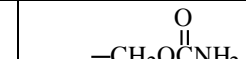
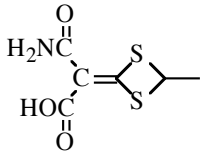
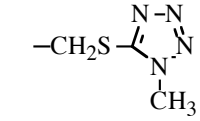
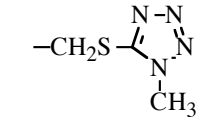
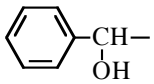
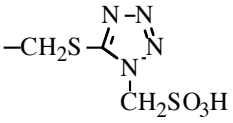
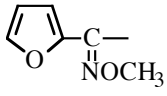
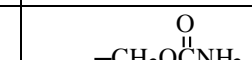
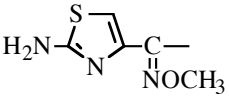
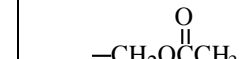
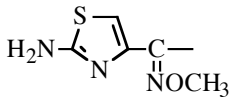
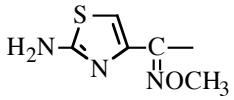
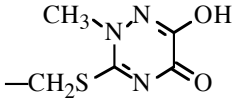
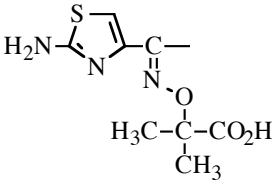
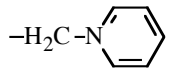
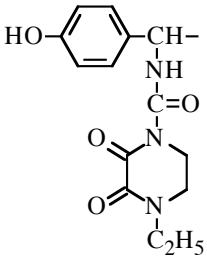
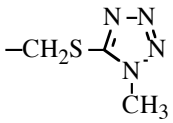
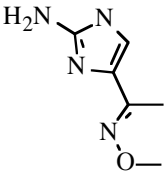
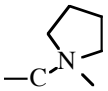


Table - Parenteral Cephalosporins and Cephamycins Cephalosporin *Cephamycin

generation	name	brand name	structure		dose
			R_1	R_2	
1	cefazolin	generic			TID
2	cefoxitin*	generic			QID
2	cefotetan*	Cefotan®			BID
2	cefmetazole*	Zefazone®	$NCCH_2SCH_2$—		TID
2	cefonicid				
2	cefuroxime	generic			TID
3	cefotaxime	Claforan®			TID

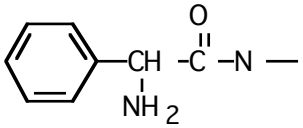
3	ceftizoxime	Cefizox®			TID
3	ceftriaxone	Rocephin®			qd
3	ceftazidime	generic			TID
3	cefoperazone	Cefobid®			BID
4	cefepime	Maxipime®			BID

7. Formulary Oral Cephalosporins

a) General comments: used for follow-up and ambulatory patient therapy, UTI (pen. Allergic), otitis media, staph. URI, LRI

b) First Generation

Cephalexin Keflex ® Dista and generics



Indications:
1) respiratory tract – *Strep. pneumoniae* and *Strep. pyogenes*
2) otitis media – *Strep. pneumonia, H. flu, M. cat.* (the *H. flu* and *M. cat* may be resistant)
3) skin – *Staph., Strep.*
4) bone – *Staph., Proteus mirabilis*
5) GU – *E. coli, Klebsiella, Proteus mirabilis*

c) Second Generation – not on formulary in 2008

Cefuroxime Axetil Ceftin® Glaxo Wellcome and generic
Broad spectrum oral cephalosporin that gets into CNS
Indications:
1) pharyngitis and tonsillitis – *Strep. pyogenes*

2) otitis media – *Strep. pneumoniae, M. cat., H. flu*, including β-lactamase producing
3) sinusitis – *Strep. pheumoniae, H. flu*
4) exacerbation of chronic bronchitis – *Strep. pneumoniae, H. flu, H. parainfluenzae*
5) UTI – *E. coli, Klebsiella, Proteus*
6) skin – *Staph., Strep.*
7) GU – *E. coli, Klebsiella, Proteus*
8) impetigo – *Staph., Strep.*

d) Third Generation

Cefpodoxime proxetil Vantin® Pharmacia and now generic

Broad spectrum, beta lactamse resistant cephalosporin with an unusual structure
Indications:
1) acute CAP Strep. pneumo, H. flu, M. cat
2) chronic bronchitis Strep. pneumo., H. flu, M. cat
3) otitis media
4) pharyngitis
5) STD - N. gonorrheae, 200mg stat single dose
6) uncomplicated skin infections Staph., Strep. pyogenes
7) UTI

