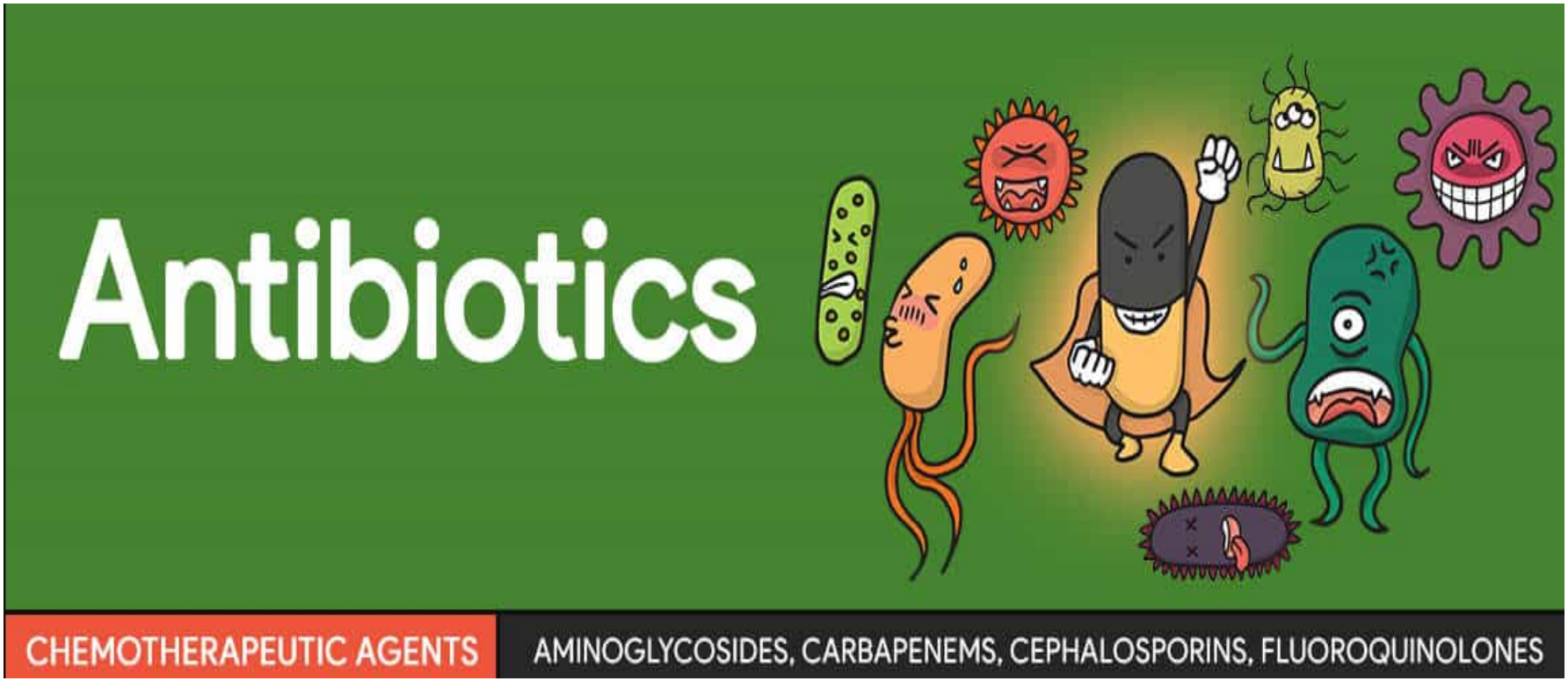
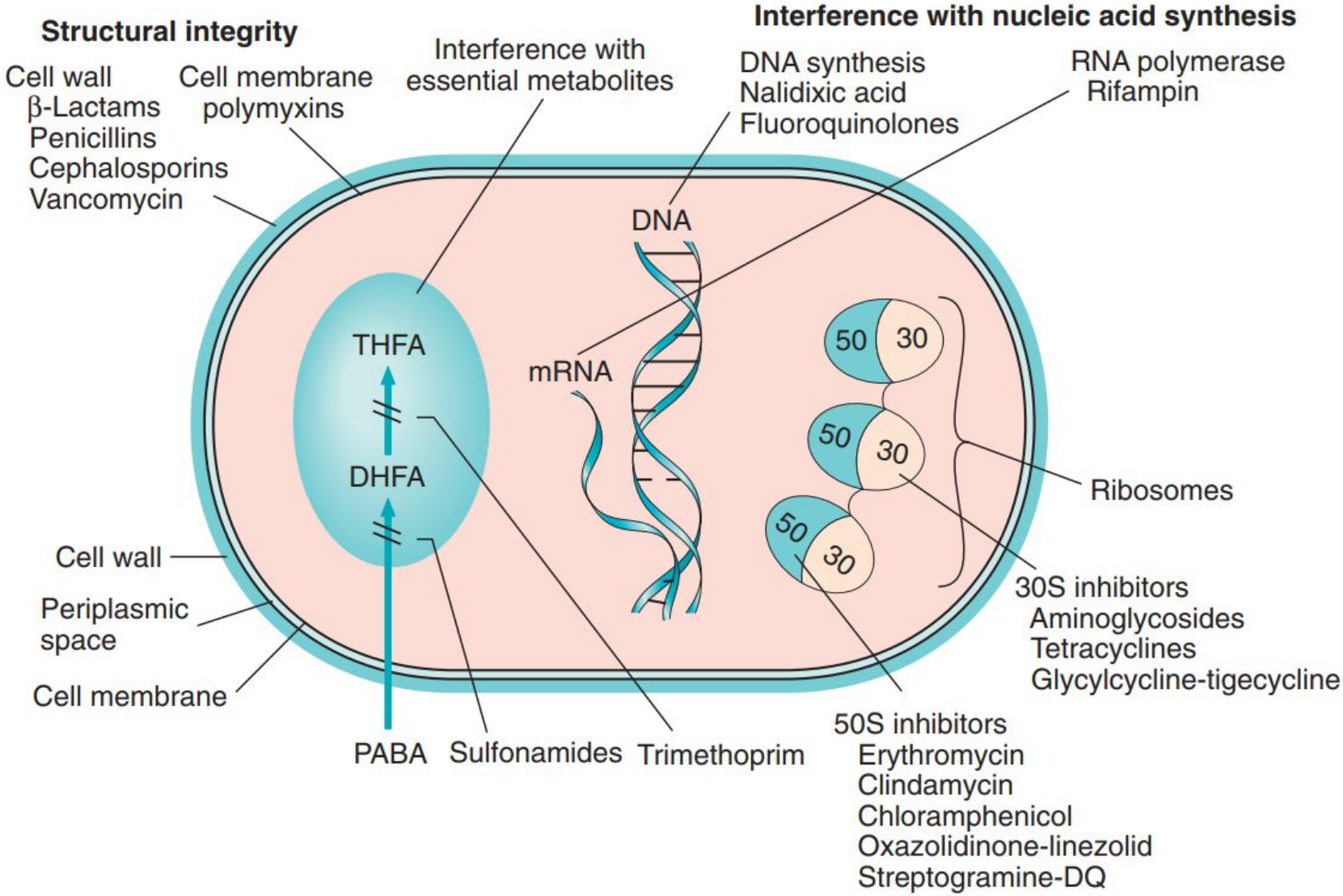


