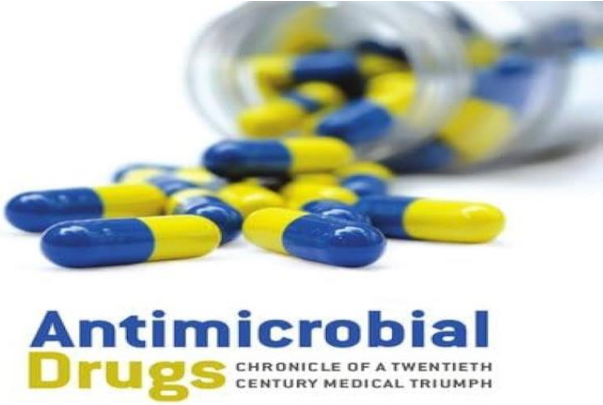

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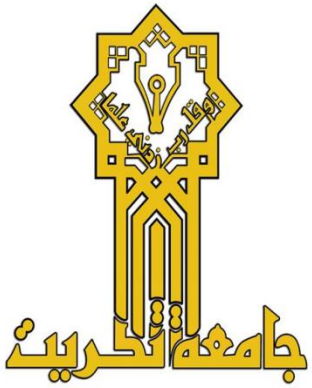

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كلية التمريض – جامعة تكريت

المرحلة الثانية \ أدوية

أ د حسام الدين النجار

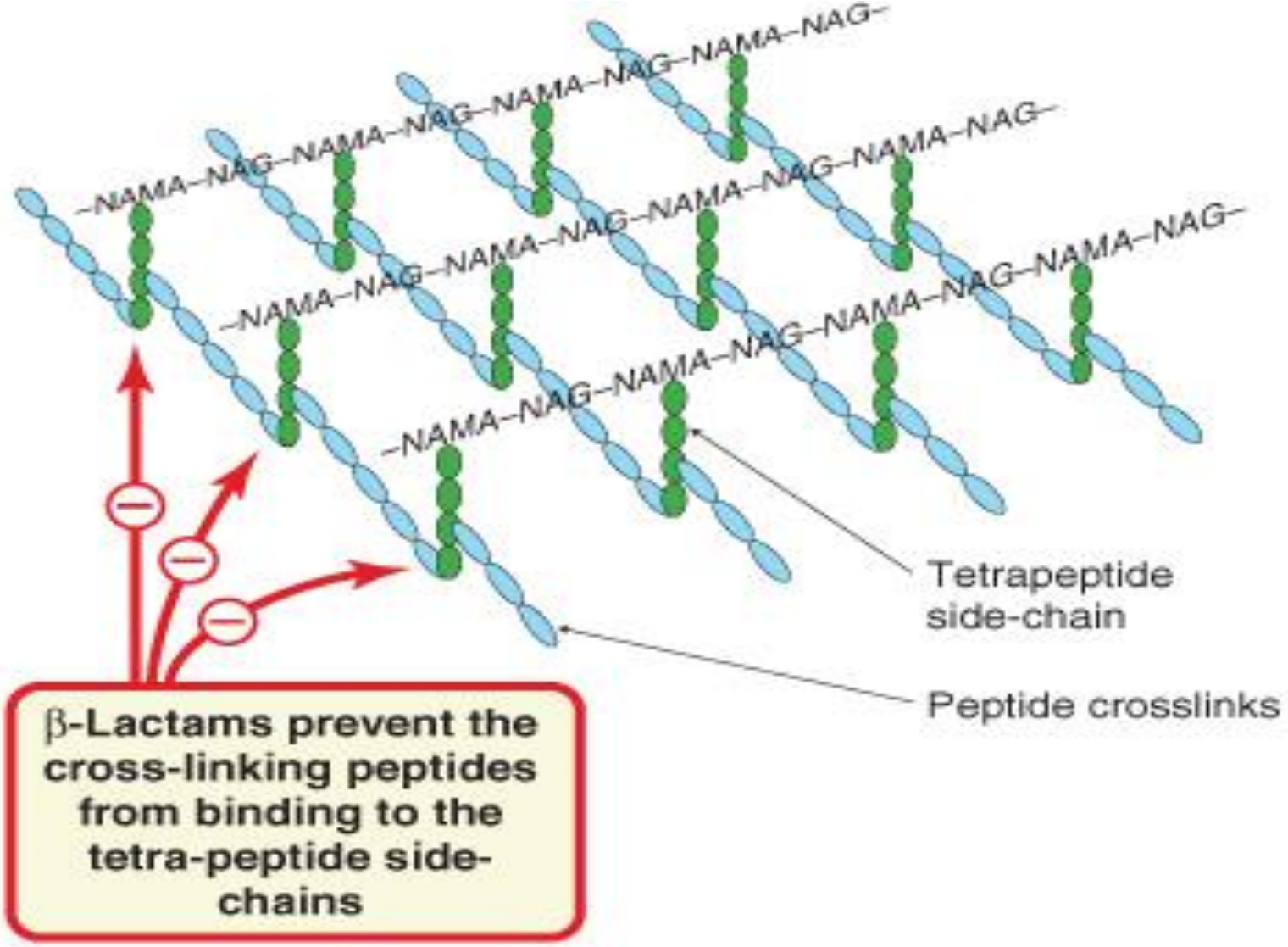
2024-2025 \ First Term

Penicillins , Cephalosporins , Macrolides and Sulfonamides.

Inhibitors of Cell Wall Synthesis

- **Inhibitors of Cell Wall Synthesis**
  - **β-lactams Penicillins & Cephalosporins**

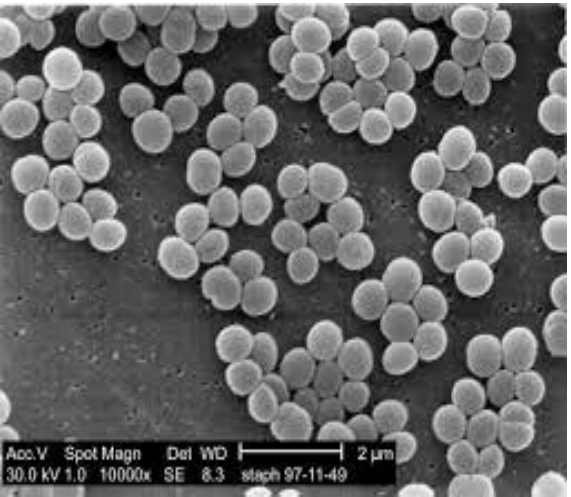
- Are only effective against rapidly growing organisms that synthesize a peptidoglycan cell wall (little or no effect on bacteria that are not growing and dividing).
- Are inactive against organisms devoid of cell wall, such as mycobacteria, protozoa, fungi, and viruses.



Penicillins

Classification:

1. Natural penicillins
2. Antistaphylococcal Penicillins (β-lactamase-resistant pen.)
3. Extended-Spectrum Penicillins .
4. Antipseudomonal penicillins.



1. **Natural penicillins (Biosynthetic):**

- Penicillin G (benzylpenicillin)
- Penicillin V (phenoxymethylpenicillin)

➢ **Semisynthetic penicillins (e.g. Amoxicillin)**

➢ **Antimicrobial spectrum:**

➢ Natural Penicillins have greatest activity against G+ve organisms, G- cocci, and non–β-lactamase producing anaerobes.

➢ Have little activity against G-ve rods

➢ Are susceptible to hydrolysis by β-lactamases (Inactivated by β-lactamases).

