Sulfonamides

Learning Outcomes

Students/Learners will be able to

- Understand the basic pharmacology of Sulfonamides
- Classify sulfonamides and related drugs
- Outline the Mechanism of Action (MOA) of Sulfonamide
- Summarize microbial resistance to sulfonamides
- Recall the Th. Uses of sulfonamides

- Reflection spot? Think about structure of general sulfonamide??
- Doubt Karo Out
- Pharm-khulash

Sulfonamides

- First AMA against pyogenic bacteria
- Prontosil dye included by G. Domagk
- Prontosil broken down & release sulfonilamide

Demerits/Limitations of Sulfonamides

✓Rapid development of resistance
✓availability of many safer and more effective antibiotics
✓Current use is limited
✓In combination with trimethoprim (as cotrimoxazole)

Chemistry

The basic formulas of the sulfonamides and their structural similarity to p-aminobenzoic acid (PABA)

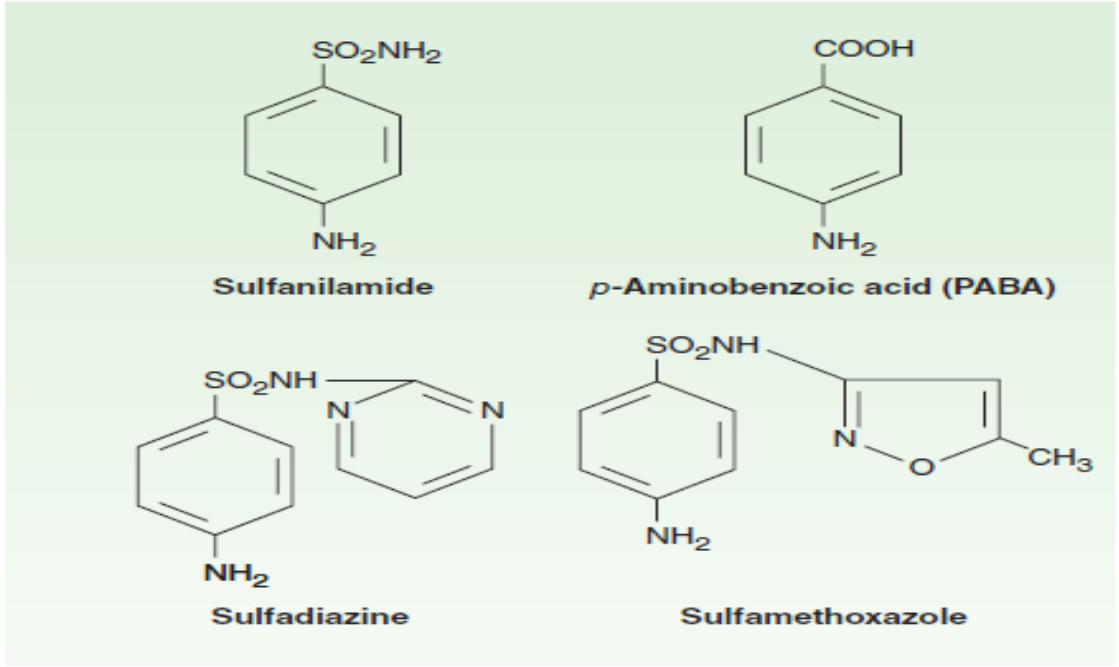
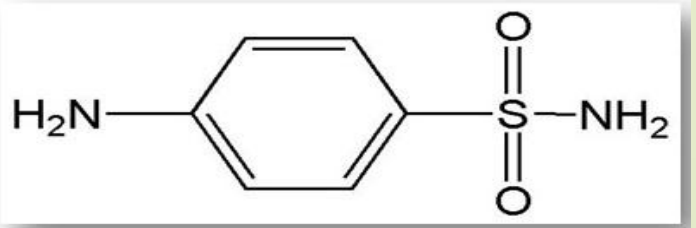
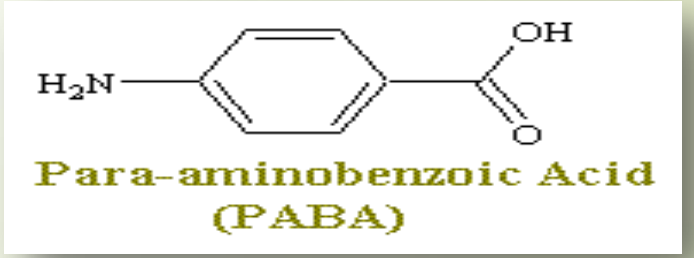


FIGURE 46–1 Structures of some sulfonamides and *p*-aminobenzoic acid.



Basic structure of Sulfonamide



Classifications

1. Short acting	2. Intermediate acting	3. Long acting	4. Special purpose sulfonamides:
• (4–8 hr): • Sulfadiazine	• (8–12 hr): • Sulfamethoxazole	• (~7 days): • Sulfadoxine, Sulfamethopyrazine	• Sulfacetamide sod., Mafenide, • Silver sulfadiazine, Sulfasalazine

SULFONAMIDES

Short acting	Intermediate acting	Long acting	Special purpose
Sulfadiazine	Sulfamethoxazole	Sulfadoxine Sulfamethopyrazine	Sulfacetamide sod. Sulfasalazine Silver sulfadiazine Mafenide

QUINOLONE ANTIMICROBIALS

Nonfluorinated quinolone	Fluoroquinolones	
	First generation	Second generation
Nalidixic acid	Norfloxacin Ciprofloxacin Ofloxacin Pefloxacin	Levofloxacin Moxifloxacin Gemifloxacin Prulifloxacin Lomefloxacin Sparfloxacin