Anti-metabolites

Learning Objectives

- ✔ **Source/Chemistry/classification of antimetabolites**
- ✔ **Pharmacokinetics**
- ✔ **Pharmacodynamics**
- ✔ **Clinical Uses**
- ✔ **Adverse Effects**
- ✔ **Drug Interaction**
- ✔ **Contrandications**


Structural integrity
Cell wall
β-Lactams
Penicillins
Cephalosporins
Vancomycin
Cell membrane
polymyxins
Interference with
essential metabolites
Interference with nucleic acid synthesis
DNA synthesis
Nalidixic acid
Fluoroquinolones
RNA polymerase
Rifampin
DNA
THFA
DHFA
mRNA
50
30
Ribosomes
Cell wall
Periplasmic
space
Cell membrane
30S inhibitors
Aminoglycosides
Tetracyclines
Glycylcycline-tigecycline
PABA
Sulfonamides
Trimethoprim
50S inhibitors
Erythromycin
Clindamycin
Chloramphenicol
Oxazolidinone-linezolid
Streptogramine-DQ

Anti-metabolites

- Sulfonamides
- Trimethoprim
- Pyrimethamine
- Co-trimoxazole

Chemistry of Sulfonamides:-

- Weakly acidic compounds
- Have common nucleus resembling p-aminobenzoic acid (PABA)
- Different Sulfonamide are produced by substitution at :
  - Amino gp ($-SO_2 - NH - R$)
  - Amino gp. (-NH2) of sulfanilamide nucleus.
- They are more soluble at alkaline than acid pH

