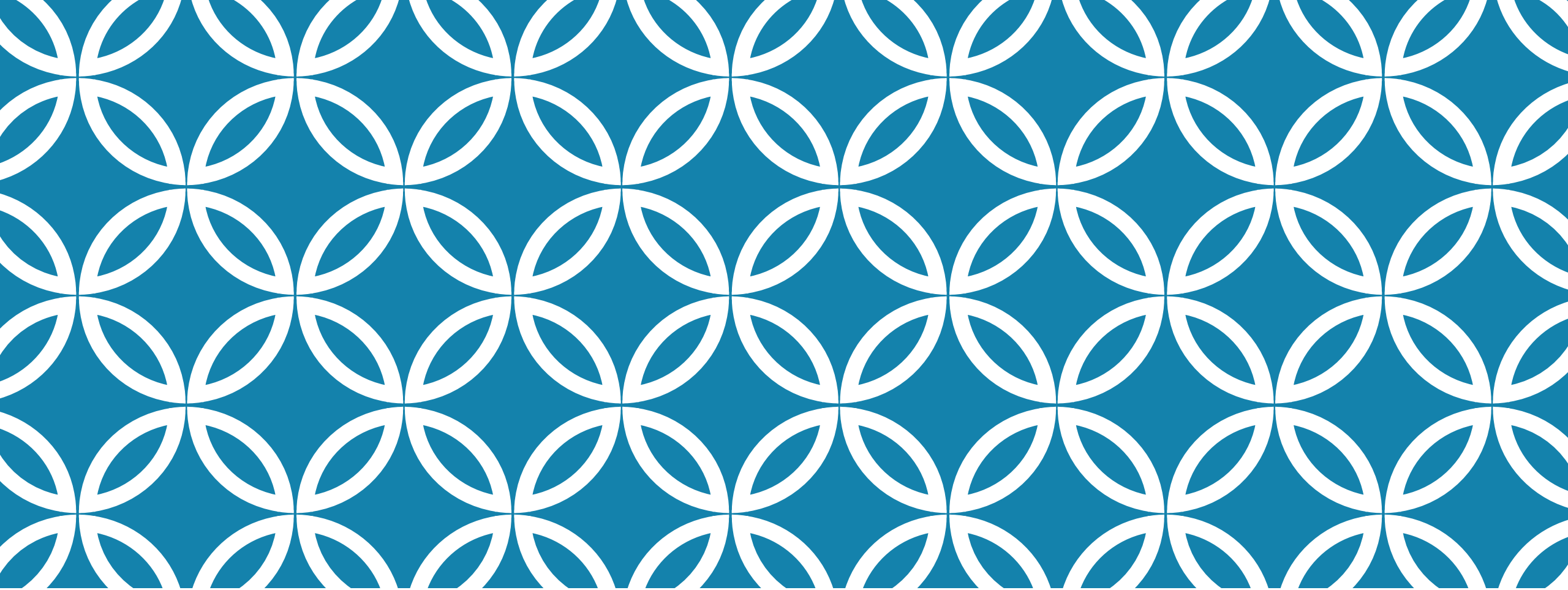


PHARMACOLOGY – II

Dr Shariq Syed
Associate Professor
AIKTC, SoP

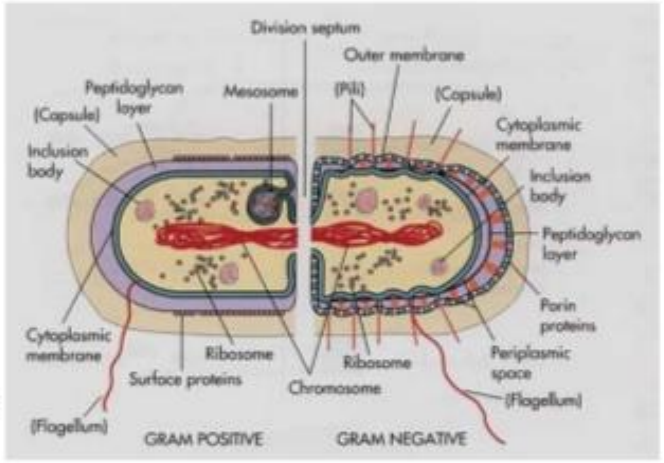
INTRODUCTION TO BACTERIA !