2. Antistaphyllococal penicillins (β-lactamase-resistant penicillins)

- Cloxacillin, Dicloxacillin, Oxacillin (oral).
- Nafcillin, Methicillin (Parentral).
- Resistant to hydrolysis by β-lactamase.
- Indicated for infections caused by β-lactamase–producing staphylococci (Drugs of choice).

3. Extended-Spectrum Penicillins (Aminopenicillins) Ampicillin and Amoxicillin

- Antibacterial spectrum: similar to penicillin G but have improved activity against G-ve bacilli (Broad spectrum activity against G+ve, G-ve cocci and G-ve bacilli)
- Resistance is the major problem.
- Not active against klebsiella, enterobacter, Pseudomonas aeruginosa, and other gram-negative aerobes that are commonly encountered in hospital-acquired infections.
- Inactivated by lactamases
- Formulation with β-lactamase inhibitor (clavulanic acid or sulbactam) protects them from hydrolysis and extends their antimicrobial spectrum.

- **<u>Clavulanic acid</u> + Amoxicillin**
- **<u>Sulbactam</u> + Ampicillin**

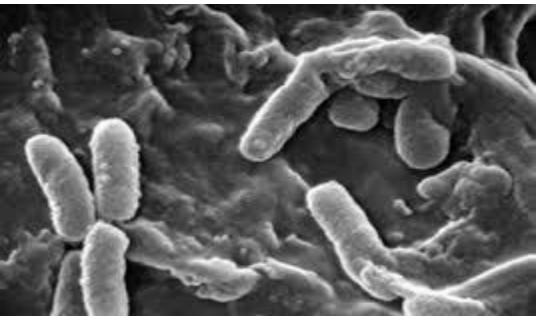
- Ampicillin: is orally absorbed (affected by the presence of food). It undergoes entero-hepatic cycling and excreted in bile.
- Amoxicillin: Better oral absorption than ampicillin, not affected by food, most of the drug is excreted in urine.

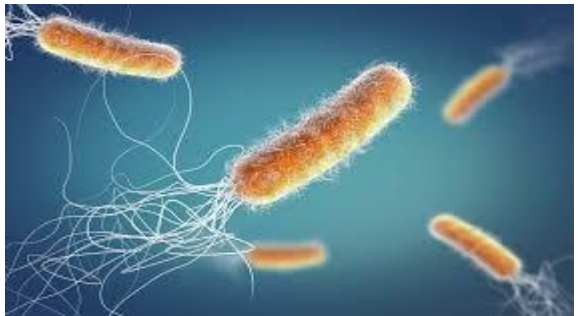
Therapeutic indications:

- **Upper and lower respiratory tract infections**
- **Urinary tract infection**
- **Meningitis**
- **Salmonella infection and bacterial diarrhea.**

4. Antipseudomonal penicillins (Carbenicillin, Ticarcillin and Piperacillin):

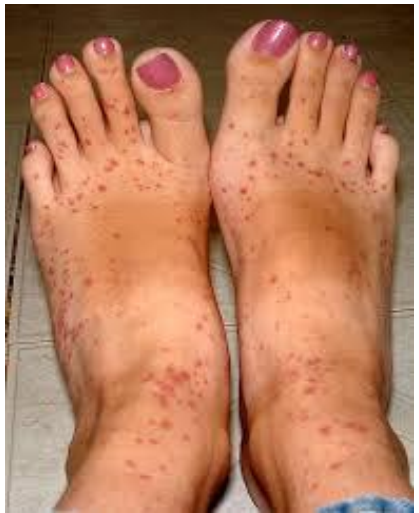
- are active against *Pseudomonas aeruginosa* and certain indole-positive *Proteus* spp
- Used for community-acquired pneumonia caused by Pseudomonas aeruginosa.





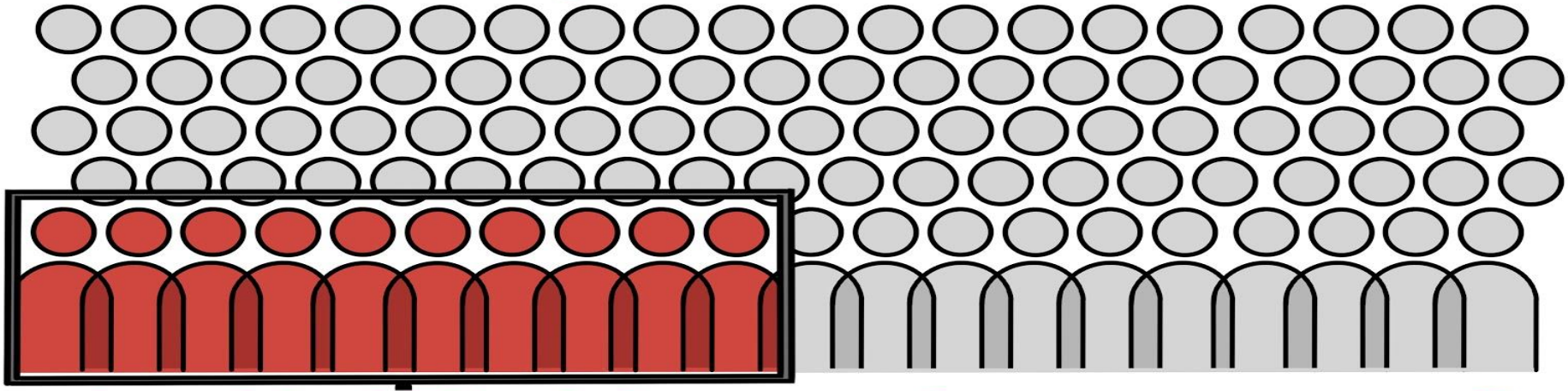
Adverse reactions of penicillins:

- **Hypersensitivity reactions** Skin rashes, fever, angio-odema and anaphylactic shock.
- In patients with renal failure, penicillin in high doses can cause seizures.
- Large doses of penicillins given orally may lead to GIT upset, particularly nausea, vomiting, and diarrhea.
- Ampicillin has been associated with pseudomembranous colitis.
- Secondary infections such as vaginal candidiasis may occur.



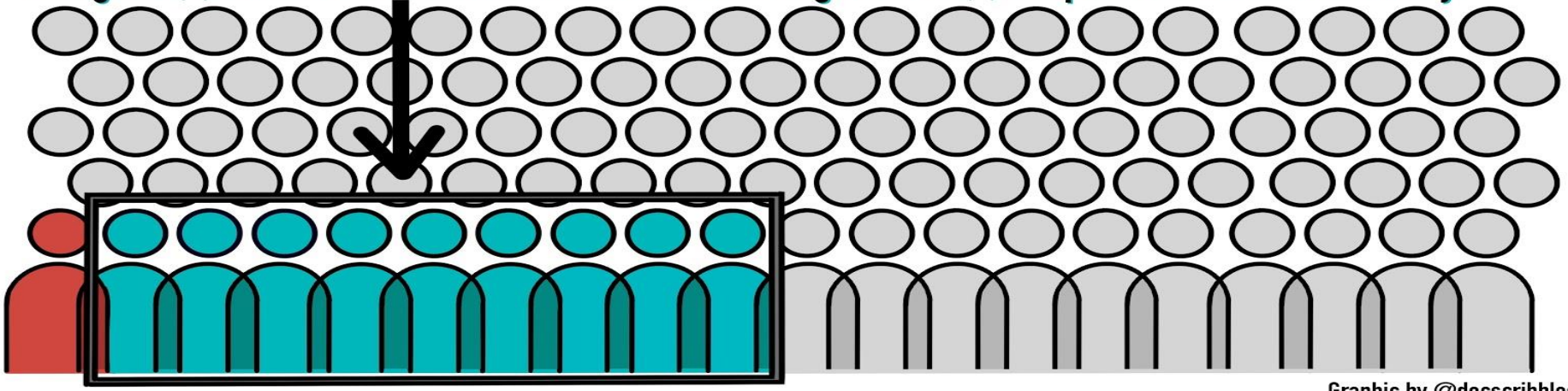
5–10% of the population thinks they are allergic to penicillins...