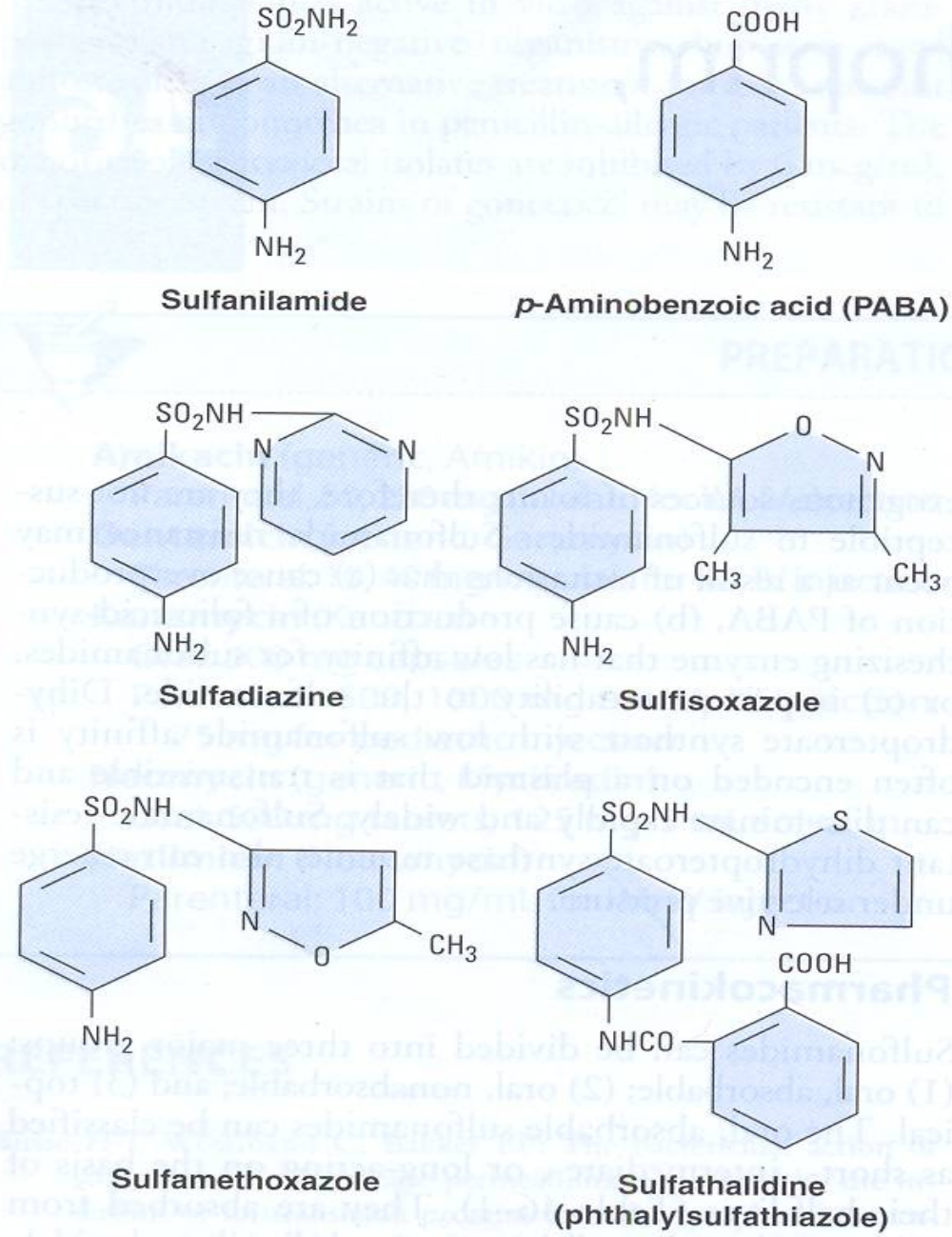


Figure 46–1. Structures of some sulfonamides and *p*-aminobenzoic acid.

Classification

A. Oral absorbable agents

I. Short Acting ----- Half life 6-9hrs
   - Sulfacytine
   - Sulfisoxazole
   - Sulfamethizole

II. Intermediate Acting ----- Half life 10- 17 hrs
   - Sulfadiazine
   - Sulfamethoxazole
   - Sulfapyridine

III. Long Acting ----- Half life 7-9 days
   - Sulfadoxine

B. Oral non-absorbable agents

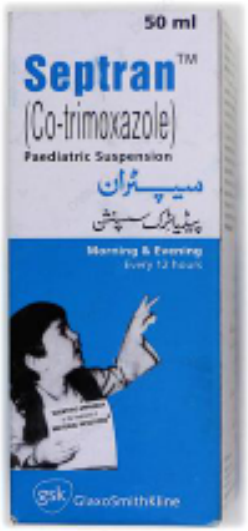
- Sulfasalazine (salicylazosulfapyridine)

C. For Topical Application

- Sulphacetamide
- Silver sulfadiazine
- Mefenide

D. Sulfonamide Combination

- **Cotrimoxazole** (Sulfamethoxazole & trimethoprim)
- **Fansidar** (Sulfadoxine & Pyrimethamine)



Trimethoprim-sulfamethoxazole

Bactrim, Septran

Pharmacokinetics

Absorption**:** Mostly well absorbed after oral adm. On the basis of their half lives divided into :

Short , Medium , Long acting

Distribution: Wide to tissues & fluids including CSF, Placenta & Fetus.