MOA of Sulfonamide

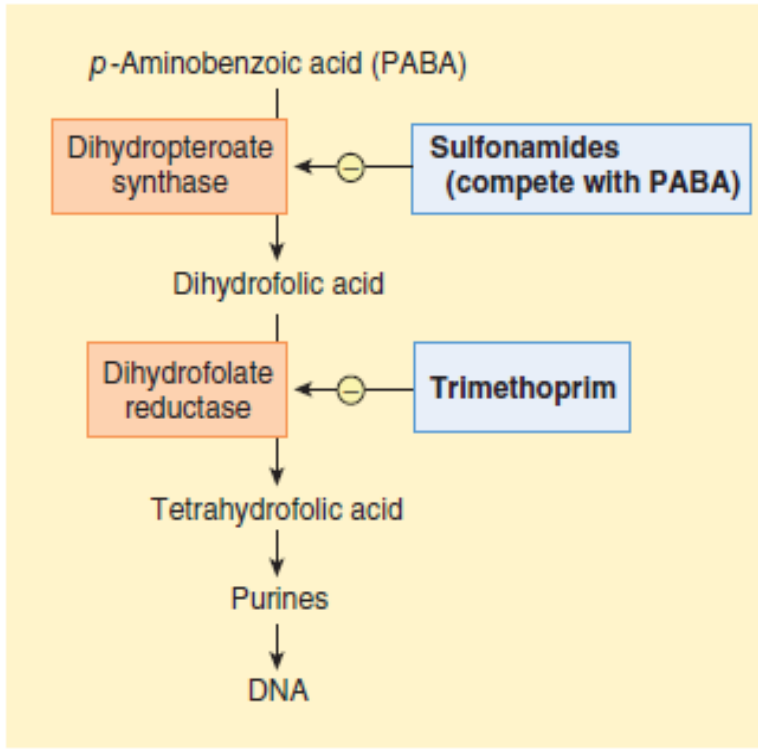
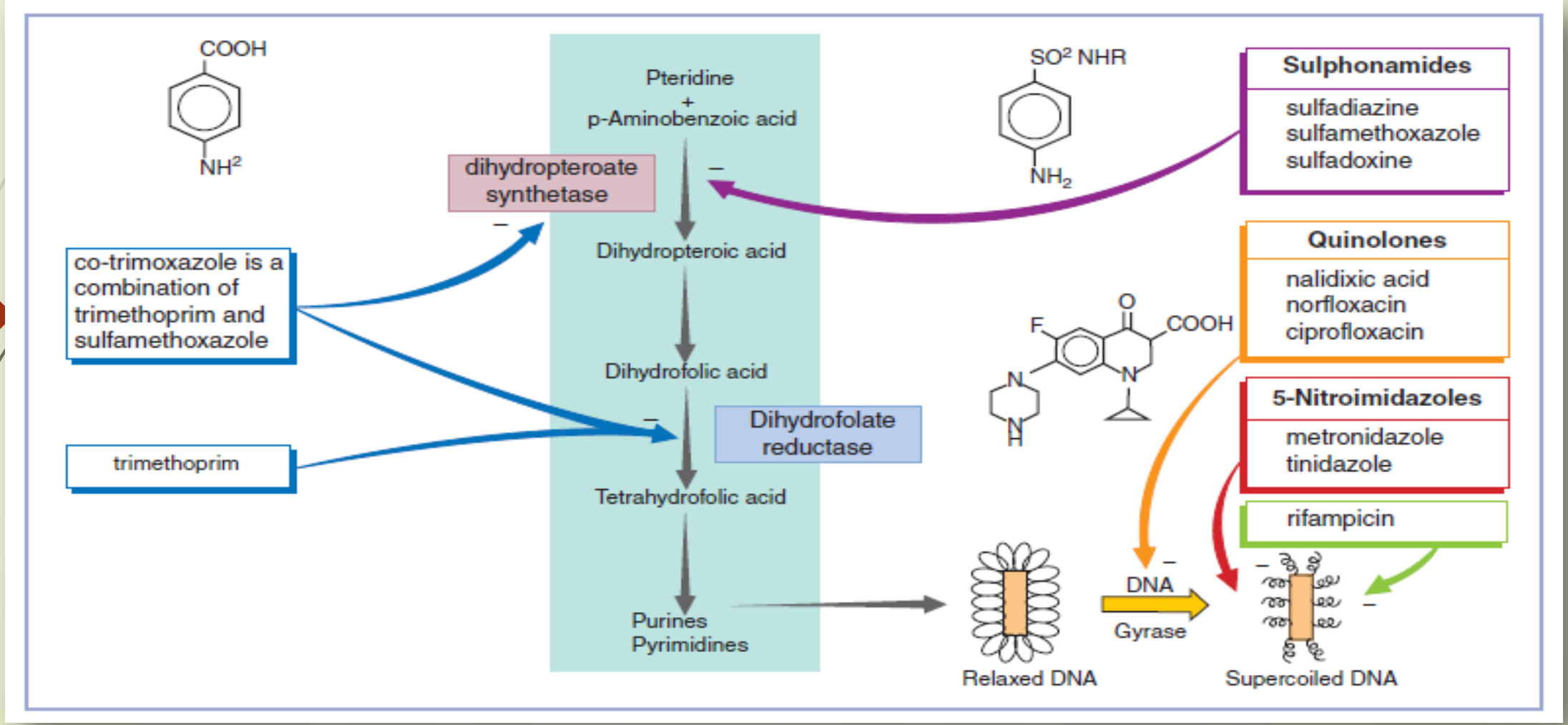


FIGURE 46–1 Inhibitory effects of sulfonamides and trimethoprim on folic acid synthesis. Inhibition of 2 successive steps in the formation of tetrahydrofolic acid constitutes sequential blockade and results in antibacterial synergy.