e) cefdinir Omnicef ® Abbott – suspension only is on formulary; good taste

8. Formulary parenteral Cephalosporins

a) First Generation

Cefazolin (generic)
T1/2 = 1.8 h.
0.5 – 1 g q. 8 h.
1M or IV

b) Second Generation

Cefuroxime (generic)
1) introduced in 1984
2) T1/2 = 1.5 h. ∴ q. 8 h. dosing
3) penetrates CSF well and ∴ used successfully for meningitis

c) Third Generation

Cefotaxime (generic)
1) desacetyl metabolite is active ∴ high urine levels
2) T1/2 - ~ 1 h. q. 4-6 h. doses

Ceftriaxone (generic)

1) very active against N. gonorrhea – 250 mg stat dose used
2) penetrates CSF
3) T1/2 6-8 h. ∴ once a day dose used
4) convenient, potent antibiotic; not the best for *Pseudomonas* infections

Ceftazidime (generic)
Tazidime ® Lilly
1) good Pseudomonas activity
2) penetrates CNS
3) BID – TID dose

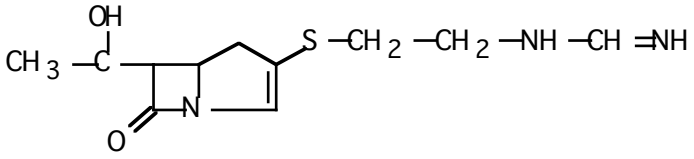
d) Fourth Generation

Cefepime Maxipime ® Bristol-Myers Squibb
1) is more resistant to beta lactamases than others
2) relatively resistant to chromosomal beta lactamases and does not induce these enzymes like other cephalosporins
3) good Gm (+) activity as well
4) note: now has an FDA warning of neurotoxicity (encephalopathy, myoclonus, seizures). Mostly observed in patients with renal impairment.

C. CARBAPENEM ANTIBIOTICS

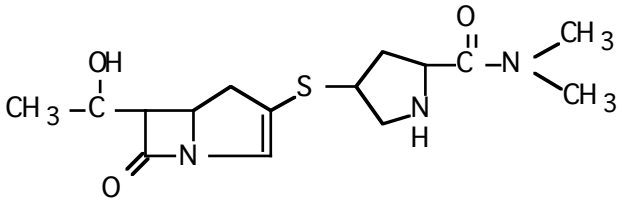
1. General Comments
   a) lack the sulfur in the 5-membered ring but still retain the beta lactam bond
   b) are similar in structure to penicillins but have a spectrum broader than penicillins and cephalosporins
   c) are very resistant to beta lactamases including type 1
   d) MRSA and PRSP are resistant because of altered PBP's
   e) some Pseudomonas are resistant due to altered porin channels
   f) E. faecalis is usually resistant and E. faecium is almost always resistant
   g) all are on the UW formulary
   h) none are absorbed orally
   i) The drugs induce chromosomal beta lactamases though they are not hydrolyzed. Don't switch to a cephalosporin after carbapenem therapy

2. Imipenem/Cilastatin Primaxin ® MSD- formulary drug



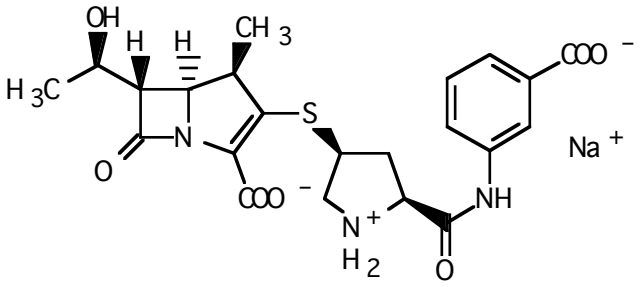
   a) the first carbapenem available
   b) Cilastatin inhibits renal dipeptidase which would otherwise inactivate the antibiotic in urine
   c) 0.5 g q. 6 h. is a common IV dose
   d) not approved for meningitis due to risk for seizures (~1.5%) but has 9 approved indications
   e) nausea if push IV dose too fast

3. Meropenem Merrem ® Zeneca, approved June 1996 - formulary



   a) for now only indicated for intra-abdominal infections caused by Strep. viridans, E. coli, K. pneumoniae, P. aeruginosa, B. fragilis, B. thetaiotaomicron Peptostreptococcus, and bacterial meningitis caused by Strep. pneumonia, H. flu, N. mengingitidis
   b) less seizures (0.4%) and less nausea than imipenem
   c) 1 g q 8h
   d) not MRSA or PRSP