PPB: 20 – 90 % to serum albumin

PPL: 2 – 6 hrs

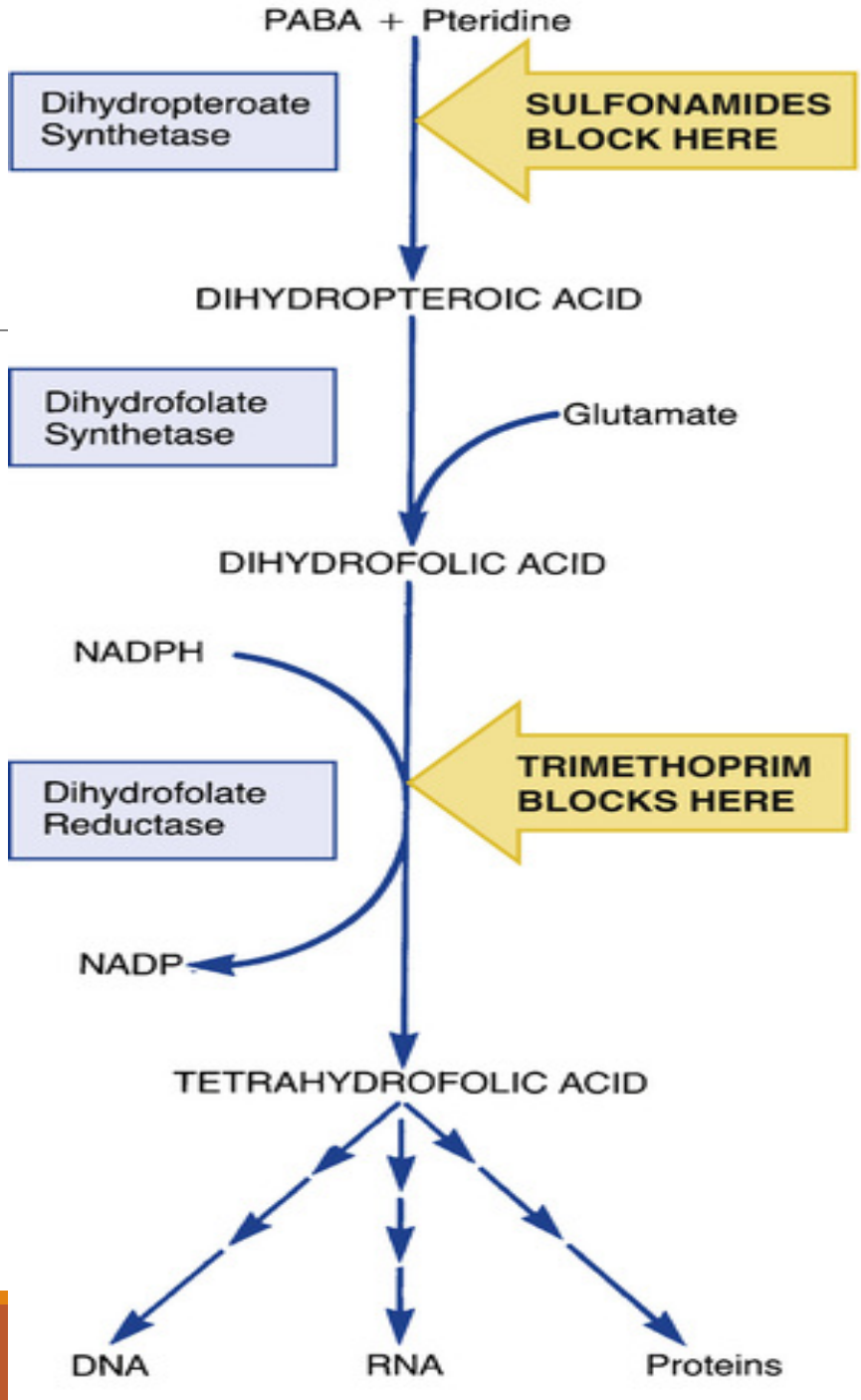
Metabolism –in Liver by Acetylation & Glucuronide conjugation

Excretion – Urine

MOA of Sulfonamides:

Bacteriostatic , Anti-folate drugs

- Folate is required for synthesis of purines & subsequently DNA.
- Sulfonamide are structural analogs of PABA.
- They act as anti- metabolites & compete for Dihydro-pteroate synthase enzyme which converts PABA into Dihydrofolic acid.
- So they inhibit Folate production.
- Synthesis of purines & subsequently DNA can not occur.
- Bacterial growth is inhibited.


PABA + Pteridine
Dihydropteroate Synthetase
SULFONAMIDES BLOCK HERE
DIHYDROPTEROIC ACID
Dihydrofolate Synthetase
Glutamate
DIHYDROFOLIC ACID
NADPH
Dihydrofolate Reductase
TRIMETHOPRIM BLOCKS HERE
NADP
TETRAHYDROFOLIC ACID
DNA
RNA
Proteins

MOA of Trimethoprim & Pyrimethamine:

- They selectively inhibit Dihydrofolate reductase enzyme (DHFR) which converts Dihydrofolic acid. into Tetrahydrofolic acid.
- Synthesis of purines & subsequently DNA can not occur.
- Bacterial growth is inhibited

Trimethoprim is 50000 times < efficient in inhibiting mammalian DHFR.