- Bacteria synthesize their own folic acid (FA) from p-aminobenzoic acid (PABA)
- Structural analogues of PABA, inhibit bacterial folate synthase → FA
- Sulfonamides are bacteriostatic inhibitors of folic acid synthesis.
- Antimetabolites of PABA, they are competitive inhibitors of dihydropteroate synthase
- Sulfonamides competitively inhibit the union of PABA with pteridine residue to form dihydropteroic acid
- Human cells also require FA, but they utilize preformed FA (ready made)
- Pus and tissue extracts antagonize sulfonamide as pus rich in thymidine, purine and PABA

MOA of Sulfonamide



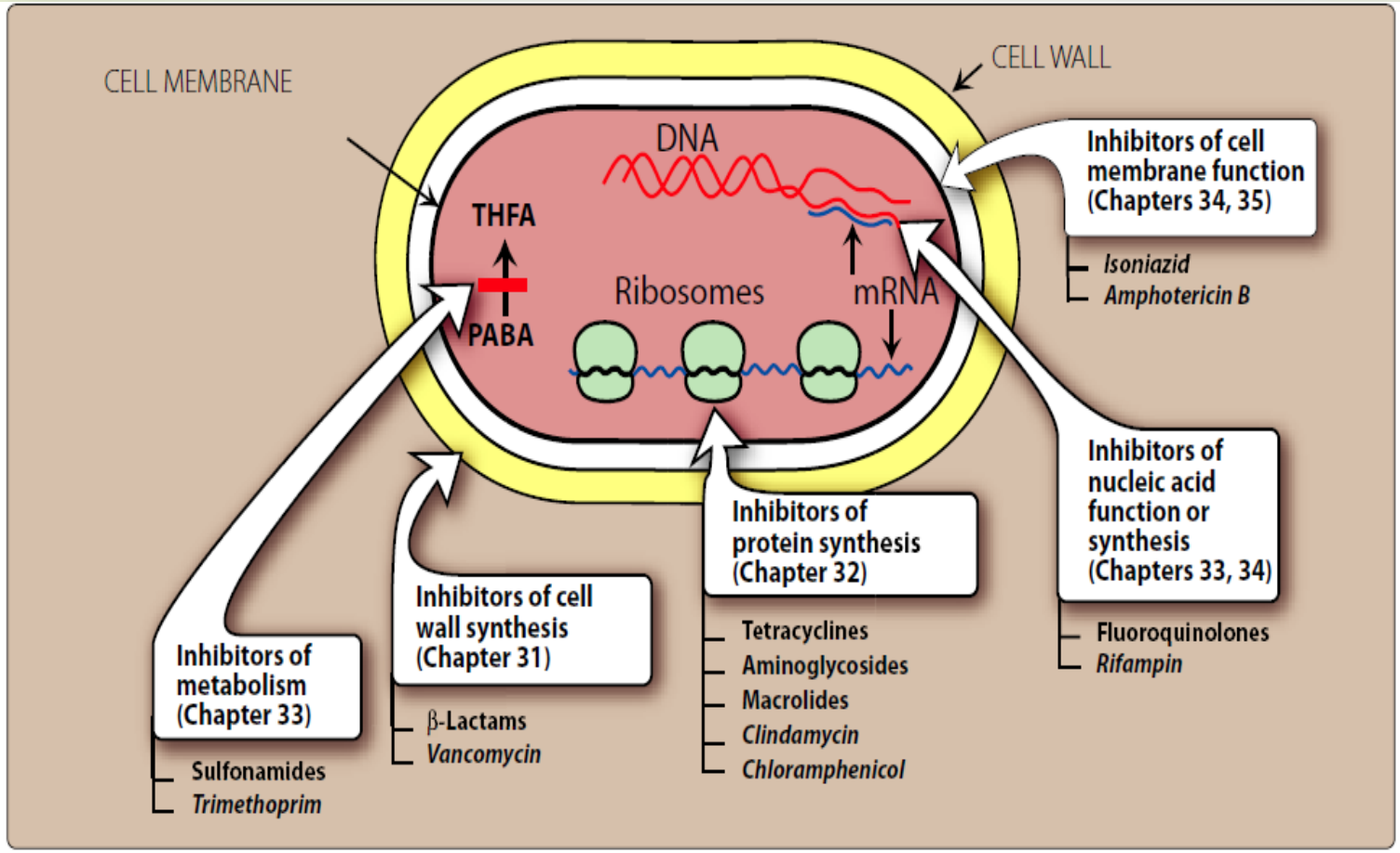


Figure 30.13
Classification of some antimicrobial agents by their sites of action. (THFA = tetrahydrofolic acid; PABA = *p*-aminobenzoic acid.)