Bacterial Classification Based on Staining Methods

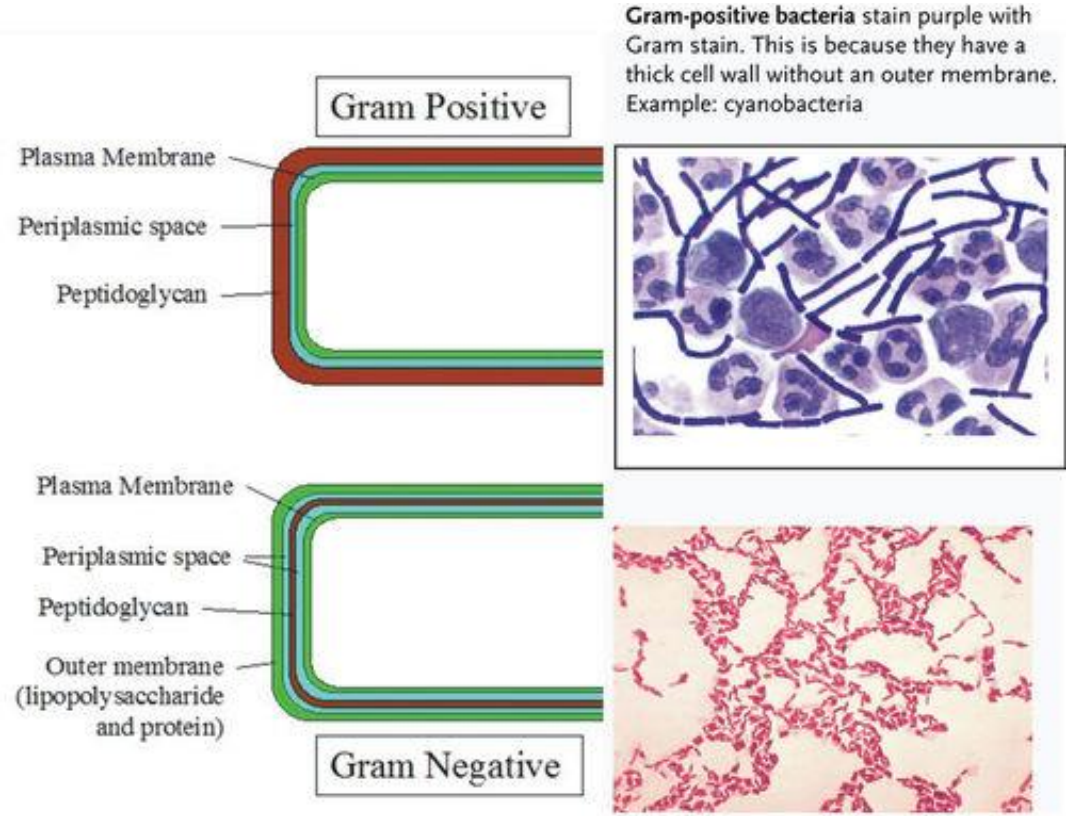
Bacteria are grouped as 'Gram positive' and 'Gram negative' bacteria, based on the results of Gram staining method, wherein an agent is used to bind to the cell wall of the bacteria.

Gram positive bacteria - take up crystal violet dye and retain their blue or violet color.

Gram negative bacteria - do not take up crystal violet dye, and thus appear red or pink.



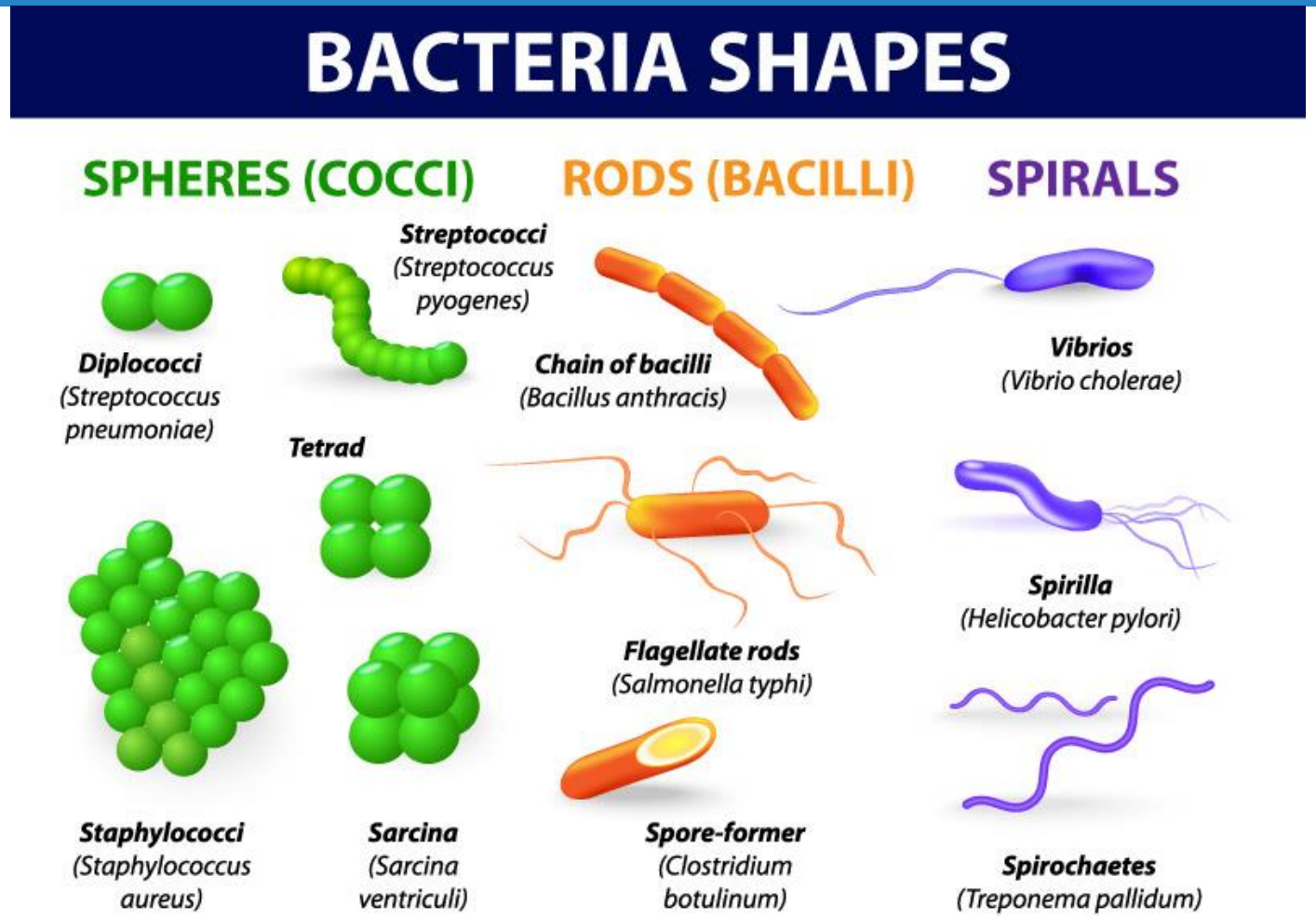
INTRODUCTION TO BACTERIA !