Pyrimethamine: Selectively inhibits protozoal as compared to mammalian DHFR

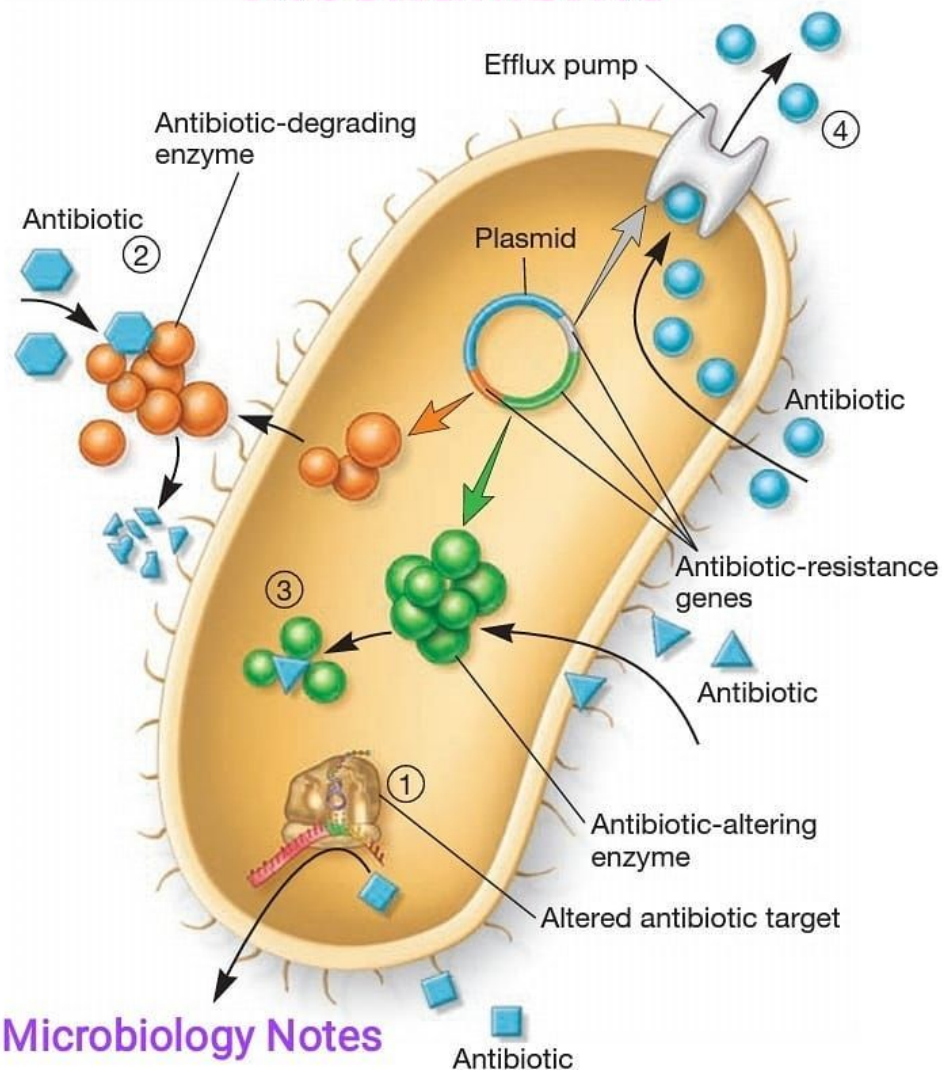
MOA of Co-Trimoxazole

Cotrimoxazole..combination of Trimethoprim & Sulfamethoxazole

Fansidar combination of Trimethoprim & Pyrimethamine:

- The combination is bactericidal
- These drugs block sequential steps in the folate synthesis pathway.
- There is synergistic effect (potentiation).
- Synthesis of purines & subsequently DNA can not occur.
- Bacteria are killed

Antibiotic Resistance Mechanisms



Resistance:

Mammalian cells & some bacteria lack the enzymes for folate synthesis from PABA& depend on exogenous sources of folate.– so not susceptible

Resistance to Sulfonamides can result from :

- Overproduction/ alteration of Dihydropteroate synthase.– Less binding.
- Reduced cell permeability

Antibacterial Spectrum of Sulfonamides

- G +ve , G-ve bacteria
- Nocardia
- Chlamydia trachomatis
- Some protozoa.
- Some enterobacteria E.Coli, Shigella ,Salmonella, Klebsiella

Therapeutic Uses:

Infrequently used as single agents

I. As Topical Agents in
   - Adjunctive therapy for Trachoma (Na -Sulfacetamide)
   - Bacterial Conjunctivitis--- (Na - Sulfacetamide)
   - Prevention of infection of burn wounds (Silver sulfadiazine, Mafenide)

II. UTI: Short & intermediate acting drugs.

III. Ulcerative Colitis, enteritis, other inflammatory bowel diseases (Sulphasalazine)

IV. Rheumatoid arthritis (Sulphasalazine)

V. Dermatitis herpetiformis (Sulfapyridine)

Used in combination in

- (Sulfadoxine + Pyrimethamine – Fansidar) Resistant Malaria

- (oral Sulfadiazine + Pyrimethamine + Folinic acid) Acute toxoplasmosis & Leishmaniasis.
- Sulfisoxazole +Erythrocine ethylsuccinate ---Pediazole for otitis media in children
- Sulfamethoxazole + Trimethoprim -----Septran for infection with Pneumocystis jiroveci Pneumonia.
- Sulfapyridine + 5 ASA -----Sulfasalazine in IBD

ADVERSE EFFECTS

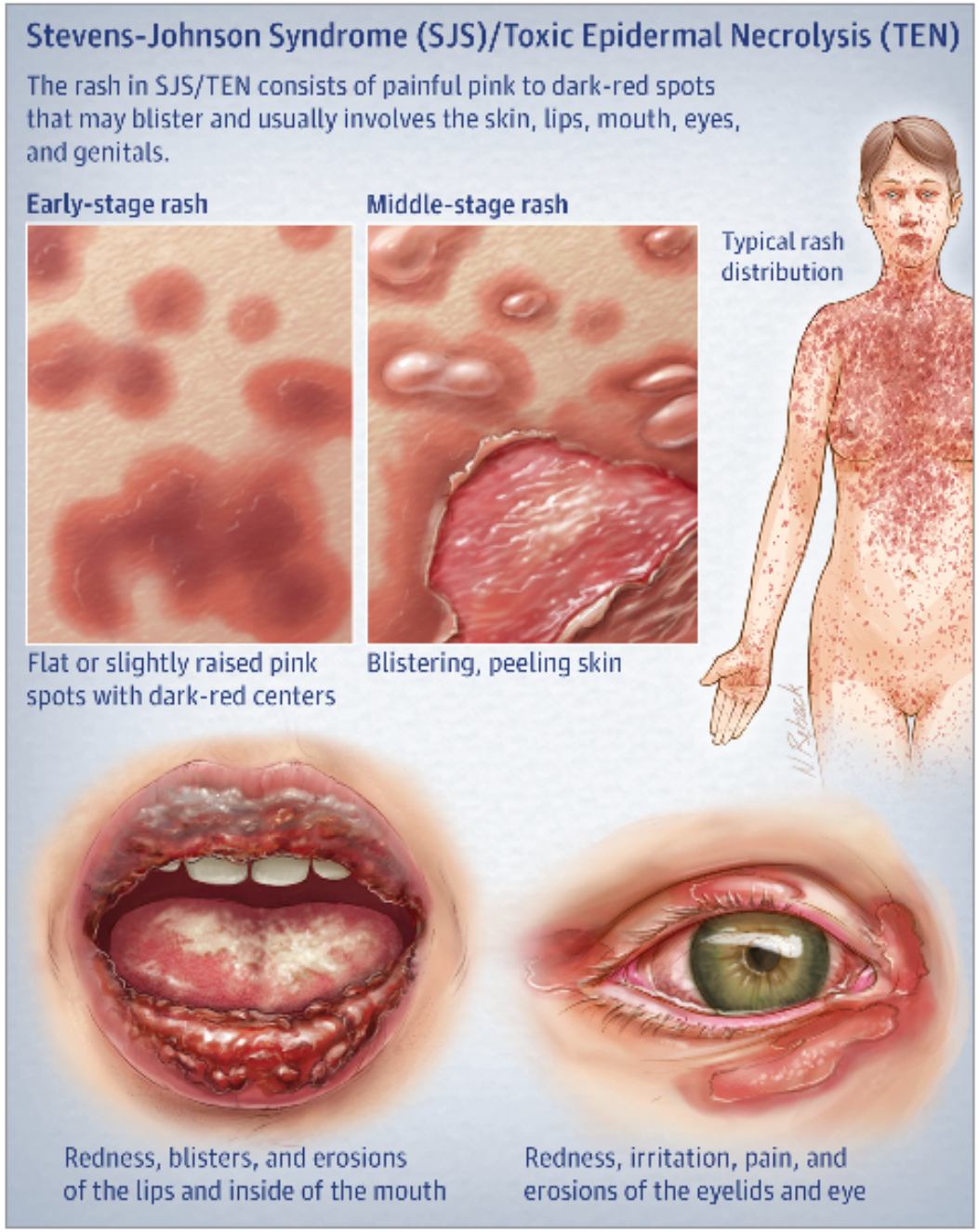
A. Hypersensitivity Reactions:-

1. Fever, Skin rashes, exfoliative dermatitis, photosensitivity, urticaria, Angioedema & Steven – Johnson syndrome (1%)

Nausea , Vomiting , Diarrhoea , Stomatitis

Conjunctivitis, Arthritis & rarely Polyarteritis nodosa.