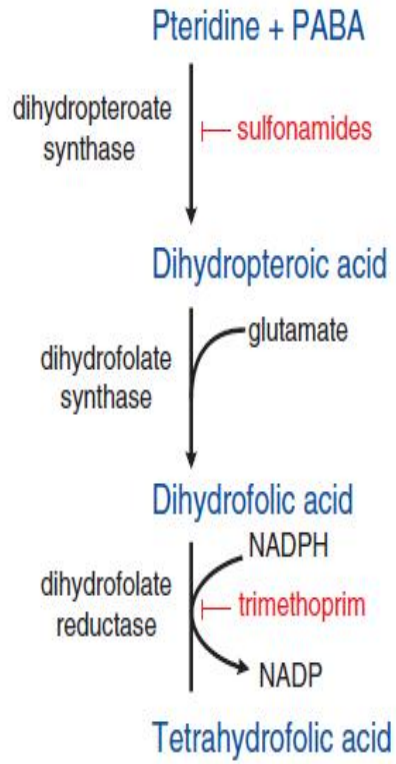


Figure 56–2 *Steps in folate metabolism blocked by sulfonamides and trimethoprim.* Coadministration of a sulfonamide and trimethoprim introduces sequential blocks in the biosynthetic pathway for tetrahydrofolate; the combination is much more effective than either agent alone.

Antibacterial spectrum of sulfonamides

Sensitive microbes	• Strepto. pyogenes, Haemophilus influenzae, H. ducreyi, Calymmatobacterium granulomatis, Vibrio cholerae • Actinomyces, Nocardia and Toxoplasma
Resistant	• Staph. aureus, gonococci, meningococci, pneumococci, Escherichia coli, and Shigella
Not susceptible.	• Anaerobic bacteria

Resistance to sulfonamides

- Most bacteria are capable of developing resistance to sulfonamides
  - E.g. gonococci, pneumococci, Staph. aureus, meningococci, E. coli, Shigella and some Strep. pyogenes, Strep. viridans and anaerobes.

Resistance is develop due to

Decreased intracellular accumulation of the drugs

Produce increased amounts of PABA

Low affinity for folate synthase enzyme

Alternative pathway developed by organisms

- Resistance is develop due to
  - Decreased intracellular accumulation of the drugs
  - Increased production of PABA by bacteria
  - Low affinity for folate synthase enzyme
  - Adopt an alternative pathway in folate metabolism.

Drug resistance

- Resistance developed in vivo *is quite persistent.*
- Sensitivity reduces after long use
- Cross resistance: resistant to one sulfonamide, it is resistant to other
- No cross resistance with other AMA
- Resistance limited the clinical usefulness

Pharmacokinetics

- **Absorption:**
  - rapidly and nearly completely absorbed from g.i.t. exception is sulfasalazine
- **Distribution**
  - plasma protein binding differs considerably
  - highly protein bound members are longer acting.
  - widely distributed
  - Sulfadiazine attains the concentration in CSF
  - cross placenta freely

Pharmacokinetics..

- **Metabolism**
  - Acetylation by microsomal acetyl transferase at N_4 in Liver
  - Acetylated derivative is inactive,
  - Less soluble in acidic urine, may precipitate and cause crystalluria
- **Excretion**
  - eliminated by glomerular fi ltration
  - require dose adjustments for renal dysfunction
  - may also be eliminated in breast milk.

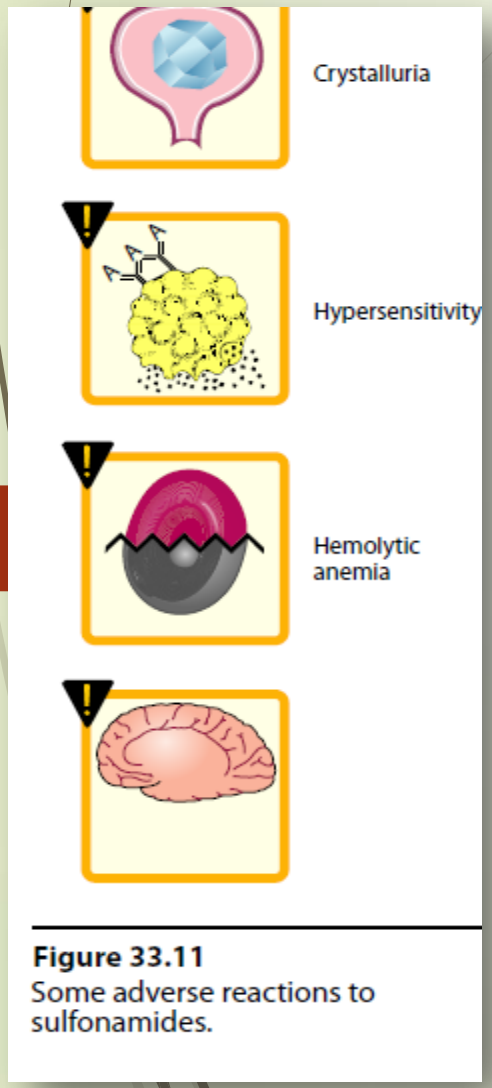


Figure 33.11
Some adverse reactions to sulfonamides.

Adverse effects

1. **Crystalluria:**
   - Nephrotoxicity as a result of crystalluria
   - Adequate hydration and alkalinization of urine prevent concentration of drug and promoting its ionization.
2. **Hypersensitivity:**
   - Rashes, angioedema, urticaria, drug fever and Stevens-Johnson syndrome
3. **Hemopoietic disturbances**
   - Hemolytic anemia in glucose 6-phosphate dehydrogenase deficiency
   - Granulocytopenia and thrombocytopenia

Adverse effects

4. Kernicterus

- occur in newborns ,
- displace bilirubin from binding sites on serum albumin,
- bilirubin is then free to pass into the CNS
- baby's blood brain barrier is not fully developed

5. Drug potentiation

- potentiation of the anticoagulant effect of *warfarin*
- displacement from binding sites on serum albumin.