Gram-positive bacteria stain purple with Gram stain. This is because they have a thick cell wall without an outer membrane. Example: cyanobacteria

Gram-negative bacteria stain red with Gram stain. This is because they have a thin cell wall with an outer membrane. Example: Salmonella.

THEY COME IN DIFFERENT SHAPES



ANTIMICROBIAL SITES OF ACTION

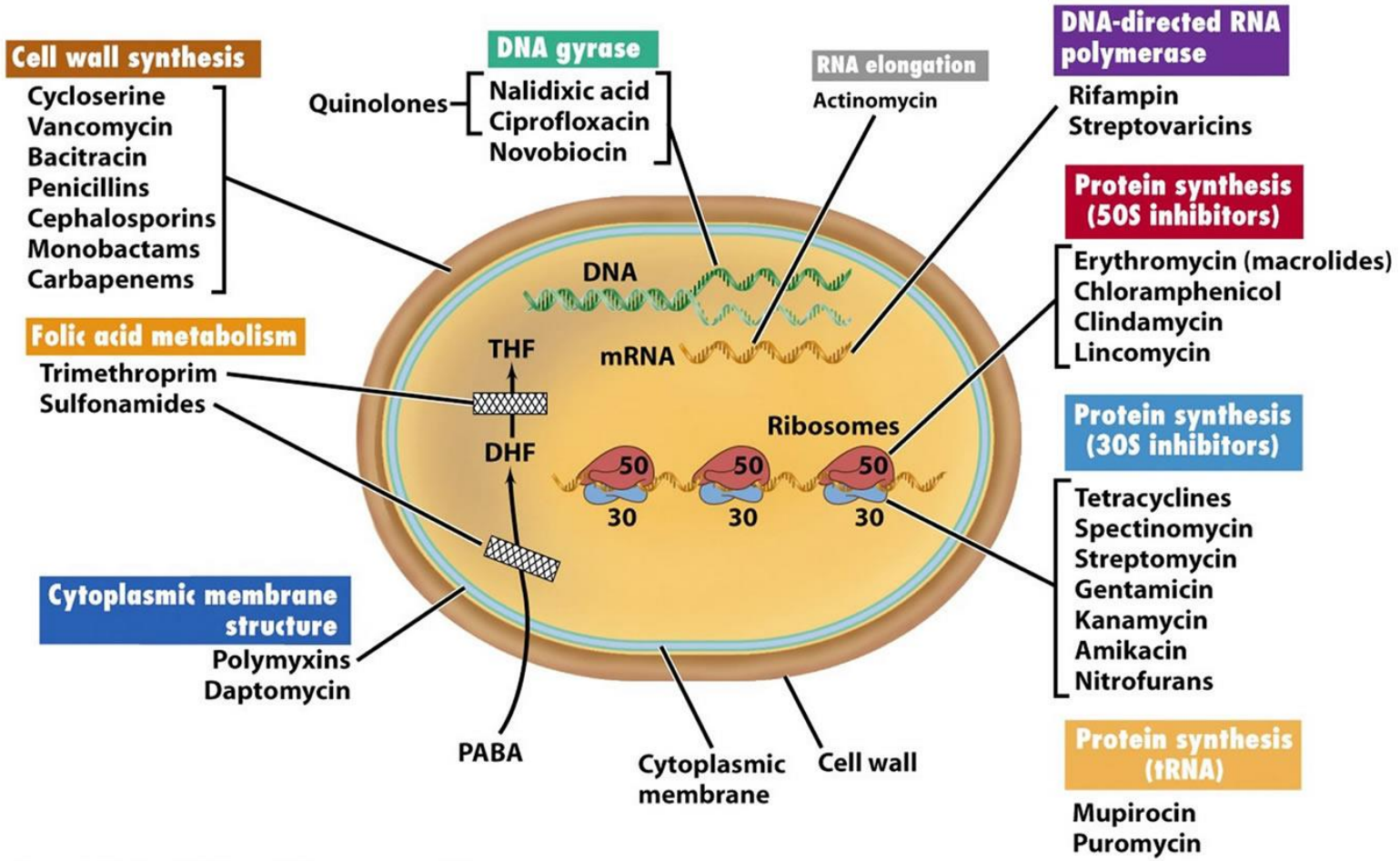


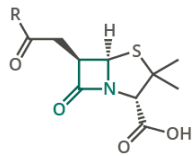
Figure 20-14 Brock Biology of Microorganisms 11/e