2. Hematopoietic Disturbances :- Hemolytic or Aplastic anemia, Granulocytopenia, Thrombocytopenia


Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)
The rash in SJS/TEN consists of painful pink to dark-red spots that may blister and usually involves the skin, lips, mouth, eyes, and genitals.
Early-stage rash
Middle-stage rash
Typical rash distribution
Flat or slightly raised pink spots with dark-red centers
Blistering, peeling skin
Redness, blisters, and erosions of the lips and inside of the mouth
Redness, irritation, pain, and erosions of the eyelids and eye

B. Urinary Tract Disturbances:-

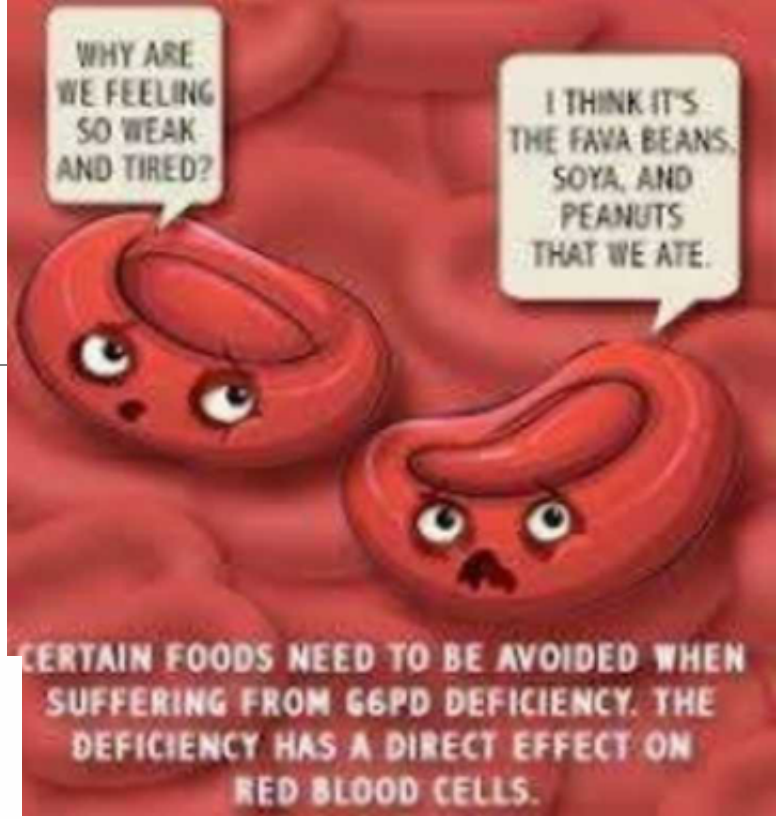
Precipitation in acidic urine causing Crystalluria, Hematuria / Obstruction. Nephrosis & Allergic Nephritis may occur.

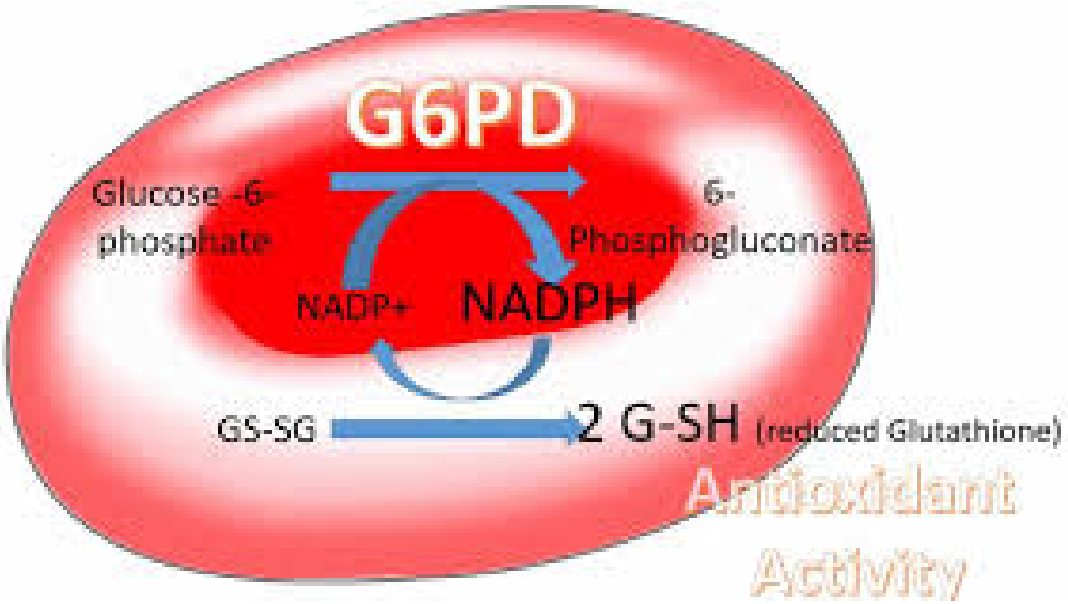
Treatment: Alkalinize urine with Sodium Bicarbonate,