CORE IM



...but 90–95% of those patients can actually tolerate penicillins

WHY? (1) Most don't know penicillin allergies fade over time, (2) Viral rashes can be confused as drug allergies, (3) Adverse effects are mislabeled as allergies, and (4) People believe it is hereditary



Graphic by @docscribbles

Cephalosporines

- **First generation:**
- Cephalexin , Cephradine, Cefadroxil (oral).
- Cephapirin, Cefazolin, Cephalothin (par.)
- **Spectrum of activity**:
- Very active against G+ve cocci (pneumococci, streptococci, and staphylococci) except MRSA .
- Low activity against G-ve cocci and bacilli but E. coli, K. *pneumoniae,* and *Proteus mirabilis* are often sensitive (EcKP).
- Anaerobic cocci are usually sensitive, but *Bacteroides fragilis* is not.
- Sensitive to B-lactamase.

First-generation cephalosporins

Gram (+) cocci

*Staphylococcus aureus**
Staphylococcus epidermidis
Streptococcus pneumoniae
Streptococcus pyogenes
Anaerobic streptococci

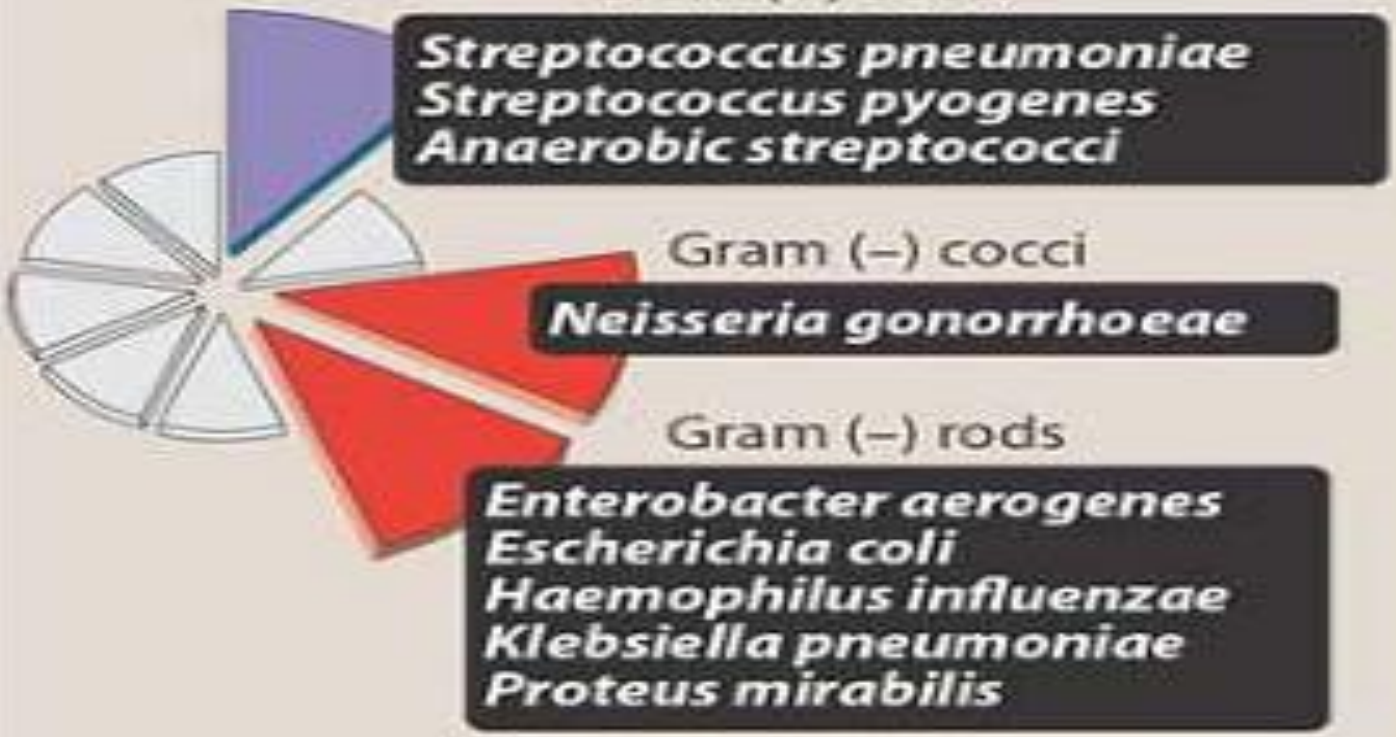
*Except methicillin-resistant Staphylococcus aureus

Gram (–) rods

Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis

- **Second generation**:
- Cefoxitin, cefotetan and cefmetazole, cefamandole, cefuroxime (injections)
- Cefaclor, cefuroxime (oral)
- **Spectrum of activity:**
- Active against organisms inhibited by first-generation drugs, but in addition they have extended gram-negative coverage (H. influenzae, Enterobacter and some Neisseria spp.
- As with first-generation agents, none is active against enterococci or *P. aeruginosa.*
- Cefotetan and cefoxitin have good activity against anaerobes (*Bacteroides fragilis)*

Second-generation cephalosporins



- **Third-Generation Cephalosporins**
- **Cefoperazone, cefotaxime, ceftazidime, ceftriaxone, ceftizoxime (injections)**
- **Cefixime, cefpodoxime, cefditoren, ceftibuten, and cefdinir (oral)**
- **Antimicrobial Activity**
- Compared with 2nd –generation:
- They have expanded G-ve coverage.
- **Are less active than 1st generations against G+ve cocci, but they are much more active against the Enterobacteriaceae, including B-lactamase-producing strains.**
- **Ceftazidime and cefoperazone are also active against P aeruginosa.**
- Activity against anaerobes is poor compare to clindamycin or metronidazole.
- And some are able to cross the blood-brain barrier.
- **Cefotaxime & Ceftriaxone has been used effectively for meningitis**

Third-generation cephalosporins

- **Clinical uses of cephalosporins:**
- **1st generation:**
- **Skin and soft tissue infections**
- **Surgical prophylaxis (cefazolin)**
- **2nd generation:**
- The oral drugs primarily used to treat sinusitis, otitis, and lower RTIs, although they are suboptimal (compared with oral amoxicillin)

- **U.T.I. and biliary tract infections (cefaclor)**

- Cefoxitin, cefotetan, or cefmetazole can be used to treat mixed anaerobic infections such as intra-abdominal, pelvic inflammatory disease & diabetic foot infections

- **For colorectal surgery, where prophylaxis for intestinal anaerobes is desired, cefoxitin or cefotetan are preferred.**