DIFFERENT CLASSES OF ANTIBIOTICS - AN OVERVIEW

Key: COMMONLY ACT AS **BACTERIOSTATIC AGENTS**, RESTRICTING GROWTH & REPRODUCTION — COMMONLY ACT AS **BACTERICIDAL AGENTS**, CAUSING BACTERIAL CELL DEATH

ß-LACTAMS

MOST WIDELY USED ANTIBIOTICS IN THE NHS



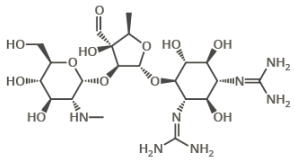
All contain a beta-lactam ring

EXAMPLES
Penicillins (shown) such as amoxicillin and flucloxacillin; *Cephalosporins* such as cefalexin.

MODE OF ACTION
Inhibit bacteria cell wall biosynthesis.

AMINOGLYCOSIDES

FAMILY OF OVER 20 ANTIBIOTICS



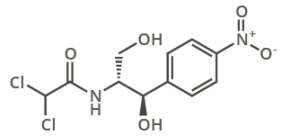
All contain aminosugar substructures

EXAMPLES
Streptomycin (shown), neomycin, kanamycin, paromomycin.

MODE OF ACTION
Inhibit the synthesis of proteins by bacteria, leading to cell death.

CHLORAMPHENICOL

COMMONLY USED IN LOW INCOME COUNTRIES



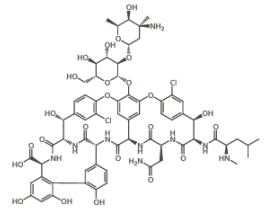
Distinct individual compound

MODE OF ACTION
Inhibit synthesis of proteins, preventing growth.

No longer a first line drug in any developed nation due to increased resistance and worries about safety.

GLYCOPEPTIDES

COMMON 'DRUGS OF LAST RESORT'



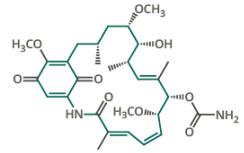
Consist of carbohydrate linked to a peptide formed of amino acids

EXAMPLES
Vancomycin (shown), teicoplanin.

MODE OF ACTION
Inhibit bacteria cell wall biosynthesis.

ANSAMYCINS

CAN ALSO DEMONSTRATE ANTIVIRAL ACTIVITY



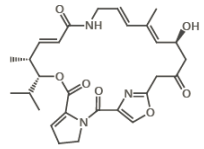
All contain an aromatic ring bridged by an aliphatic chain.

EXAMPLES
Geldanamycin (shown), rifamycin, naphthomycin.

MODE OF ACTION
Inhibit the synthesis of RNA by bacteria, leading to cell death.

STREPTOGRAMINS

TWO GROUPS OF ANTIBIOTICS THAT ACT SYNERGISTICALLY



Combination of two structurally differing compounds, from groups denoted A & B

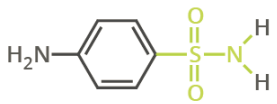
EXAMPLES
Pristinamycin IIA (shown), Pristinamycin IA.

MODE OF ACTION
Inhibit the synthesis of proteins by bacteria, leading to cell death.

DISCOVERY 1930 1940 1950 1960 1970 1980

SULFONAMIDES

FIRST COMMERCIAL ANTIBIOTICS WERE SULFONAMIDES



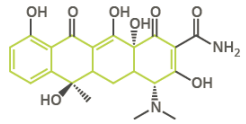
All contain the sulfonamide group

EXAMPLES
Prontosil, sulfanilamide (shown), sulfadiazine, sulfisoxazole.

MODE OF ACTION
Do not kill bacteria but prevent their growth and multiplication. Cause allergic reactions in some patients.

TETRACYCLINES

BECOMING LESS POPULAR DUE TO DEVELOPMENT OF RESISTANCE



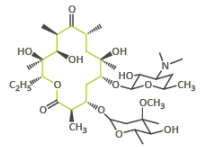
All contain 4 adjacent cyclic hydrocarbon rings

EXAMPLES
Tetracycline (shown), doxycycline, limecycline, oxytetracycline.

MODE OF ACTION
Inhibit synthesis of proteins by bacteria, preventing growth.

MACROLIDES

SECOND MOST PRESCRIBED ANTIBIOTICS IN THE NHS



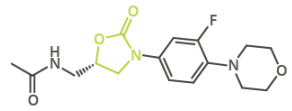
All contain a 14-, 15-, or 16-membered macrolide ring

EXAMPLES
Erythromycin (shown), clarithromycin, azithromycin.