4. Ertapenem Invanz ® Merck, approved Nov 2001 - formulary



a) 1 g q d dosing IV or IM
b) has Gram(+), Gram(-) and anti-anaerobic activity; not MRSA or PRSP or pseudomonas
c) good for polymicrobial not involving Pseudomonas
d) FDA approved for
   1) complicated intraabdominal infections
   2) complicated skin infections
   3) complicated UTI
   4) pelvic infections
   5) community acquired pneumonia

5. Doripenem Doxibax® Ortho-McNeil - not on formulary in 2008
   a) IV drug approved in 2007
   b) approved for treatment of complicated intra-abdominal and complicated urinary tract infections including pyelonephritis.
   c) pending approval for nosocomial pneumonia
   d) excellent activity against Gram negatives (including Pseudomonas) and anaerobes

D. MONOBACTAM ANTIBIOTICS

1. Aztreonam Azactam ® Squibb-formulary drug

   a) synthetic

   b) mostly gram-negative aerobic spectrum (similar to an aminoglycoside); has 8 approved indications for Gram Neg. infections

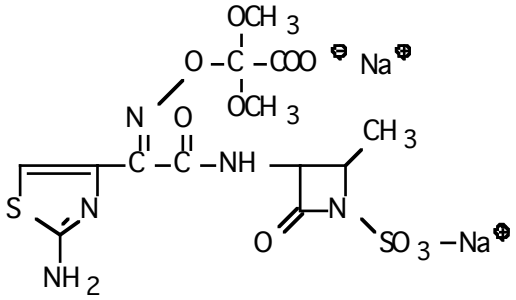
   c) defined, narrow, useful spectrum

   d) highly resistant to β-lactamases and does not induce these enzymes

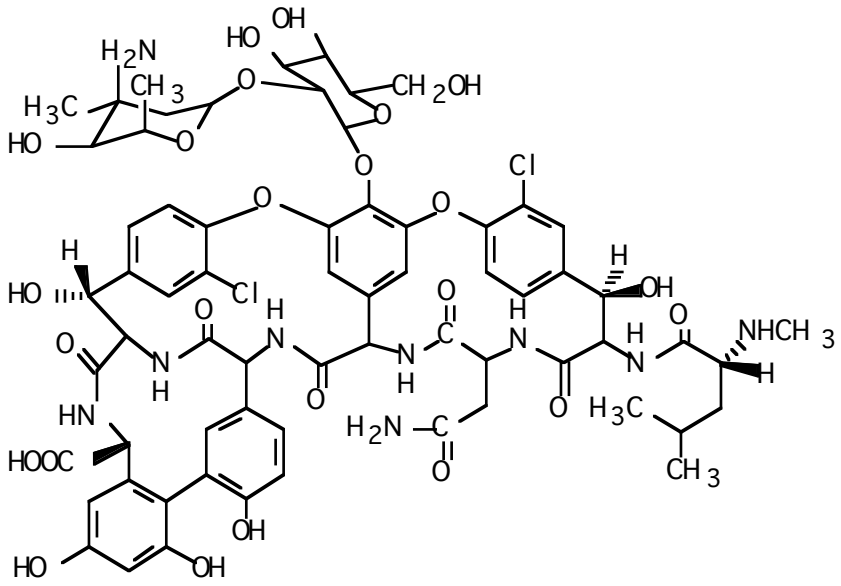
   e) dose 1-2 g q 8-12 h.

   f) no cross allergy with penicillins

   g) is on the UW formulary



E. VANCOMYCIN (UW Formulary drug)



1. Chemistry-History

   Vancomycin is a glycopeptide antibiotic (MW=1450) isolated from Streptomyces orientalis. It was introduced in 1956 for use in penicillinase producing Staph. The spread of methicillin resistant Staph. (MRS) and Enterococcus has made Vancomycin an important drug. The original product was rather impure and associated with hypersensitivity, ototoxicity, and nephrotoxicity. In 1986 a new highly purified formulation was introduced that has fewer adverse effects.