6. Contraindications

- should be avoided in newborns and infants less than 2 months
- should not be given to patients receiving methenamine for UTIs

Therapeutic Uses:

- Gram-positive and Gram-negative organisms
- Chlamydia, and Nocardia
- Simple urinary tract infections
- Ocular infections
- Burn infections
- Ulcerative colitis, rheumatoid arthritis
- Toxoplasmosis
- Trimethoprim-sulfamethoxazole (TMP-SMZ) in UTI, Resp, Ear & Sinus

Cotrimoxazole

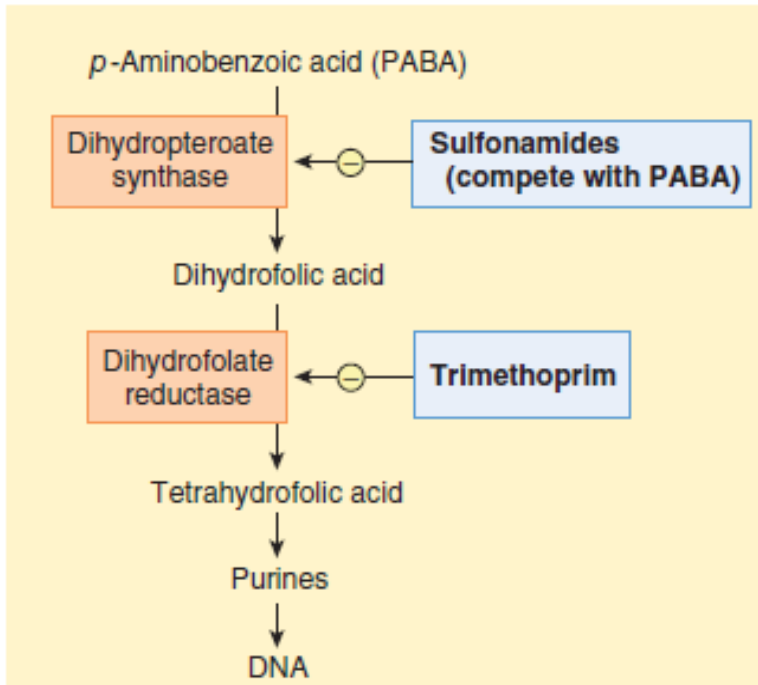
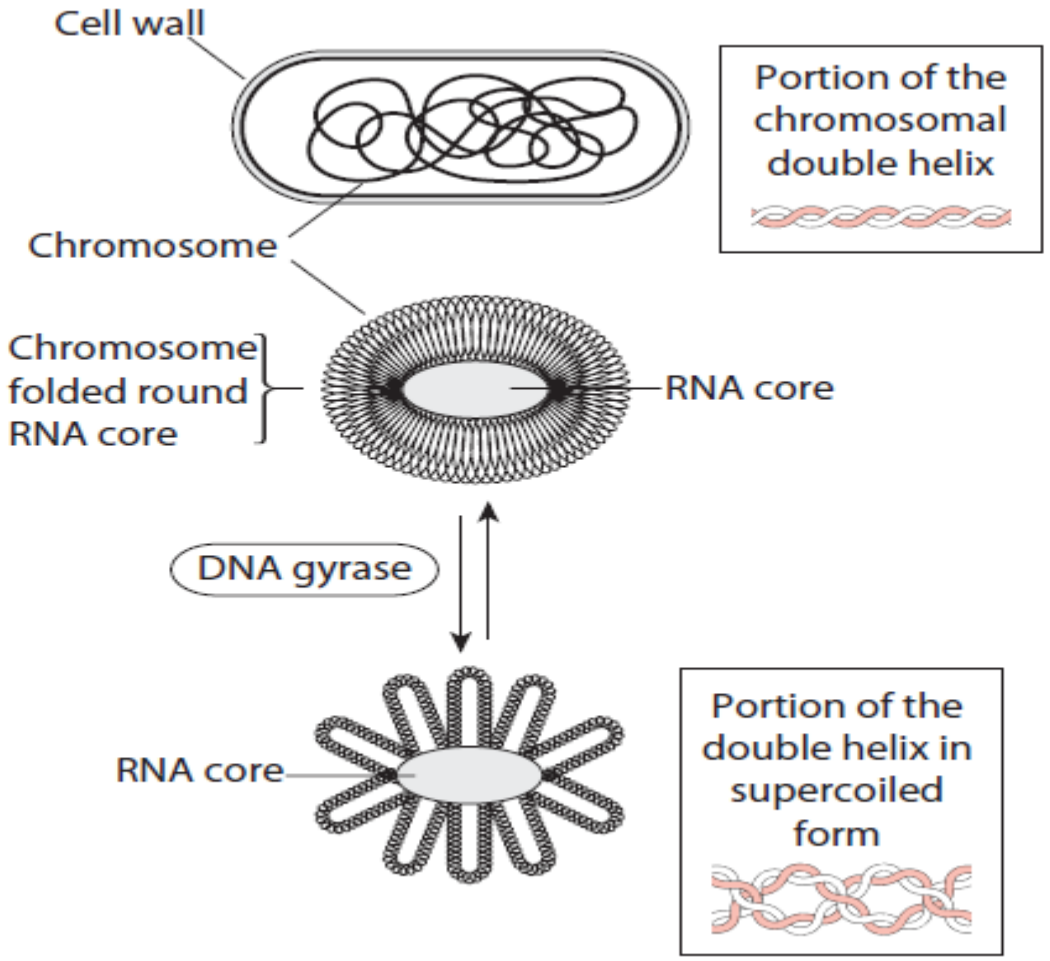