MODE OF ACTION
Inhibit protein synthesis by bacteria, occasionally leading to cell death.

OXAZOLIDINONES

POTENT ANTIBIOTICS COMMONLY USED AS 'DRUGS OF LAST RESORT'



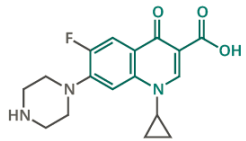
All contain 2-oxazolidone somewhere in their structure

EXAMPLES
Linezolid (shown), posizolid, tedizolid, cycloserine.

MODE OF ACTION
Inhibit synthesis of proteins by bacteria, preventing growth.

QUINOLONES

RESISTANCE EVOLVES RAPIDLY



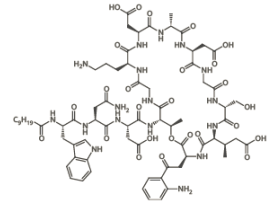
All contain fused aromatic rings with a carboxylic acid group attached

EXAMPLES
Ciprofloxacin (shown), levofloxacin, trovafloxacin.

MODE OF ACTION
Interfere with bacteria DNA replication and transcription.

LIPOPEPTIDES

INSTANCES OF RESISTANCE RARE



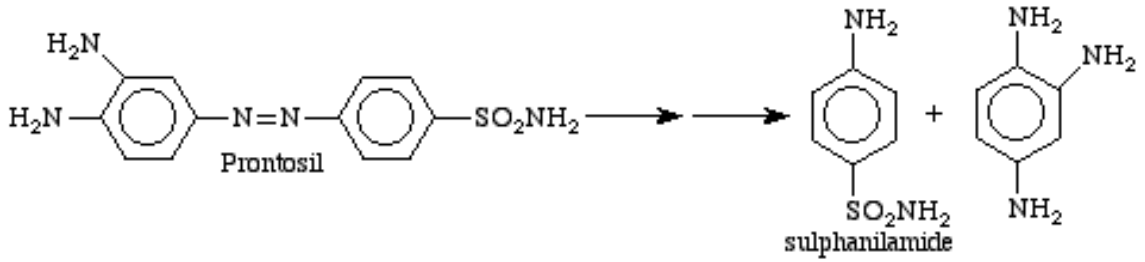
All contain a lipid bonded to a peptide

EXAMPLES
Daptomycin (shown), surfactin.

MODE OF ACTION
Disrupt multiple cell membrane functions, leading to cell death.

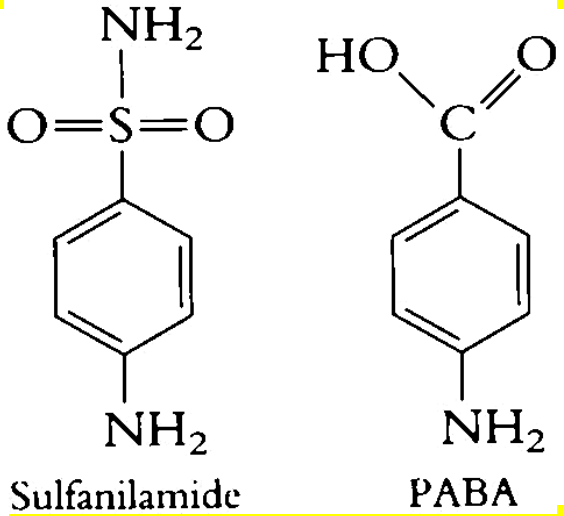
SULPHONAMIDES

- 1930, Physician/researcher Domagk showed that a drug could affect bacterial infection
- Drug was “Prontosil” by Bayer a dye, inactive pro-drug that gets converted to active Sulfanilamide
- The drug showed action against Streptococci & other infections
- Class of drug contain : SO_2NH_2 ; Sulfonamido group