2. MOA

   Inhibits the attachment of the phospholipid pentapeptide to the cell wall acceptor (see earlier notes)

   Binds to d-ala-d-ala of peptidoglycan monomer

   Is bacteriocidal for growing cells

3. Spectrum

   Has a rather narrow but useful spectrum against Gram-positive bacteria. No cross resistance with other cell wall inhibitors.

   a. Staph aureus and Staph epidermidis including MRSA and beta lactamase producing strains. Synergistic with aminoglycosides.

   b. *Enterococcus faecalis* and *Enterococcus faecium*. Synergistic with aminoglycosides; vancomycin resistant Enterococcus (VRE) is a worry. E. faecium resistance is common but this is a less common infection.

   c. Anaerobes. Used for *Clostridium difficile* as alternative to metronidazole. Is a "stronger" treatment.

   d. Strep. - is alternative agent for serious infections resistant to other agents

4. Uses

   a. Agent of choice for methicillin res. Staph and Staph epidermidis. May be combined with an aminoglycoside or rifampin for MRS.

   b. As alternative drug for endocarditis caused by Strep or other serious Strep infections resistant to beta lactams (e.g. PRSP).

   c. As important drug for use against *Enterococcus faecalis.* Combine with an aminoglycoside.

   d. C. difficile. The dose is 500 mg QID x 10d or 125 mg QID x 10d
   Metronidazole is preferred for initial infections.
   C. difficile MIC for vanco is ~ 4 μg/ml. The concentration of vancomycin in stool with 500 mg QID is ~ 3.1 mg/ml.

5. Resistance

   Fortunately, resistance is rare at present but is increasing. "Van A" gene codes for decreased binding and leads to high level vancomycin resistance. "Van B" and "Van C" may lead to intermediate resistance. "Van A" codes for d-ala-d-lactate instead of d-ala-d-ala.

6. Disposition and Excretion

   Poor oral absorption. Rather poor CNS penetration. Renally cleared and dose must be adjusted in renal disease.

7. Adverse Effects

   a. Hypersensitivity reactions, rash, 3%

   b. Phlebitis, 13% (rarely used IM due to irritation)

   c. Red Man Syndrome. Occurs with rapid infusion of large doses, red over upper body. Often associated with hypotension. Avoid rapid infusion. Pain and muscle spasms also with rapid infusion.

   d. Ototoxicity. Rare now but be careful in older patients and when drug is used with aminoglycosides.

   e. Nephrotoxicity. Reversible and often associated with use of Vanco with amino-glycosides.

8. Products

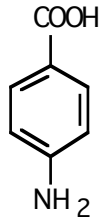
   As capsules (remember this is topical gut therapy only), powder for oral solution and powder for injection, the capsules are mainly used for C. difficile.

9. Teicoplanin Targocid ® Aventis (not UW formulary drug)
   - Glycopeptide with structure similar to vancomycin
   - has longer $T_{1/2}$ (can give qd), can be given IM, and is less irritating when given IV.
   - long available in many countries but not in USA; approval here pending

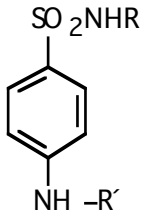
10. – Dalbavancin- modified Teicoplanin molecule; may be approved soon. Is more active against VRSA and GISA than vanco