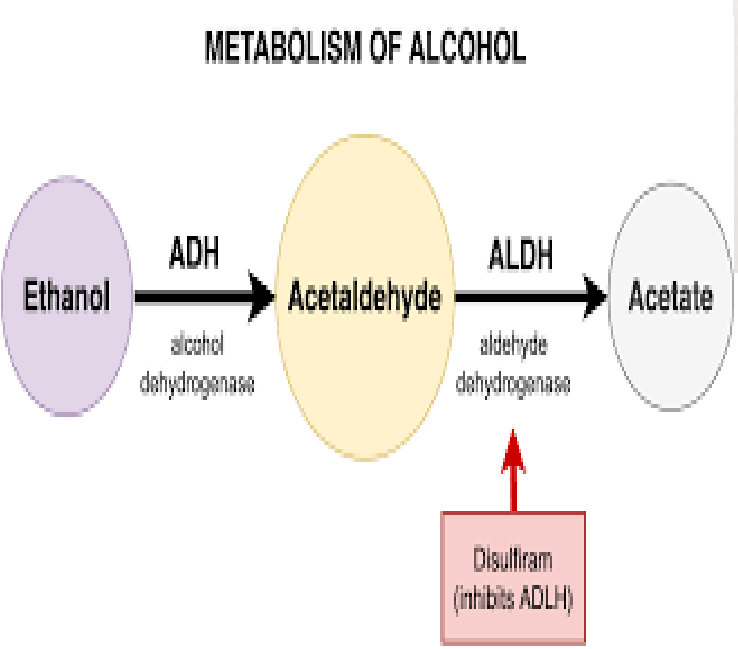
- **3rd generation:**
- Ceftriaxone or cefotaxime are the drugs of choice for the treatment of meningitis caused by pneumococci, meningococci, H influenzae, and susceptible enteric G-ve rods
- **Gonorrhoea and syphilis (ceftriaxone is the drug of choice)**
- Acute otitis media and typhoid fever (Cefixime or ceftriaxone)
- **Empirical therapy of sepsis of unknown cause.**
- In neutropenic, febrile immunocompromised patients, third-generation cephalosporins are often used in combination with an aminoglycoside.

- **Adverse Effects and Drug Interactions:**
- **Hypersensitivity reactions:**
- **5-15 % show cross-sensitivity with penicillins**
- **Bleeding**:
- Drugs with a methylthiotetrazole group (cefamandole, cefmetazole, cefotetan, cefoperazone) cause bleeding disorders (prevented by vitamin K)
- **Alcohol intolerance" disulfiram-like effect"**
- Drugs with the methylthiotetrazole ring can cause severe disulfiram-like reactions (avoid alcohol and alcohol-containing medications.
- **Nephrotoxicity:**
- Cephalothin (avoid other nephrotoxic agents).
- Severe pain after i.m, and thrombophlebitis after i.v.

DISULFIRAM LIKE REACTION

Drugs that inhibit aldehyde dehydrogenase can result in Disulfiram like reaction. Important drugs causing this adverse effect with alcohol are:

C yclic : Chlorpropamide
: Cefoperazone
: Cefomandole
: Cefotetan
G : Griseofulvin
M : Metronidazole
Moxalactam
P : Procarbazine



MACROLIDES

Macrolides are a class of antibiotics found in streptomycetes. They are natural lactones with a large ring, consisting of 14 to 20 atoms. **Macrolides** bind to the 50S subunit of the bacterial ribosome and inhibit ribosomal translocation, leading to inhibition of bacterial protein synthesis.

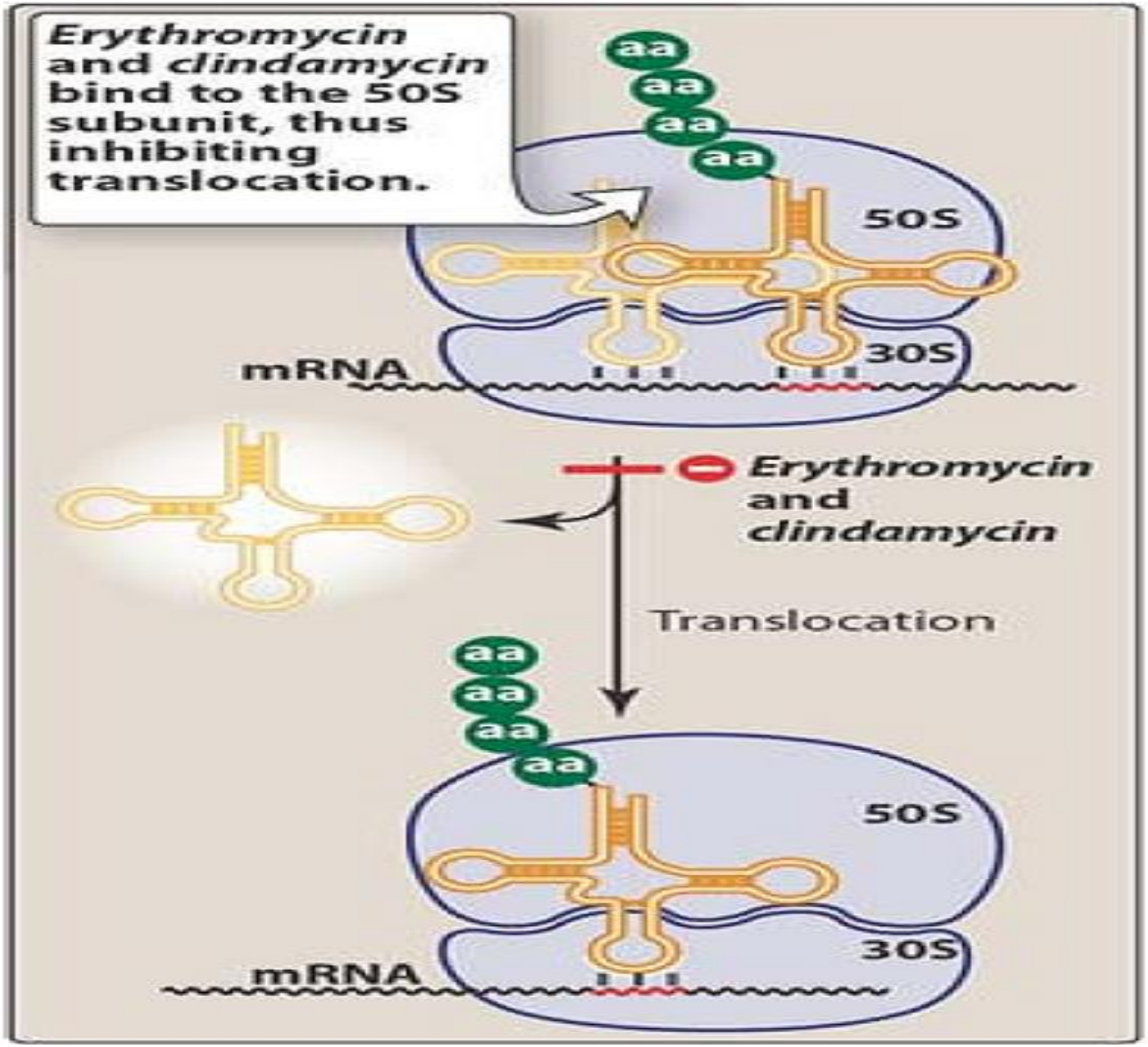
- **Erythromycin**
- **Azithromycin**
- **Clarithromycin … & others**

- **Mechanism of action:**
- They bind irreversibly to a site on the 50S subunit of the bacterial ribosome, thus inhibiting the translocation steps of protein synthesis (bacteriostatic, they may be bactericidal at higher doses)
- Their binding site is either identical or very near the site for clindamycin and chloramphenicol.