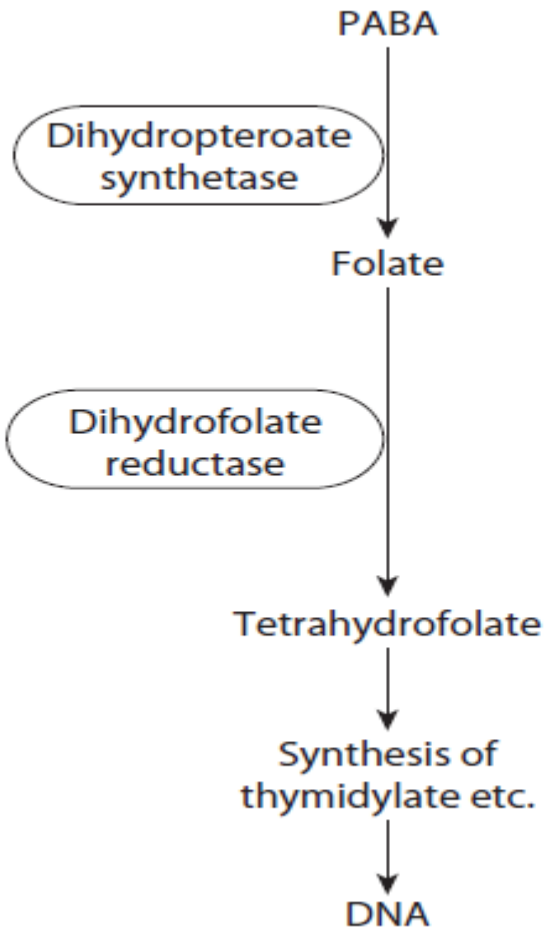
FIGURE 46–1 Inhibitory effects of sulfonamides and trimethoprim on folic acid synthesis. Inhibition of 2 successive steps in the formation of tetrahydrofolic acid constitutes sequential blockade and results in antibacterial synergy.

- **Trimethoprim is diaminopyrimidine related to pyrimethamine (antimalarial)**
- **Trimethoprim a potent inhibitor of bacterial dihydrofolate reductase (DHFRase)**
- **Have same antibacterial spectrum to that of the sulfonamides.**
- **Trimethoprim is most often combined with sulfamethoxazole, producing the combination called cotrimoxazole (fixed dose combination)**

The bacterial chromosome



Folate metabolism



Bacteriostatic antibacterial agent consisting of sulfamethoxazole + trimethoprim

Co-trimoxazole

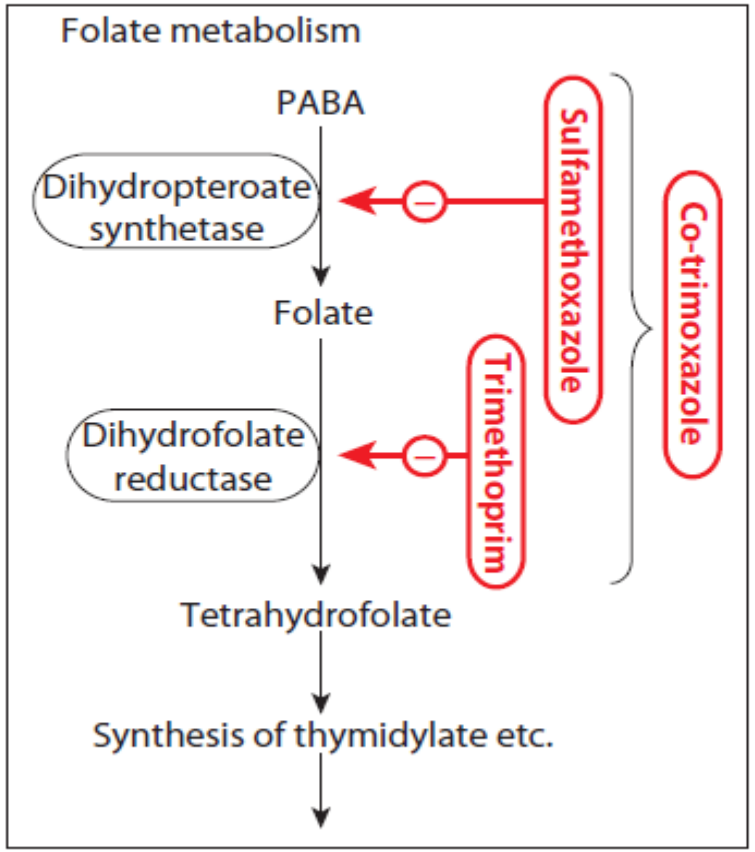
Actions Both sulfamethoxazole and trimethoprim interfere with bacterial folate metabolism and thus with DNA synthesis.

MOA Sulfamethoxazole competitively inhibits the enzyme dihydropteroate synthetase. Trimethoprim inhibits dihydrofolate reductase and thus the conversion of folate to tetrahydrofolate.

Abs/Distrb/Elim Given orally or by i.v. infusion. Sulfa drugs pass into inflammatory exudates, but are inactive in the presence of pus.

Clinical use Pneumocystis pneumonia, toxoplasmosis and nocardiasis, urinary infections, acute exacerbations of chronic bronchitis. Trimethoprim alone used for prostatitis, and for urinary and respiratory infections .

Adverse effects GIT upsets, rashes. Very rare but serious: Stevens-Johnson syndrome, blood dyscrasias, toxic epidermal necrolysis, photosensitivity.