F. FOLIC ACID ANTIMETABOLITES

SULFONAMIDES AND TRIMETHOPRIM



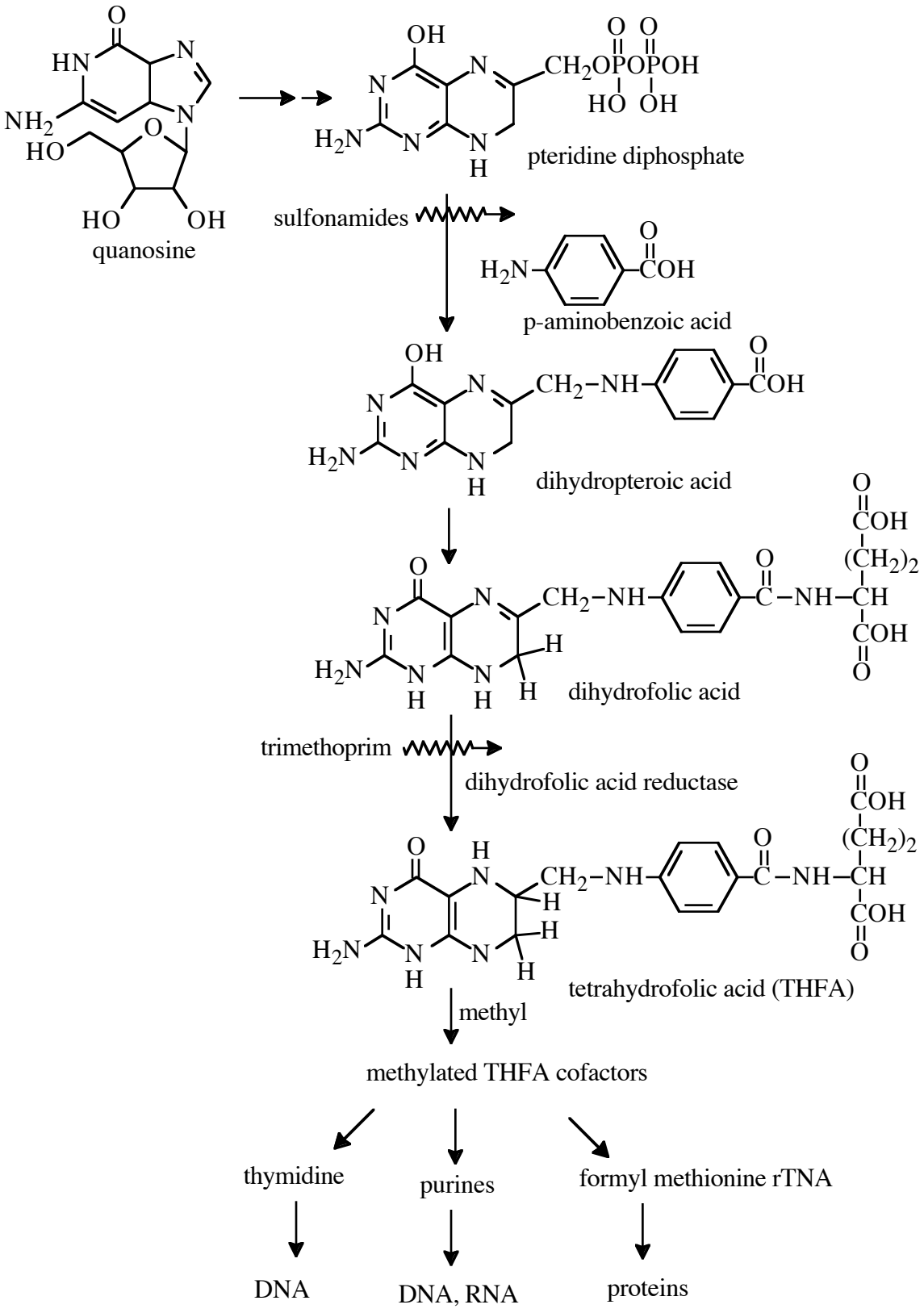
PABA



Sulfonamide

1. MOA – competitive inhibitor for PABA in the biosynthesis of folic acid; bacteriostatic

2. Biosynthesis of folic acid in bacteria



Mammalian cells take up preformed folic acid or dietary folates by an active transport process. Bacteria do not have this transport and hence make their own folic acid.

2. Spectrum – have rather broad spectrum of antimicrobial activity, are bacteriostatic drugs and don't work well in purulent infections due to the presence of thymine and purines. Because of their long history of use, resistance is a problem. They are commonly used to treat acute UTI. The combination with trimethoprim is more useful in therapy (see below).
   a) *E. Coli*
   b) *Proteus mirablis*
   c) *H. influenza*
   d) *N. meningitidis* - now largely resistant and ideally you want a bacteriocidal drug
   e) *toxoplasma gondii*
   f) etc., but development of resistance has lessened the contribution these agents make to therapy; still useful in uncomplicated UTI and together with trimethoprim (see below) in a variety of infections. Have little activity against anaerobes and because of their bacteriostatic activity, are not used for strep infections.

3. Excretion - renal; metabolism is via hepatic acetylation - slow acetylators may experience increased toxicity

4. Distribution - penetrates into CNS and middle ear and prostate gland

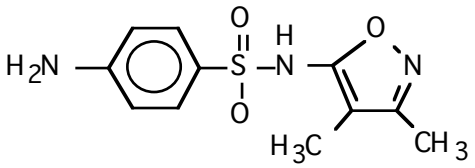
5. Adverse Reactions - hypersensivity reactions to sulfas → rash (this is quite common, ~10%), eosinophilia, fever; crystalluria, kernicterus, hemolytic anemia in glucose-6-phosphate dehydrogenase def. patients, rare Stevens Johnson Syndrome; photosensitivity reactions may occur. Due to risk of kernicterus, not for infants < 2 mos. of age.