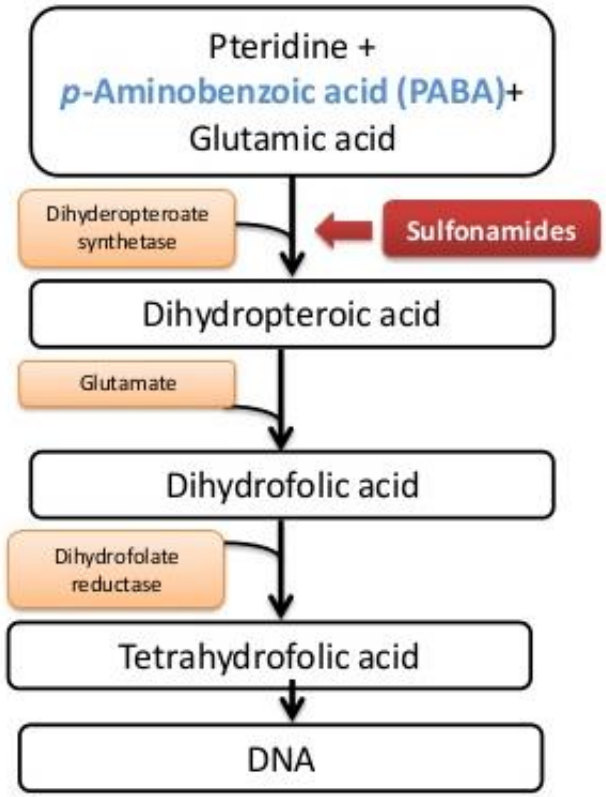


SULPHONAMIDES; MOA

Sulfonamides have structural similarity with PABA, compete & substitute PABA

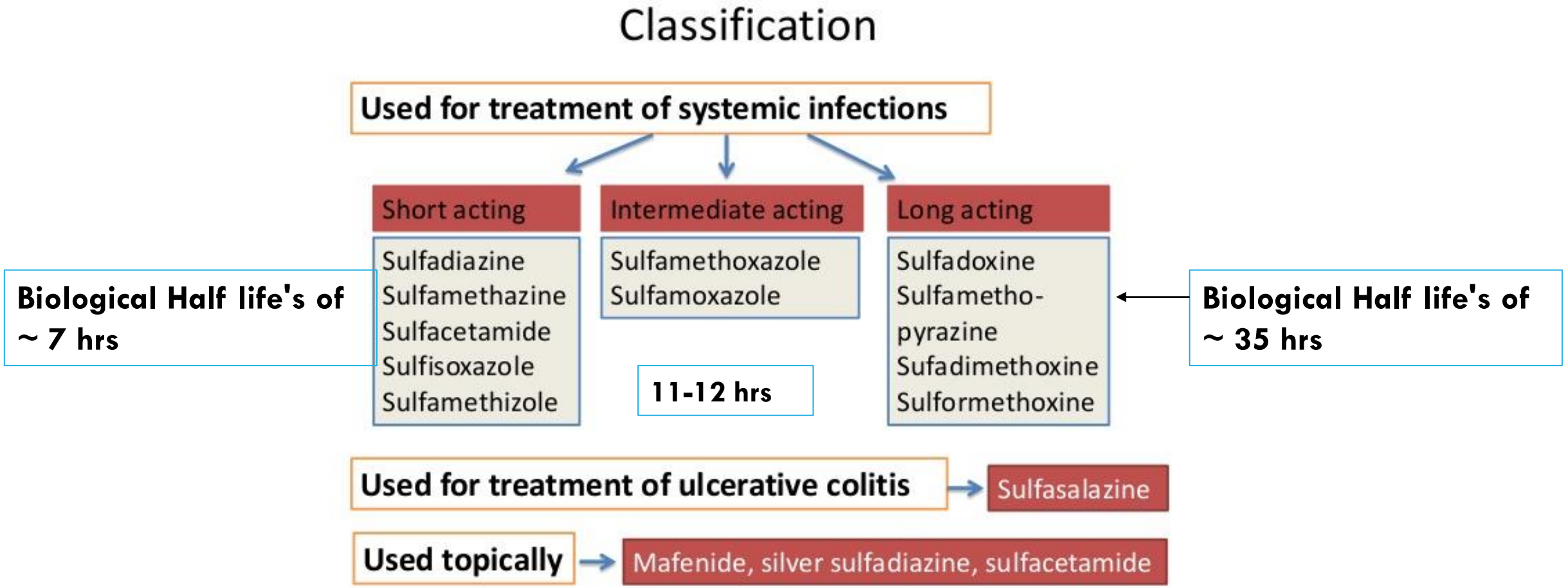


Ineffective in presence of pus & tissue breakdown with large amounts of PABA



- Inhibition of Folic Acid synthetase leads to Folic Acid deficiency
- Injury to bacterial cell,
- Injured cell easily phagocytosed

CLASSIFICATION (THERAPEUTIC UTILITY)



SULPHONAMIDES

- **Pharmacological Actions:**
- Effective against wide variety **Gram + / Gram –**
- Streptococci, Staphylococci, Gonococci, Pneumococci
- H. Influenzae, Vibrio comma
- Mainly *Bacteriostatic* but can be Bactericidal in high conc in UTI
- Clinical potency, efficacy less compared to other antibiotics
- For ex MIC for Sulphonamides is 1: 10,000 compared to 1: 50 million Penicillin

UTI : Urinary Tract infections; MIC: Minimum Inhibitory Conc

SULPHONAMIDES

- **ADME:**
- Classified in 3 groups: oral, oral non-absorbable, non-absorbable topical
- Oral absorbable category: Rapid absorption from Intestine, peak levels 2- 4 hrs
- short , medium, or long acting based in half lives (7 – 35 hrs range)
- Generally ~ Min 50 % protein bound; Higher protein binding, slower excretion
- Sulfadiazine is less bound, can penetrate brain (Higher CSF Levels) used for treatment of Brain infections (Meningococcal meningitis)

SULPHONAMIDES

- **ADME:**
- Liver is main site of elimination
- Acetylation (Phase I reaction) Major elimination reaction
- Individuals vary in acetylation capacities (Rapid, Slow Acetylators)
- Acetylated form inactive, Toxic to body
- Sulfonamides & acetylated metabolites eliminated in urine (High conc in Urine)
- Excretion rate of long acting drugs is low

SULPHONAMIDES

❖ Therapeutic Uses:

✓ Low cost drugs, Broad spectrum

❖ Single use is rare because of sever allergic reactions, development of bacterial resistance

✓ Used in primary care only when first-line recommended antibiotics have been ineffective or are contraindicated.