R&D 7e Ch 50, pp 625-626; D&H 2e Ch 47, p 111

Cotrimoxazole

- TMP >50,000 times more active against bacterial DHFRase than mammalian
- Human folate metabolism is not interfered
- Individually, both are bacteriostatic
- In combination becomes cidal against organisms
- In sensitive microorganism Maximum synergism is observed

Why combination is preferred or combined together?

Why Combination Preferred?

- Maximum synergism
- Optimal synergy at a concentration ratio of SMZ 20 : TMP 1 in Plasma
- Nearly the same t½ (~ 10 hr).
- MIC of each component reduced by 3–6 times.
- Dose ratio in the combination in tablets is 5 : 1 (400 mg SMZ & 80 mg TMP)

- TMP enters many tissues, has a larger volume of distribution than SMZ
- TMP adequately crosses BBB but poor sulfamethoxazole
- TMP more rapidly absorbed than SMZ
- TMP 40% plasma protein bound, while SMZ is 65% bound.
- TMP Metabolized in liver and excreted in urine.

Antibacterial spectrum

- Similar to that of sulfamethaxazole
- 20- to 50-fold more
- Salmonella typhi, Serratia, Klebsiella
- Enterobacter, Yersinia enterocolitica
- Pneumocystis jiroveci Staph. aureus, Strep. pyogenes, Shigella
- enteropathogenic E. coli, H. influenzae
- Gonococci and meningococci.

Antibacterial spectrum

- The antibacterial spectrum of trimethoprim is similar to that of sulfamethoxazole.
- TMP is 20- to 50-fold more potent than the sulfonamide.
- Additional organisms covered by the combination are—
  - Salmonella typhi, Serratia, Klebsiella, Enterobacter, Yersinia enterocolitica,
  - Pneumocystis jiroveci and many sulfonamide-resistant strains of Staph. aureus, Strep. pyogenes, Shigella, enteropathogenic E. coli, H.influenzae, gonococci and meningococci.

Resistance

- Less frequently occur
- Lower affinity for the inhibitor drug
- Altered dihydrofolate reductase (DHFRase)
- Resistance in combination slow to develop
- Overproduction of the enzyme (decrease drug permeability)
- Reduced responsiveness after long use
- Resistance can emerge by mutation, due to plasmid-encoded trimethoprim-resistant dihydrofolate reductases

Adverse effects

- **Dermatologic:** skin rashes in elderly patients
- **Gastrointestinal:** Nausea and vomiting, drug fever, vasculitis, headache, rashes etc.
- **Hematologic:** megaloblastic anemia, leukopenia, thrombocytopenia and granulocytopenia, Blood dyscrasias, Hemolytic anemia may occur in G6PD deficiency
- **Patients infected with HIV:** drug-induced fever, rashes, diarrhea, and/ or pancytopenia
- **Drug interactions:** Prolonged prothrombin times, warfarin, plasma half-life of phenytoin may be increased Methotrexate levels may rise

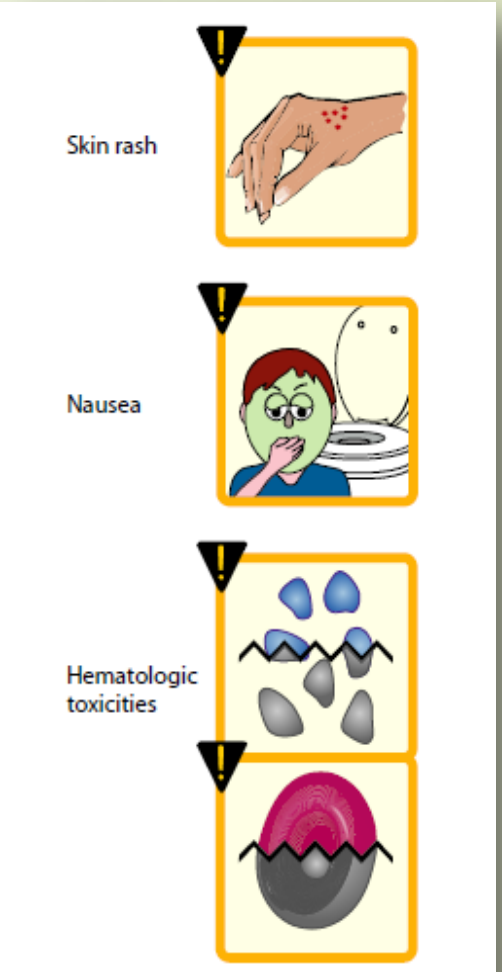


Figure 33.16
Some adverse reactions to *cotrimoxazole*.