6. Products systemic
   a) sulfisoxazole - UTI drug
   b) sulfadiazine - chloroquin resistant Plasmodium falciparum (malaria)
   c) trimethoprim-sulfanethoxazle - see below
   d) sulfadoxine-pyrimethamine Fansidar® Roche - chloroquin resistant Plasmodium falciparum
   e) sulfadiazine-pyrimethamine - toxoplasmosis
   f) pyrimethamine - malaria (resistance ↑)
   g) trimethoprim - UTI
   h) Dapsone - leprosy

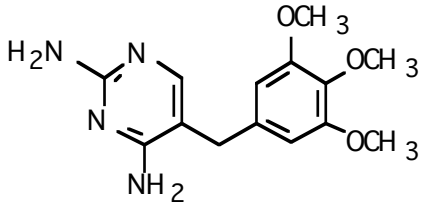
7. Patient counseling
   a) take with full glass of water
   b) notify if fever, yellowing of skin, rash or bleeding occurs

8. UW formulary sulfur drugs and combinations

a) Sulfisoxazole-: 2-4 g stat, then 1 g q. 4-6 h; 3% require discontinuation due to rash, fever, and GI upset; T1/2 = 5 h



b) Trimethoprim - Sulfamethoxazole (TMP-SMZ, cotrimoxazole)
Bactrim ® Roche and generic



trimethoprim

inhibits DHFA reductase

Table 7–4. Binding of trimethoprim to bacterial and mammalian dihydrofolate reductases. Folate reductase, purified from bacteria or from mammalian livers, was incubated with 50 μM dihydrofolate, NADPH, and varying concentrations of trimethoprim. Enzyme activity was recorded by the change in absorbance at 340 nm. The values in the table represent the concentrations of trimethoprim required for 50% inhibition of the enzyme activity. Thus, 60,000 times as much trimethoprim is required to inhibit the human enzyme as is required to inhibit that of *E. coli.*

Source of enzyme	Trimethoprim concentration required for 50% inhibition (n*M*)
BACTERIAL	
Escherichia coli	5
Staphylococcus aureus	15
Proteus vulgaris	5
MAMMALIAN	
Rat	260,000
Rabbit	370,000
Human	300,000

Source: Data from Burchall and Hitchings.[56]

1) A 1:4 ratio of TMP-SMX; double hit on bacterial folate coenzyme biosynthesis

2) T1/2 for both is 10-16 h. BID dosing

3) Spectrum
- includes sulfur drug spectrum but has broader activity due to decreased resistance to this combination
- E. coli, other Enterobacteriaceae, Klebsiella, Enterobacter, Morganella, Proteus vulgarus, Proteus mirabilis, H. Influenzae
- Pneumocystis carinii
- Strep. pneumoniae maybe
- MRSA, community strains may be sensitive
- Shigella
- Salmonella
_ Stenotrophomonas maltophilia may be sensitive

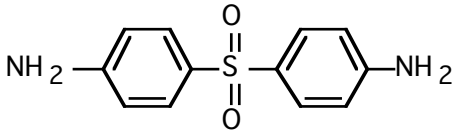
4) Uses
- UTI
- Salmonella
- Pneumocystis carinii pneumonia - in HIV infected patients; used for prophylaxis treatment

- otitis media
- bronchitis
- traveler's diarrhea
- acute and chronic prostatitis
- community MRSA
- other

5) Adverse effects: No more than SMX alone; possible rash, pruritis, GI upset; if patient is low in folic acid, can cause megaloblastic anemia (folate dep.)

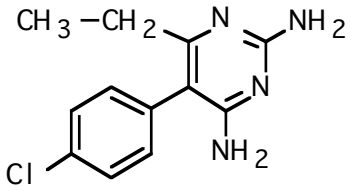
c) Trimethoprim alone (Proloprim ® BW, Trimpex ® Roche) for sulfa allergic patient; FDA allowed indications as "For initial episodes of acute, uncomplicated UTI due to susceptible strains"

d) diaminodiphenylsulfone (dapone)



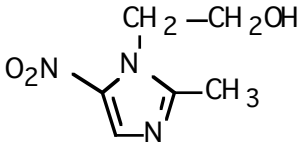
- has high affinity for PABA site in synthesis of folic acid in Mycobacterium leprae but low for other bacteria
- sometimes used alone or in combination with TMP-SMX for Pneumocystis carinii pneumonia.
- diminished use as a single agent for significant infections due to ↑ resistance