Spectrum of activity:

Erythromycin:

- **Is effective against many of the same organisms as penicillin G therefore, it is used in patients who are allergic to penicillins.**
- **Active against G+ve bacteria especially pneumococci, streptococci, staphylococci, and corynebacteria**
- **Active against Mycoplasma, Chlamydia , Treponema pallidum, and certain mycobacteria**
- **Less effective against G -ve organisms except Neisseria, Bordetella pertussis, legionella and Campylobacter species are susceptible,**
- **It has modest activity against H. influenzae**


Erythromycin and clindamycin bind to the 50S subunit, thus inhibiting translocation.
aa
aa
aa
aa
50S
30S
mRNA
Erythromycin and clindamycin
Translocation
aa
aa
aa
aa
50S
30S
mRNA

Clarithromycin:

- **Spectrum: similar to that of erythromycin, but it is also effective against H. influenzae and more active against Mycobacterium avium complex .**
- **Its activity against Chlamydia, Legionella, and H. pylori, is higher than that of erythromycin.**
- **Clarithromycin also has activity against M leprae and Toxoplasma gondii.**

Azithromycin:

- **Less active than erythromycin against G+ve but more active against respiratory infections due to H. influenzae and Moraxella catarrhalis.**
- **Preferred therapy for urethritis caused by Chlamydia trachomatis.**
- **It also has activity against Mycobacterium avium as well as Toxoplasma gondii in patients with HIV**

Clinical Uses:

- Erythromycin is a drug of choice for pertussis, Legionnaires disease, diphtheria and chlamydial infection in infants and pregnant woman.
- *Streptococcal Infections & staphylococcal Infections:* Pharyngitis, scarlet fever, pneumonia, soft tissue infection and periodontal infection in patient allergic to penicillins.
- Mycoplasma pneumoniae infections: A macrolide or tetracycline is the drug of choice
- Azithromycin is useful in treatment uncomplicated non-gonococcal urethritis, especially during pregnancy when tetracyclines are contraindicated.

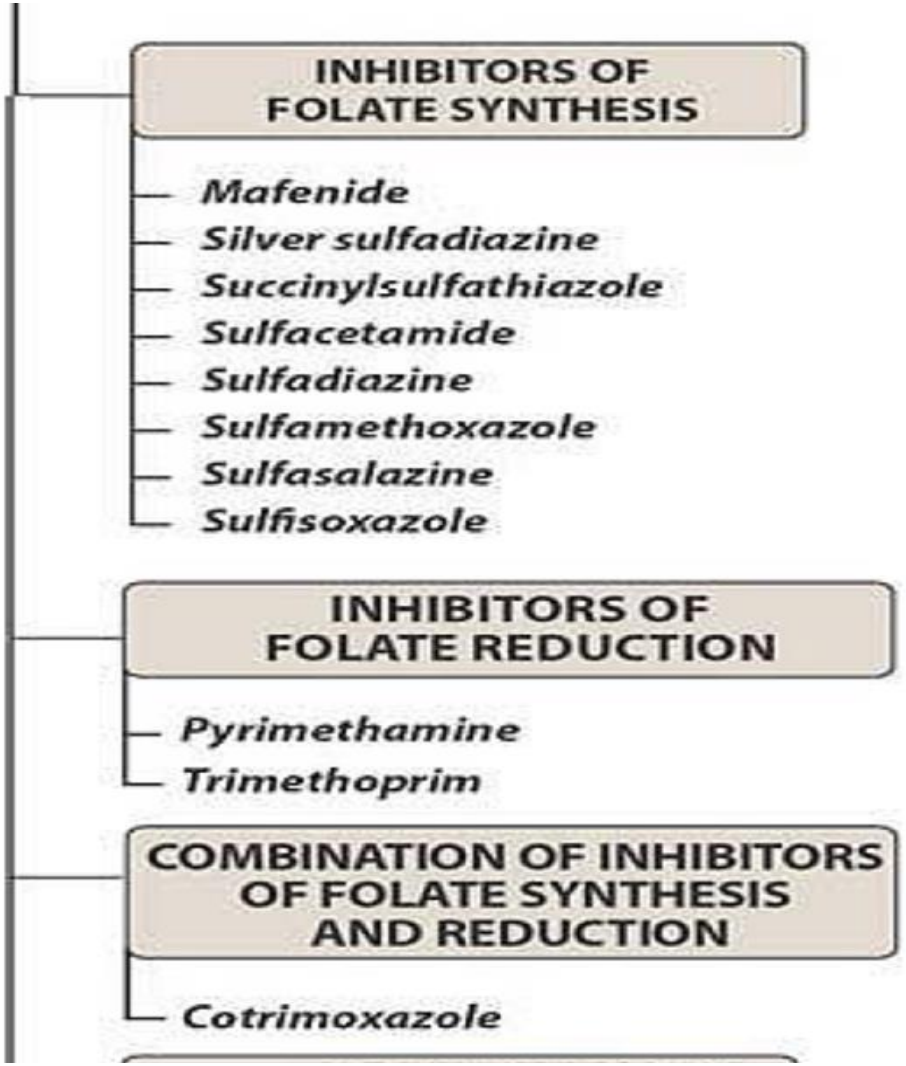
- **Syphilis**: in patient allergic to penicillins
- **Tetanus**: in patients allergic to penicillin.
- **Peptic ulcer:** caused by H. pylori (clarithromycin)
- **Mycobacterial infections:**

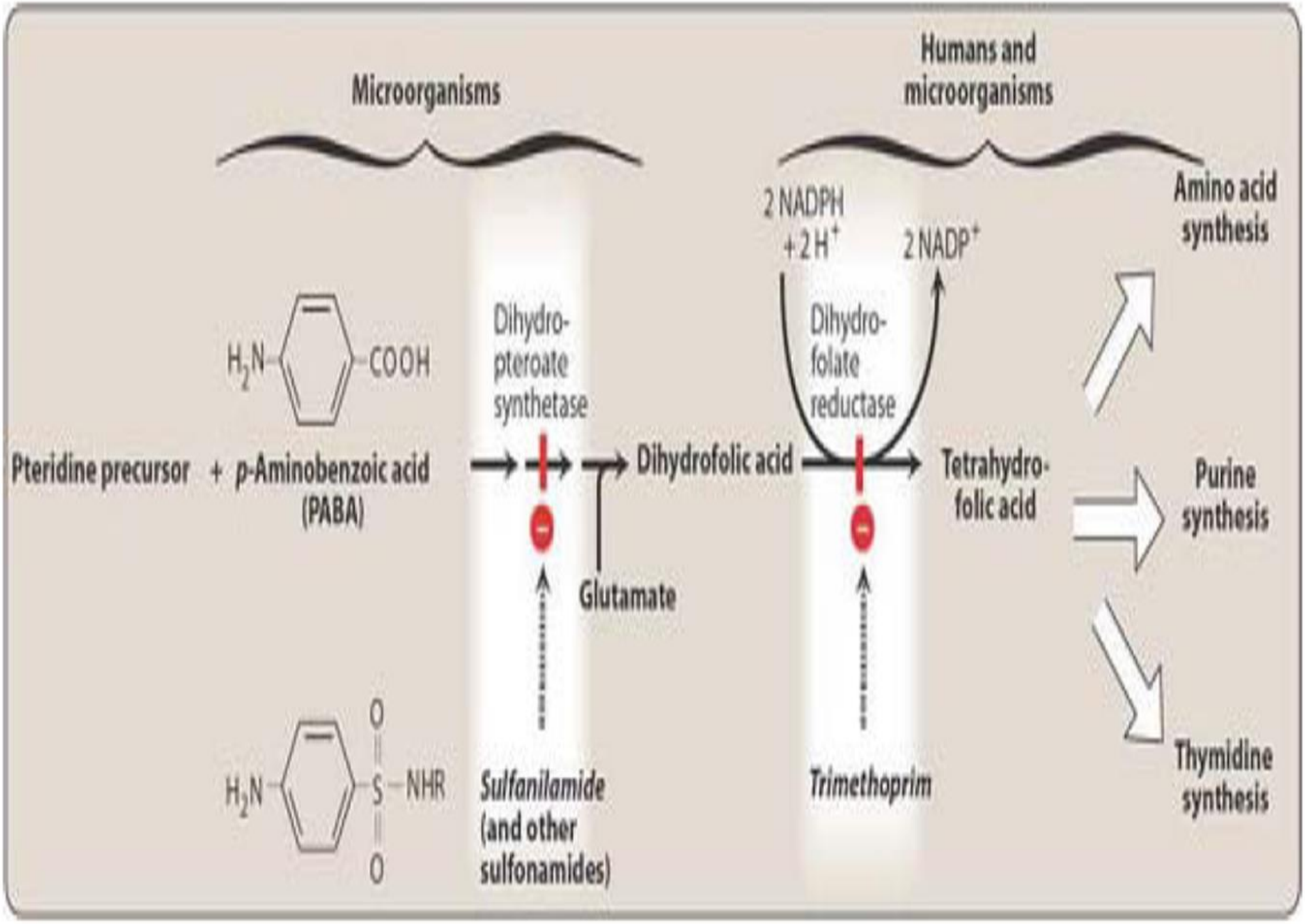
- Treatment or prophylaxis of M. avium infection in AIDS patients (azithromycin and clarithromycin)
- Clarithromycin with minocycline for the treatment of *Mycobacterium leprae*
- **Toxoplasmosis:** (azithromycin and clarithromycin)
- Campylobacter **gastroenteritis** in children.