Therapeutic Uses

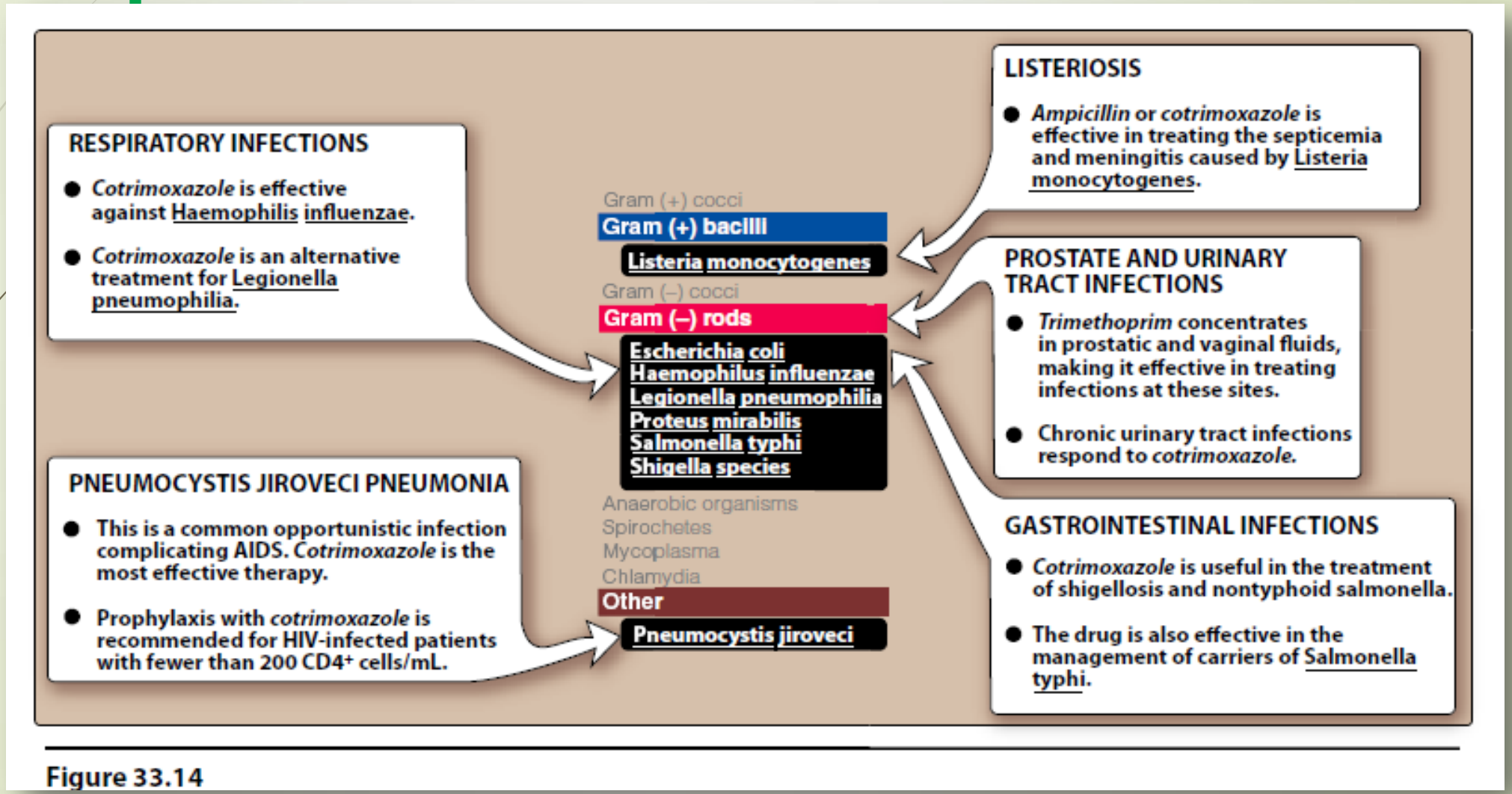


Figure 33.14

Therapeutic Uses

Urinary tract infections

- **Respiratory tract infections**
- **Pneumocystis jiroveci**
- **Bacterial diarrhoeas and dysentery**
- **Chancroid**
- **Typhoid**
- **alternative to penicillin for protecting agranulocytosis**

Drug	Therapeutic Uses	Clinical Pharmacology and Tips
Sulfonamides: Competitive inhibitors of bacterial dihydropteroate synthase, thereby disrupting folate synthesis **General: Bacteriostatic; limited efficacy as monotherapy, renal elimination, hypersensitivity reactions**		
Sulfisoxazole (PO)	• Lower UTIs • Otitis media (with erythromycin)	• Some activity vs. *Streptococcus pyogenes, S. pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Escherichia coli, Nocardia* • Rapid renal excretion
Sulfadiazine (PO)	• Toxoplasmosis (with pyrimethamine)	• Similar to sulfisoxazole, with good activity against *Toxoplasma gondii* • Reasonable CSF penetration • Higher risk of crystalluria, requires hydration
Sulfadoxine (PO)	• Prophylaxis and treatment of malaria (with pyrimethamine)	• Similar to sulfisoxazole, with some activity vs. *Plasmodium falciparum* • Long $t_{1/2}$
Sulfacetamide (ophthalmic)	• Treatment of ocular infections	• Activity similar to sulfisoxazole • High penetration into ocular fluids
Silver sulfadiazine (topical) Mafenide (topical)	• Prevention of infection in burn patients	• Activity similar to sulfisoxazole • Burning and itching at application site • Application over large surface may lead to systemic absorption and adverse effects
Sulfonamide and Dihydrofolate Reductase Inhibitor Combination: Sequential inhibition of folate synthesis		
Trimethoprim-sulfamethoxazole (IV, PO)	• UTI • Upper respiratory tract infections • Shigellosis • *Pneumocystis jiroveci* pneumonia • Skin/soft tissue infections due to *S. aureus* • Infections due to *Nocardia, Stenotrophomonas maltophila, Cyclospora, Isospora*	• Excellent activity vs. *S. aureus, Staphylococcus epidermidis, Streptococcus pyogenes* • Good activity vs. *Proteus, E. coli, Klebsiella, Enterobacter, Serratia, Nocardia, Brucella* • Some activity vs. *S. pneumoniae* • Formulated in 5:1 (sulfa:TMP) ratio, giving 20:1 serum levels • Well absorbed on oral administration • Good penetration into CSF • Metabolized and renally eliminated • Hypersensitivity reactions (i.e., rash) common • Dose-related bone marrow suppression, hyperkalemia

Keep Learning...!!

Happy Learning...!!