h) Pyrimethamine



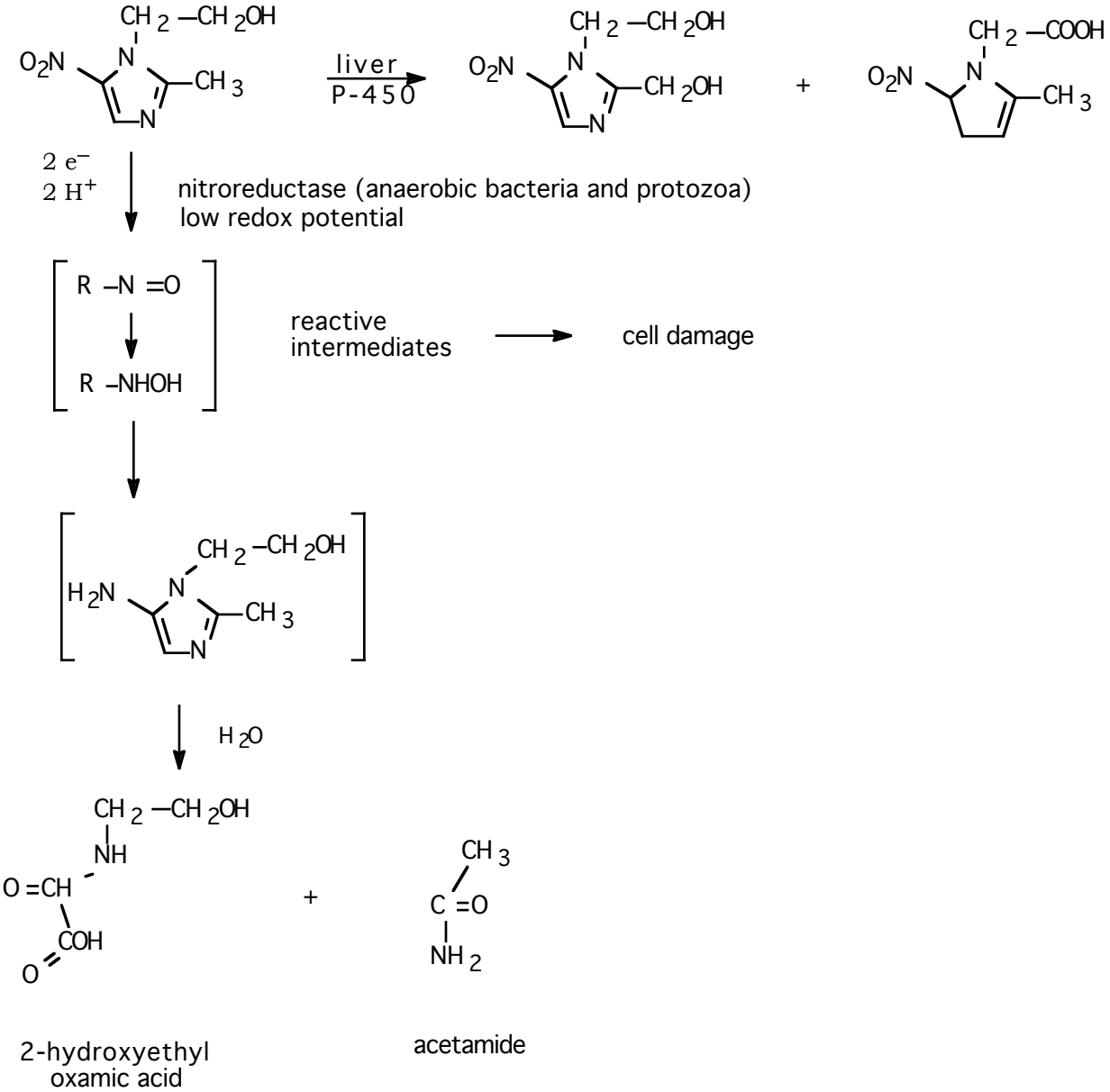
- is a folic acid antagonist for Plasmodium sp.
- used with sulfadoxine (Fansidar®) for prophylaxis for malaria

G. METRONIDAZOLE, FLAGYL® Pharmacea and generics; is UW Formulary drug



a) History - primarily developed for protozoal infections

b) Metabolism - "suicide substrate" for anaerobes



c) Spectrum

1) excellent activity against gram-negative anaerobic bacilli, e.g. Bacteroides, also gram-positive anaerobes
2) antiprotozoal
3) has bacteriocidal activity

d) Properties

1) well absorbed and good tissue levels and CSF levels

e) Uses

1) *Trichomonas vaginalis* "Tric"
   2 g stat dose or 4 tabs BID x 1d or 250 mg TID x 7d; treat male partner also
2) *Amebiasis (Entamoeba histolytica)* – 750 mg TID x 10d
3) Giardiasis - 250 mg TID x 7
4) anaerobic bacterial infections - IV use for serious infections
5) Bacterial vaginosis (BV) - associated with Gardnerella vaginalis and many anaerobes - 0.5 g BID x 7, also 2 g stat dose
6) Helicobacter pylorii - used together with tetracycline and Bismuth, or amoxicillin or clarithromycin
7) Clostridium difficile - 1 g/d x 10d; is "first time" therapy
8) topical use in acne
9) CNS infections, often together with another antibiotic to cover aerobes