Adverse Reactions

- **Gastrointestinal effects:**
- Anorexia, nausea, vomiting, and diarrhea
- **Liver Toxicity:**
- Erythromycins (estolate) can produce acute cholestatic hepatitis, probably as a hypersensitivity reaction.
- Other allergic reactions include fever, eosinophilia, and rashes.
- A rare cases of hepatitis and liver failure have been reported with telithromycin
- **Ototoxicity**:
- Transient deafness has been associated with erythromycin (high dosages)
- **Telithromycin prolongs QT interval** in some patients.

Inhibitors of bacterial metabolism (Antifolates)




Microorganisms
Humans and microorganisms
Amino acid synthesis
2 NADPH + 2 H+
2 NADP+
Dihydro-pteroate synthetase
Dihydro-folate reductase
H2N
COOH
Pteridine precursor + p-Aminobenzoic acid (PABA)
Dihydrofolic acid
Tetrahydro-folic acid
Purine synthesis
Glutamate
Thymidine synthesis
H2N
S
NHR
O
O
Sulfanilamide (and other sulfonamides)
Trimethoprim

Mechanism:

- Both trimethoprim and the sulfonamides interfere with folate metabolism in the bacterial cell by competitively blocking the biosynthesis of tetrahydrofolate in sequential steps.
- **Sulfonamides inhibit the synthesis of dihydrofolic acid, while trimethoprim inhibit further reduction and conversion of dihydrofolic acid into tetrahydrofolic acid (synergistic effect)**
- **Tetrahydrofolate acts as a carrier of one-carbon fragments and is necessary for the ultimate synthesis of DNA, RNA and bacterial cell wall proteins.**
- **Unlike mammals, bacteria and protozoan parasites usually lack a transport system to take up preformed folic acid from their environment**
- **Most of these organisms must synthesize folates**

- Sulfonamides are structural analogues of p-aminobenzoic acid (PABA).

Sulfonamides:

- Competitively block the conversion of pteridine and p-aminobenzoic acid to dihydrofolic acid by the enzyme **dihydropteroate synthase**.
- Sulfonamides have a greater affinity than p-aminobenzoic acid for dihydropteroate synthase.

Trimethoprim:

- has a tremendous affinity for bacterial dihydrofolate reductase (50,000 times higher than for the mammalian enzyme); when bound to this enzyme, it inhibits the synthesis of tetrahydrofolate.

Antibiotic Drug Names Made Easy

Sulfonamides

Begin with "Sulfa"

Sulfasalazine Sulfamethoxazole

Sulfonamides

Spectrum of activity

- Bacteriostatic, broad spectrum antibiotics.
- Against a wide range of G+ve and G-ve bacteria, Nocardia, *Chlamydia trachomatis,* and some protozoa.
- Enteric bacteria, such as *E coli,* klebsiella, salmonella, shigella, and enterobacter, are also sensitive.
- Activity is poor against anaerobes.

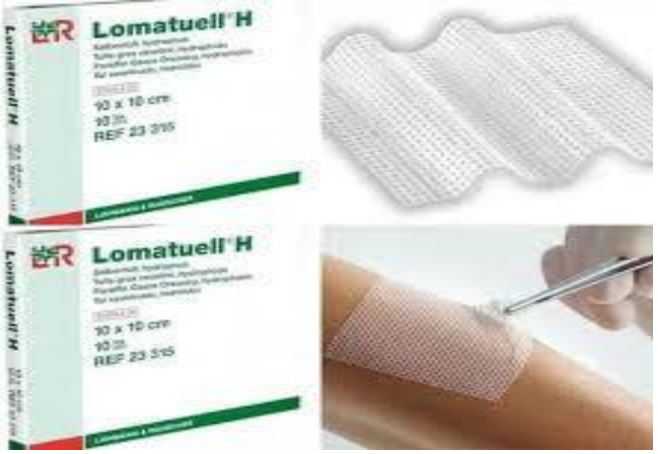
Pharmacokinetics:

Sulfonamides can be divided into three major groups:

- (1) oral, absorbable.
- (2) oral, nonabsorbable.
- (3) topical.

Oral, absorbable sulfonamides:

- **Short:** Sulfacytine, Sulfisoxazole and Sulfamethizole
- **Intermediate:**Sulfadiazine, Sulfamethoxazole and Sulfapyridine
- **long-acting:**. Sulfadoxine



ONEMED
Dermafix TULLE 10cm x10cm
Steril Paraffin Gauze Dressing

Oral non-absorbable Sulfonamides:

Sulfasalazine(Have anti-inflammatory effect).

Topical sulfonamides: Silver sulfadiazine , Sodium sulfacetamide, Mafenide acetate

Clinical Uses:

Sulfonamides are infrequently used as single agents.

1- Sulfisoxazole and sulfamethoxazole used almost exclusively to treat **urinary tract infections.**

2-The fixed-drug combination of trimethoprim-sulfamethoxazole is the **drug of choice for infections such as pneumonia.**

3-Sulfadiazine in combination with pyrimethamine is first-line therapy for **acute toxoplasmosis.**

4-Sulfadoxine in combination with pyrimethamine used as a **second-line agent in treatment for malaria.**

5-Sulfasalazine is used in **ulcerative colitis, enteritis, and other inflammatory bowel disease .**

6-Sodium sulfacetamide ophthalmic solution or ointment is effective in the treatment of **bacterial conjunctivitis and as adjunctive therapy for trachoma.**

7-Mafenide acetate and Silver sulfadiazine are used **topically for prevention of infection of burn wounds (flamazine).**

The Right Way to Use Silvadene Cream

1. Clean your wound
2. Apply in 1/16th" thickness twice a day under sterile conditions
3. Reapply when daily activities remove the cream
4. Cover wound with dressings if desired
5. Use until burn area heals or is ready for grafting