❖ Routine use: Short acting; Sulfadimidine, Sulfadiazine

SULPHONAMIDES

❖ Therapeutic Uses:

1. UTI (Urinary Tract Infections)
   1. Rarely used as single agents
   2. Fixed drug combination of trimethoprim-sulfamethoxazole (800 mg BID)
   3. Sulfisoxazole and sulfamethoxazole are used almost exclusive to treat UTI

SULPHONAMIDES

❖ Therapeutic Uses:

1. Meningococcal Meningitis
   1. Fixed drug combination of trimethoprim-sulfamethoxazole
2. IBD (Inflammatory Bowel Disease)

   1. Ulcerative Colitis (Oral, Non-absorbable drugs: Sulfasalazine)
   2. Crohns Disease

SULPHONAMIDES

❖ Adverse Drug Reactions:

1. Allergic reactions
   a) Most common skin rash, drug fever
   b) Uncommon is cutaneous photosensitization
   c) Sever skin lesions: Steven Johnson Syndrome (Long acting sulfa drugs)
2. GI Symptoms (nausea, vomiting)
   a) Manageable, not as serious as other broad spectrum drugs
3. Renal Toxicity
   a) Due to metabolites precipitation
   b) Obstruction, tubular necrosis
   c) Changing the pH of urine can prevent precipitation

SULPHONAMIDES

❖ Adverse Drug Reactions:

1. Haemopoietic Toxicity
   a) Thrombocytopenia, granulocytopenia
   b) Drugs tend to oxidise hemoglobin to Methhemoglobin

2. Bilirubin Metabolism

3. Nervous System Toxicity
   a) CNS disturbances: confusion, depression, ataxia common in children

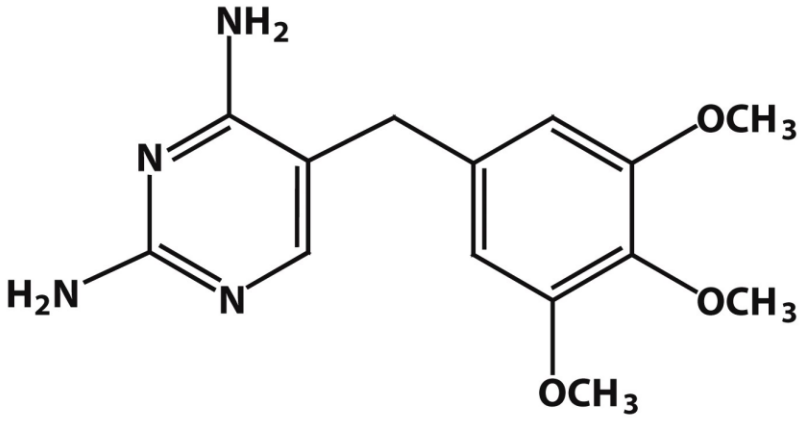
SULPHONAMIDES

❖ Drug Resistance

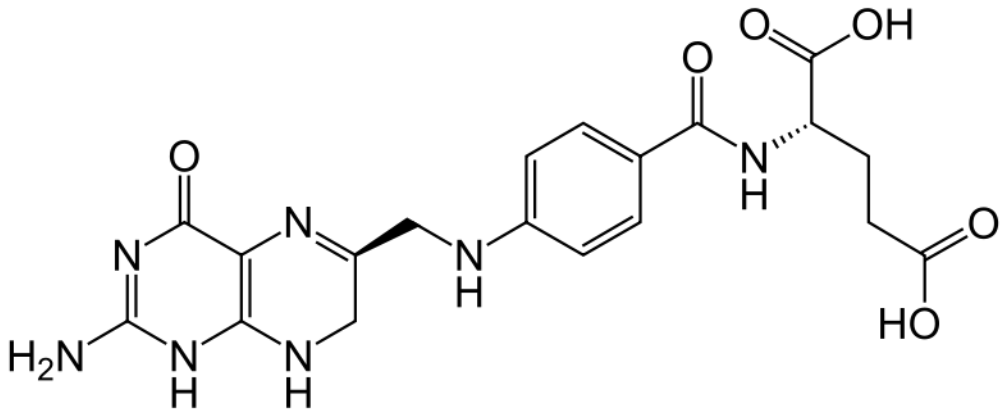
1. Major issue with Sulfa drugs
2. Staphylococci, Streptococci, Pneumococci, Meningococci can acquire resistance
3. Resistance in Enterobacteria is common
4. Resistance mediated by R-plasmids
5. Resistant strains synthesize enzymes with low affinity for sulfonamides, while others overproduce PABA
6. Widespread resistance has limited clinical use of Sulfomamides

TRIMETHOPRIM

- Structurally similar to Folate, Pyrimidine derivative
- Interferes in Folic Acid Pathway