f) Adverse effects

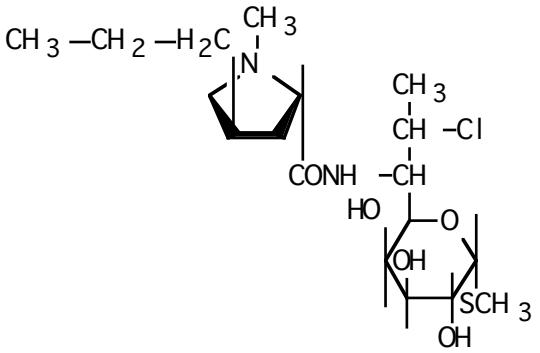
1) metallic taste, nausea, disulfuram reaction, rare peripheral neuropathy
2) is CYP2C9 inhibitor therefore interactions with warfarin, tolbutamide, diclofenac, etc.
3) teratogenic ?
4) carcinogenic ?

} CDC now considered safe but prudent use is warranted as long term, high dose feeding to rats and mice result in tumors

g) Patient counseling
1) avoid alcohol during and for up to 3d after stopping

H. BACTERIOSTATIC INHIBITORS OF BACTERIAL PROTEIN SYNTHESIS

CLINDAMYCIN (Formulary Drug)



1. Chemistry

   Clindamycin is a derivative of Lincomycin, an antibiotic from a soil organism found near Lincoln, Nebraska by workers at Upjohn (then Pharmacia, then Pfizer).

2. Mechanism of Action

   a) Binds to the 50S ribosomal subunit (a site shared by macrolides and chloramphenicol) to prevent translocation. It is bacteriostatic but is 'cidal in high conc. Cross resistance to other drugs binding to 50S ribosomal subunit exists (macrolides & chloramphenicol).

   b) Is metabolized in humans to a N-demethyl inactive metabolite and excreted in urine. Not for urinary tract infections. Sulfation of OH group also occurs.

3. Spectrum

   a) Gram-positive cocci, especially Strep. Staph may be sensitive although resistance is important. *Enterococcus faecalis* and *E. faecium* are resistant.

   b) Anaerobes. This is a big feature of this antibiotic. Good activity against Bacteriodes fragilis and other Bacteriodes sp. Active against other anaerobes and Propionibacterium acnes.

   c) Parasites. Toxoplasma gondii and Pneumocystis carnii (alternative drug)

   d) Others. Gardnerella vaginalis, Chlamydia trachomatis (alternative drug)

   e) Gram (–). resistant (doesn't get in)

   f) Resistance can occur by production of methylated ribosomal binding sites for clindamycin. MRS is resistant to clindamycin.

4. Uses

   a. As an alternative drug for treatment of serious Strep and Staph infections in the penicillin allergic patient. Not 1st or 2nd line drug

   b. Use for nectrotizing faeciitis

c. An important drug for serious anaerobic infections particularly B. frag.; good penetration into bone

d. Topical treatment for acne

e. Alternate drug for Bacterial vaginitis

f. Alternative drug for Toxoplasmosis treatment

g. Alternative drug for Pneumocystis carinii pneumonia

h. Alternative agent for Chlamydia trachomatis pelvic inflammatory disease (PID)

5. Disposition, Metabolism, Excretion

Well absorbed but undergoes hepatic metabolism. Distributed very well into tissues and abscesses but not into CNS. Extensively excreted in bile and undergoes entero hepatic recycling. High gut levels even after IV admin.

6. Adverse Effects

a. diarrhea in 20-30%

b. risk for PMC but no worse than beta lactam antibiotics. "Boxed Warning" on PMC risk on package insert. Risk for topical products is very low as the drug is not absorbed.

c. hepatic toxicity - elevation of transaminases; reversible; rare jaundice

d. hypersensitivity reactions, hematopoietic abnormalities, renal toxicity have been reported.

7. Products

Cleocin ® (Pharmacia) and generic products

capsules, suspension, solution for injection and topical products for acne and for vaginal use

8. Summary

A useful drug for serious anaerobic infections. It is not an agent of choice but an alternative drug. Topical use has minimal risk.

9. Patient counseling

a. Warning about prolonged or severe diarrhea