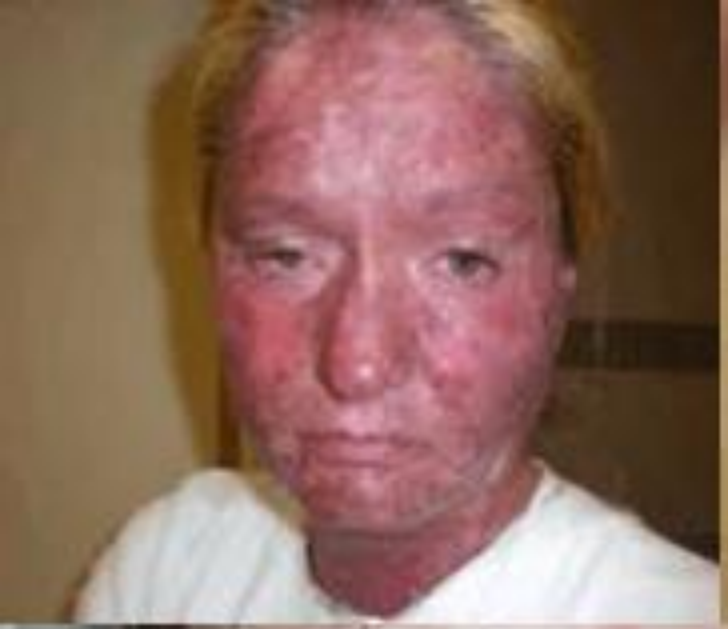
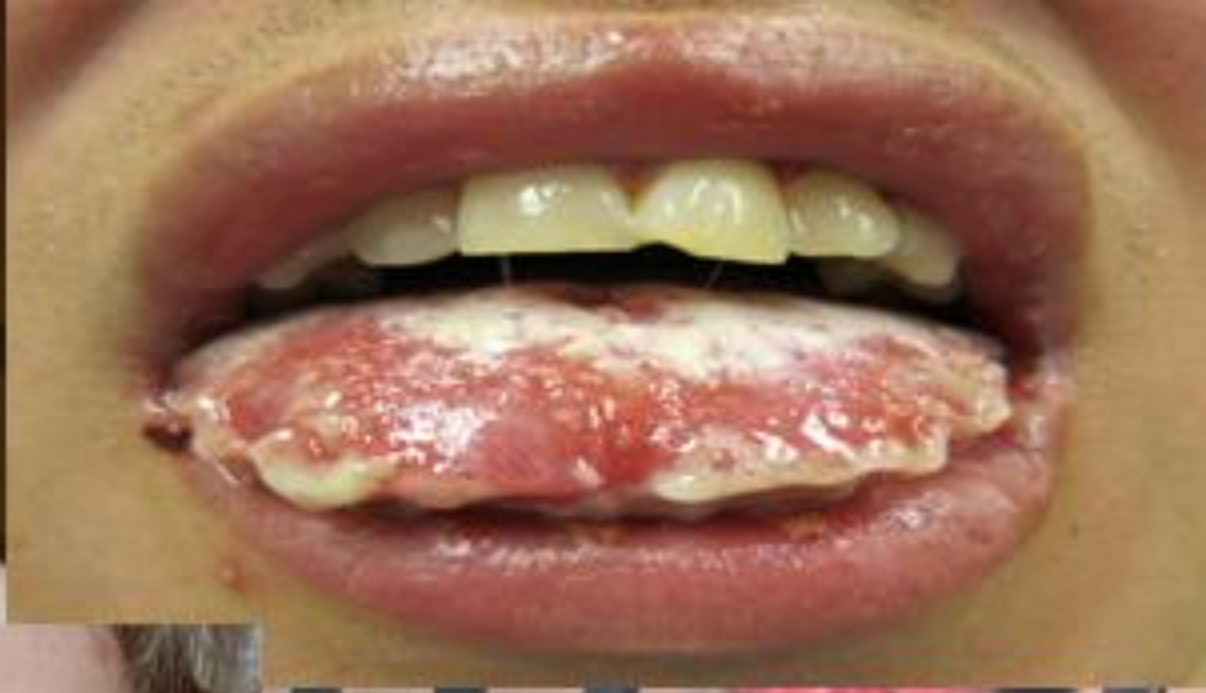
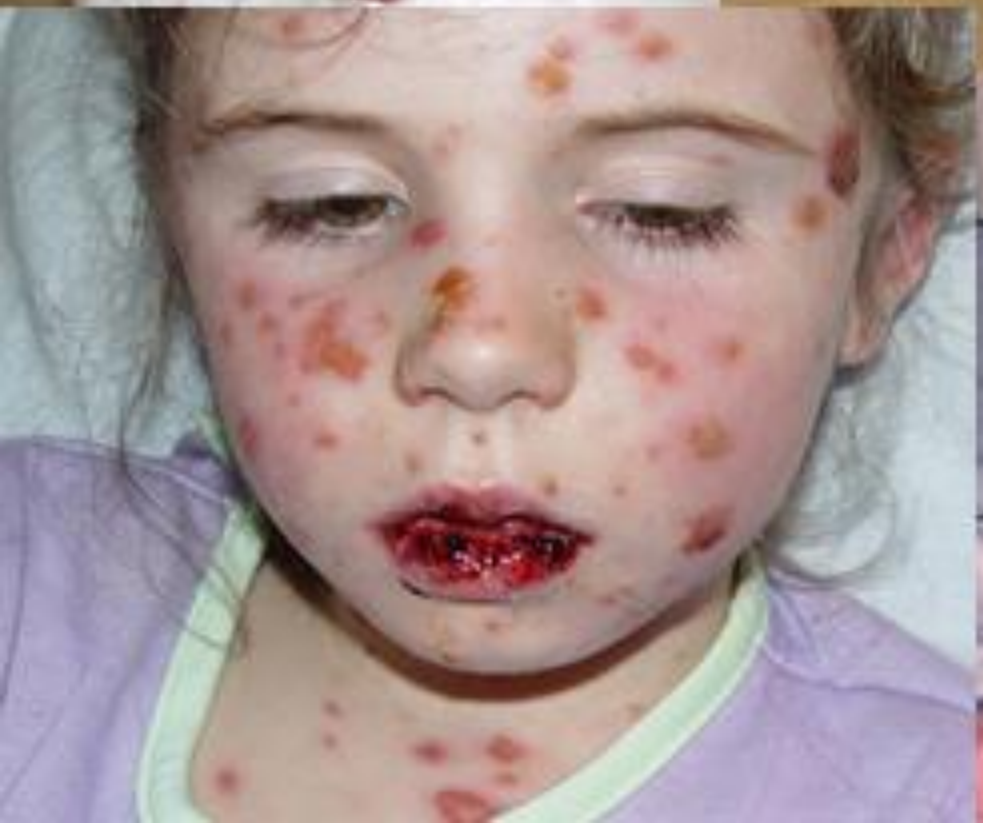
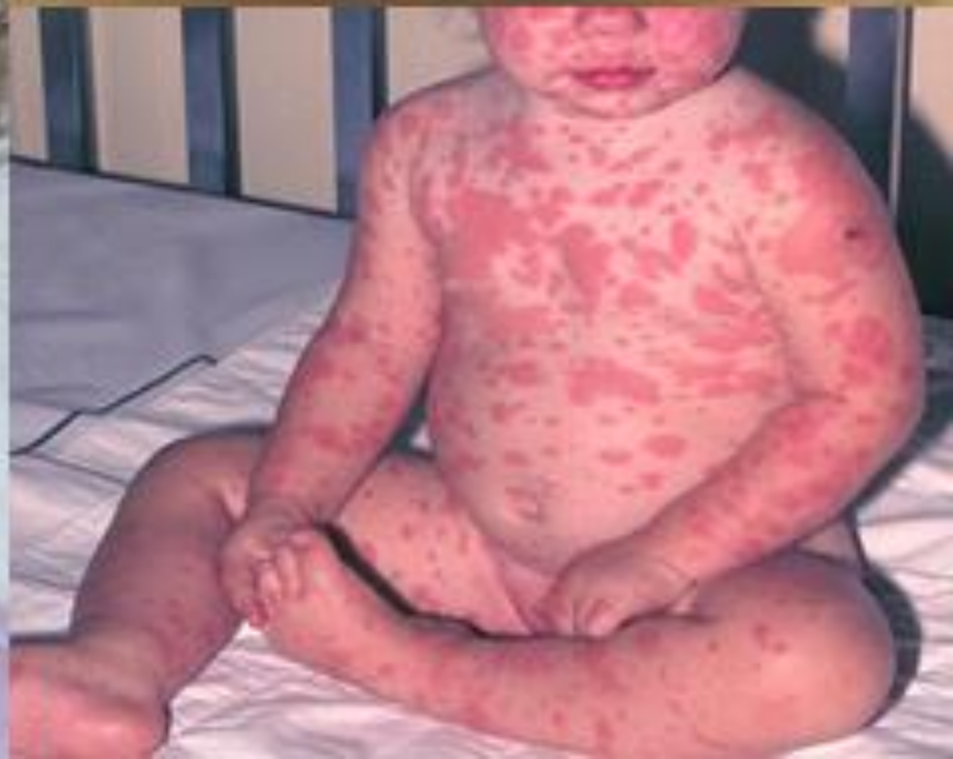
Adverse Reactions:

1-Hypersensitivity reactions:

- Fever, skin rashes, dermatitis, photosensitivity and Stevens-Johnson syndrome (rare but serious).
- All sulfonamides (antimicrobial sulfas, diuretics, diazoxide, and the sulfonylurea) partially cross-allergenic.

2-Urinary Tract Disturbances:

- **a-**Sulfonamides may precipitate in urine, especially at neutral or acid pH, producing crystalluria, hematuria, or even obstruction.
- Rare with the more soluble sulfonamides (Sulfisoxazole)
- Crystalluria is treated by administration $NaHCO_3$ and fluids to maintain adequate hydration.
- **b**-Sulfonamides have also been implicated in various types of nephrosis and in allergic nephritis

3-Hematopoietic Disturbances

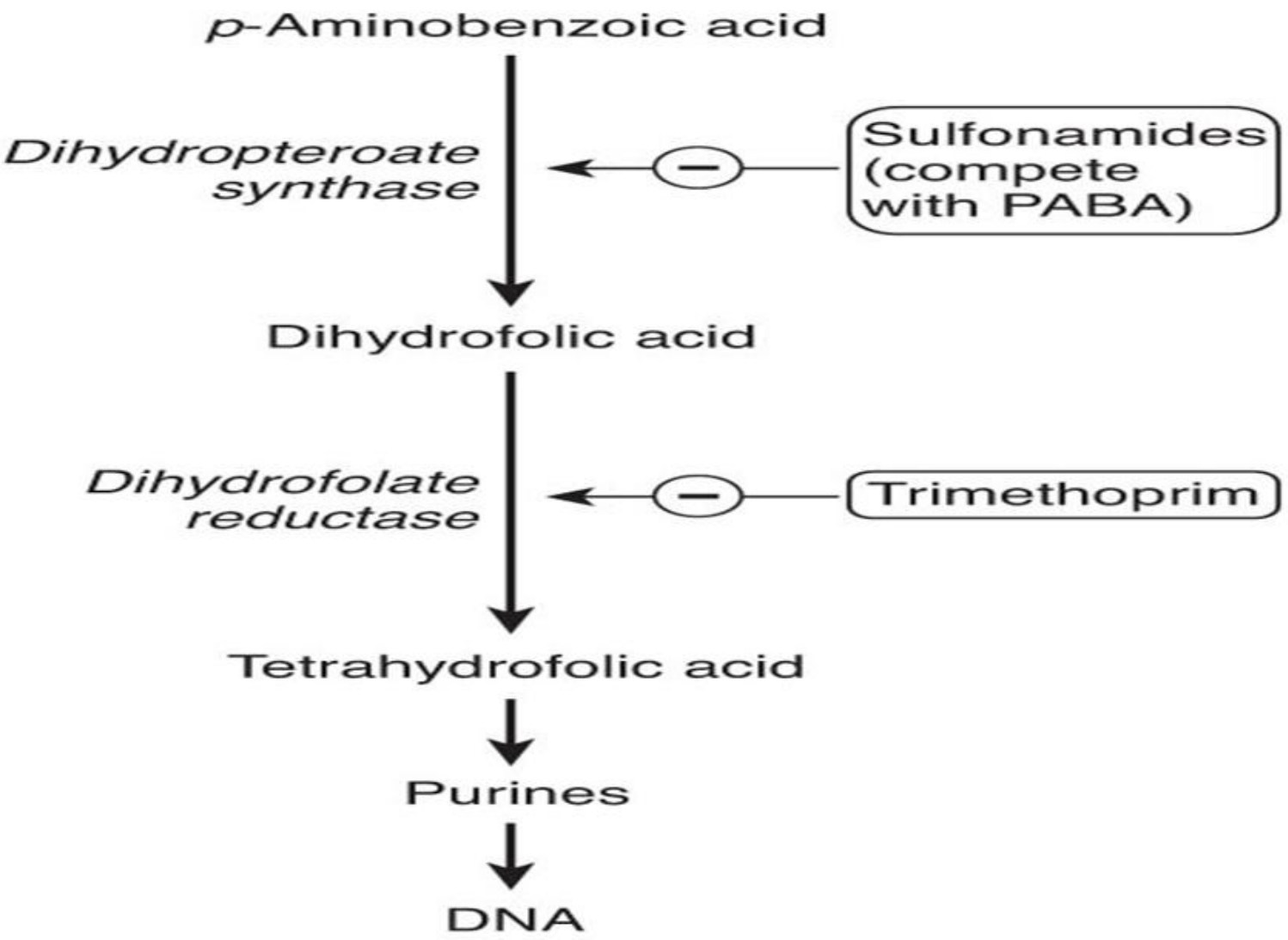
- **a-**Sulfonamides can cause hemolytic or aplastic anemia, granulocytopenia, thrombocytopenia.
- **b**-Sulfonamides may provoke hemolytic reactions in patients with glucose-6-phosphate dehydrogenase deficiency (G6PD).

4-Sulfonamides taken near the end of pregnancy increase the risk of kernicterus in newborns.

5-GIT Disturbances:

- Nausea, vomiting, diarrhea.

Trimethoprim



Mechanism of action:

- Selectively inhibits bacterial dihydrofolic acid reductase.
- Trimethoprim is bacteriostatic.

Spectrum:Co-trimoxazole:

- Trimethoprim plus sulfamethoxazole) → synergism.
- It is bactericidal and give effective coverageа gainst a wide range of G+ve andG-ve bacteria.

Clinical Uses

- **Oral Trimethoprim**

Trimethoprim alone (100 mg BID) in acute UTIs.

- **Oral Trimethoprim-Sulfamethoxazole (TMP-SMZ):**
- P jiroveci pneumonia, shigellosis, systemic salmonella infections, UTIs, prostatitis, and some nontuberculous mycobacterial infections.
- It is active against most Staphylococcus aureus strains, both methicillin-susceptible and MRSA, and against RT pathogens such as the pneumococcus, Haemophilus sp, Moraxella catarrhalis, and Klebsiella pneumoniae.

Adverse Effects

- Megaloblastic anemia, leukopenia, and granulocytopenia.
- The combination:
- Nausea and vomiting, drug fever, vasculitis, renal damage, and CNS disturbances occasionally occur also.
- Patients with AIDS and pneumocystis pneumonia have a particularly high frequency of untoward reactions to the combination.


THANK YOU FOR LISTENING
ANY QUESTION
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