- Plenty of fluids 2 L/day intake or maintain urine
- output 1200 ml/day

C. Kernicterus in premature babies

D. Haemolysis in Glucose 6-Phosphate Dehydrogenase deficient patients.


WHY ARE WE FEELING SO WEAK AND TIRED?
I THINK IT'S THE FAVA BEANS, SOYA, AND PEANUTS THAT WE ATE.
CERTAIN FOODS NEED TO BE AVOIDED WHEN SUFFERING FROM G6PD DEFICIENCY. THE DEFICIENCY HAS A DIRECT EFFECT ON RED BLOOD CELLS.


G6PD
Glucose -6-phosphate
6-Phosphogluconate
NADP+
NADPH
GS-SG
2 G-SH (reduced Glutathione)
Antioxidant Activity

Drug interactions:

Competition with warfarin & methotrexate & oral hypoglycemics for PPB ---- increase level

Contraindication

Known hypersensitivity.

Newborns & infants less than 2 months

Pregnant woman at term – Kernicterus

TRIMETHOPRIM

Chemically related to pyrimethamine--- -folate antagonist.

Pharmacokinetics: Given orally , fully absorbed from GIT.

Distribution: Wide, in body fluids and tissues, including CSF

Concentrates in prostatic & vaginal fluid.– more acidic than plasma

It is more lipid soluble than sulfamethoxazole , has large Vd.

PPB: 65 – 70 %

Excretion : 50-60- in urine within 24 hrs.

Clinical Use: Acute UTI: 100 mg –twice daily.

Resistance to trimethoprim : Overproduction/ altered of Dihydrofolate reductase.– Less binding.

CO-TRIMOXAZOLE: (Oral/IV)

Combination of trimethoprim with sulfamethoxazole.

Sulfamethoxazole – 400 mg.

Trimethoprim – 80 mg.

Ratio 1:5

Clinical uses

1. Pneumocystis Jiroveci Pneumonia in AIDs patient

   For treatment & prevention.

2. Respiratory , ear & sinus infections by:

   Hemophilis influenzae , Pneumococcus, Moraxella Catarrhalis

   Staphylococcus (methicillin sensitive /resistant) .

   Klebsiella Pneumoniae

3. Nocardosis. ---DOC
4. Shigellosis , Typhoid Fever ,cholera-- Back up drug

5. G-ve bacterial sepsis. By resistant micro-organisms specially Enterobacter & Serretia.
6. UTI: For treatment & prophylaxis of recurrent UTI
7. Prostatitis by susceptible micro-organisms.

Advantages of Using Co-Trimoxazole

1. The combination produces synergistic effect – Potentiation.
2. Bactericidal. (Individual drugs are bacteriostatic)
3. Wider antibacterial spectrum than individual drugs
4. More efficacy than individual drugs.
5. Less dose of each drug.
6. Less incidence of toxicity.

Adverse Effects

1. **Hematological**

Trimethoprim (Anti-folate) Megaloblastic Anemia, Leukopenia, Granulocytopenia …. Prevented by simultaneous administrations of folinic acid

2. **Due to Sulphamethoxazole---**

Nausea ,Vomiting, Rashes, Fever, Vasculitis

Occasionally: renal damage & CNS disturbances

3. AIDS patients with pneumocystis jiroveci pneumonia show high incidence of fever, rashes, leukopenia, diarrhea, elevation of hepatic aminotransferases, hyperkalemia, hyponatremia.

Summary

Basic characteristics (remember of **SULFA**):

Solubility low

Useful for Urinary tract infections

Large spectrum (active against gram positive and gram negative bacteria)

Folic acid synthesis blocker (DHPS inhibitor)

Antimetabolite /**A**nalog of PABA

Side effects of Sulfonamides include (remember of **SULFA**):

Steven-Johnson syndrome / **S**kin rashes

Urticaria / **U**rine precipitation (crystalluria)

Leucopenia

Folic acid deficency

Aplastic Anemia

Assignment

- What are non anti microbial sulfonamides?
- Enlist drugs causing Steven Johnson syndrome.
- Enlist drugs causing hemolysis in G6PD deficient patients.