Trimethoprim



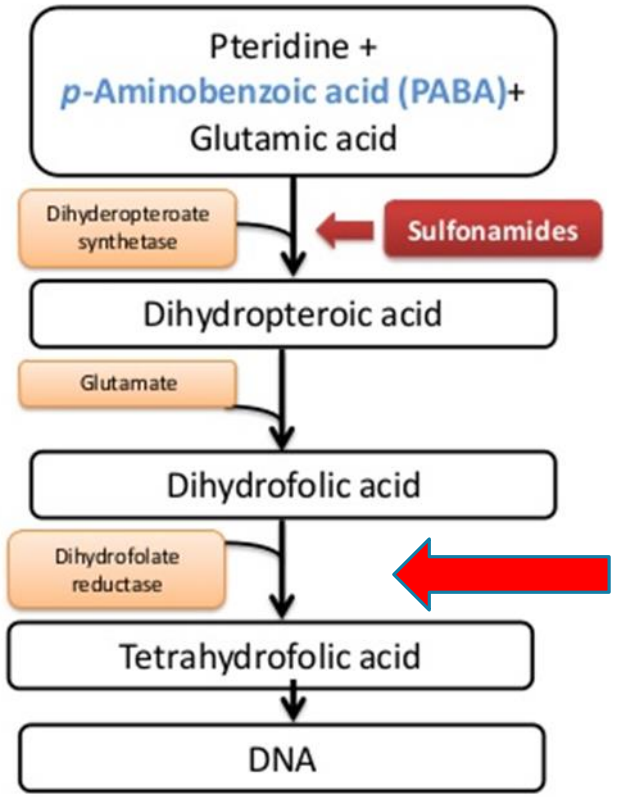
Dihydrofolic Acid

Unnumbered 25 p750b
Biochemistry, Seventh Edition

TRIMETHOPRIM

Mechanism of Action:

- Trimethoprim inhibits enzyme Di-hydrofolate reductase
- Bacterial enzyme is MORE sensitive than Human
- Human can also get Folic Acid from diet, Bacteria CANNOT !



Trimethoprim

TRIMETHOPRIM

❖ Mechanism of Action:

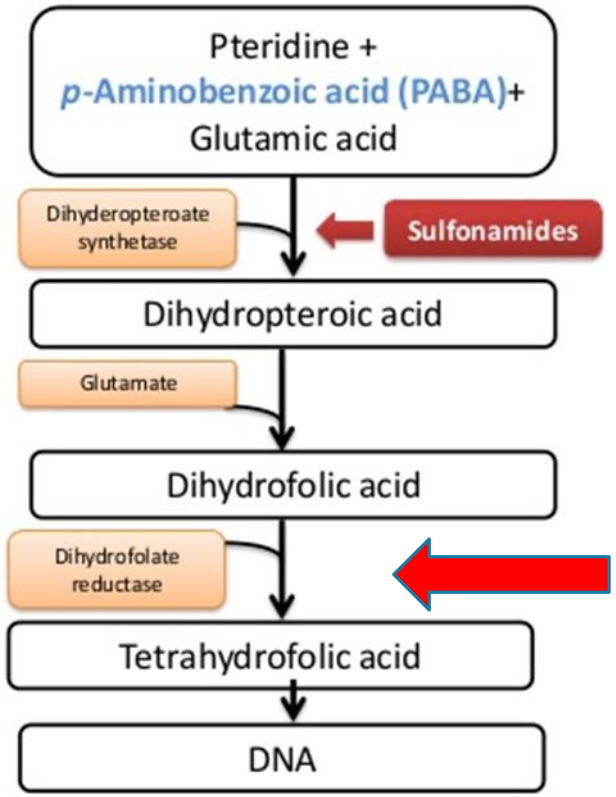
Trimethoprim

+

Sulfamethoxazole

Cotrimoxazole

- *Combines action of both*
- *Trimethoprim is >> sulfa*
- *Combination is bactericidal, resistance not easily developed*



Trimethoprim

TRIMETHOPRIM

- **ADME:**
- Oral administered, Rapid absorption from GI tract
- Peak levels : 1- 3 hrs
- Half life : 16 hrs, Distributed extensively in body (ECF, Bile)
- Weak base, acidification of Urine increases Urinary Excretion
- 80 % Dose excreted in Urine

TRIMETHOPRIM

- ADME:
- Administered in combination with Sulfamethoxazole
- 1:5 combination (80:400 mg), less drug used due to good distribution properties

TRIMETHOPRIM

- ADVERSE REACTIONS:
- Combination (Sulfa+Tri) has more GI (Pain, nausea, diarrhea) than drugs alone
- Trimethoprim may cause megaloblastic anemia in folic acid deficient patient
- Liver toxicities in AIDS patients
- Dose reduction needed in kidney damaged pts
- Avoided in pregnant women due to teratogenic effect of large doses

TRIMETHOPRIM, THERAPEUTIC USES

- Urinary Tract Infections: Due to E. Coli, S. Aureus, Proteus group
- Prostatitis: Alone & also in combination with Sulfa; Drugs of choice
- Respiratory tract infections : Bronchitis, Sinusitis
- Infection by Pneumocystis Jiroveci: Serious Pneumonia esp amongst immunocompromised patients,
- Trimethorprim also used as prophylactic in special category of susceptible patients
-