Vancomycin, chemotherapeutics

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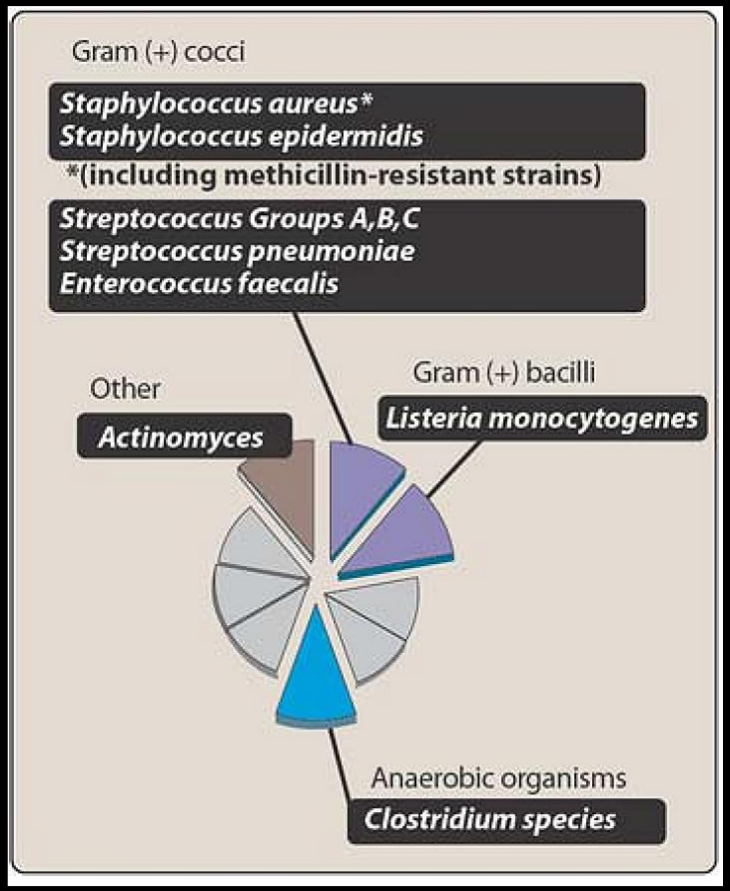
Vancomycin

- is a tricyclic glycopeptide
- It inhibits synthesis of bacterial cell wall phospholipids as well as peptidoglycan polymerization ⇨ weakening the cell wall and damaging the underlying cell membrane
- is effective primarily against G+ organisms
- It has been lifesaving in the treatment of MRSA and MRSE (S. epidermidis) infections
- oral vancomycin – pseudomembranous colitis
- It acts synergistically with the AMG, and this combination can be used in the treatment of enterococcal endocarditis

Antimicrobial spectrum and adverse effects



Lippincott's Illustrated Reviews: Pharmacology, 4th Edition

Adverse effects

- **serious problem - fever, chills, and/or phlebitis at the infusion site.**
- **Flushing (red neck syndrom) and shock results from histamine release associated with a rapid infusion.**
- **Dose-related hearing loss in patients with renal failure**
- **Ototoxicity and nephrotoxicity are more common when vancomycin is administered with another drug (for example, an aminoglycoside) that can also produce these effects.**

CHLORAMPHENICOL

Adverse effects

Anemia: Hemolytic anemia in patients with low levels of G6-PD

Other types of anemia include reversible anemia (is dose-related and occurs concomitantly with therapy) and aplastic anemia, which is idiosyncratic and usually fatal !!!

Bone marow supression

Potential teratogenic effects

Gray baby syndrome

QUINOLONES

FIRST GENERATION

Nalidixic acid

FLUOROQUINOLONES

SECOND GENERATION

Ciprofloxacin, Norfloxacin
Ofloxacin

THIRD GENERATION

Gatifloxacin, Levofloxacin
Moxifloxacin, Sparfloxacin

FOURTH GENERATION

Trovafloxacin

FLUOROQUINOLONES

Old drug, NALIDIXIC ACID and NORFLOXACIN *used mainly for recurrent urinary tract infections (UTIs).*

Newer fluorinated quinolones - greater potency, broader spectrum of antimicrobial activity, systemic effects.

New compounds - more active against G+ organisms, yet retain favorable activity against G- microorganisms.

A. Mechanism of action

- they enter the bacterium by passive diffusion via water channels.
- inhibit bacterial topoisomerases which are necessary for DNA synthesis

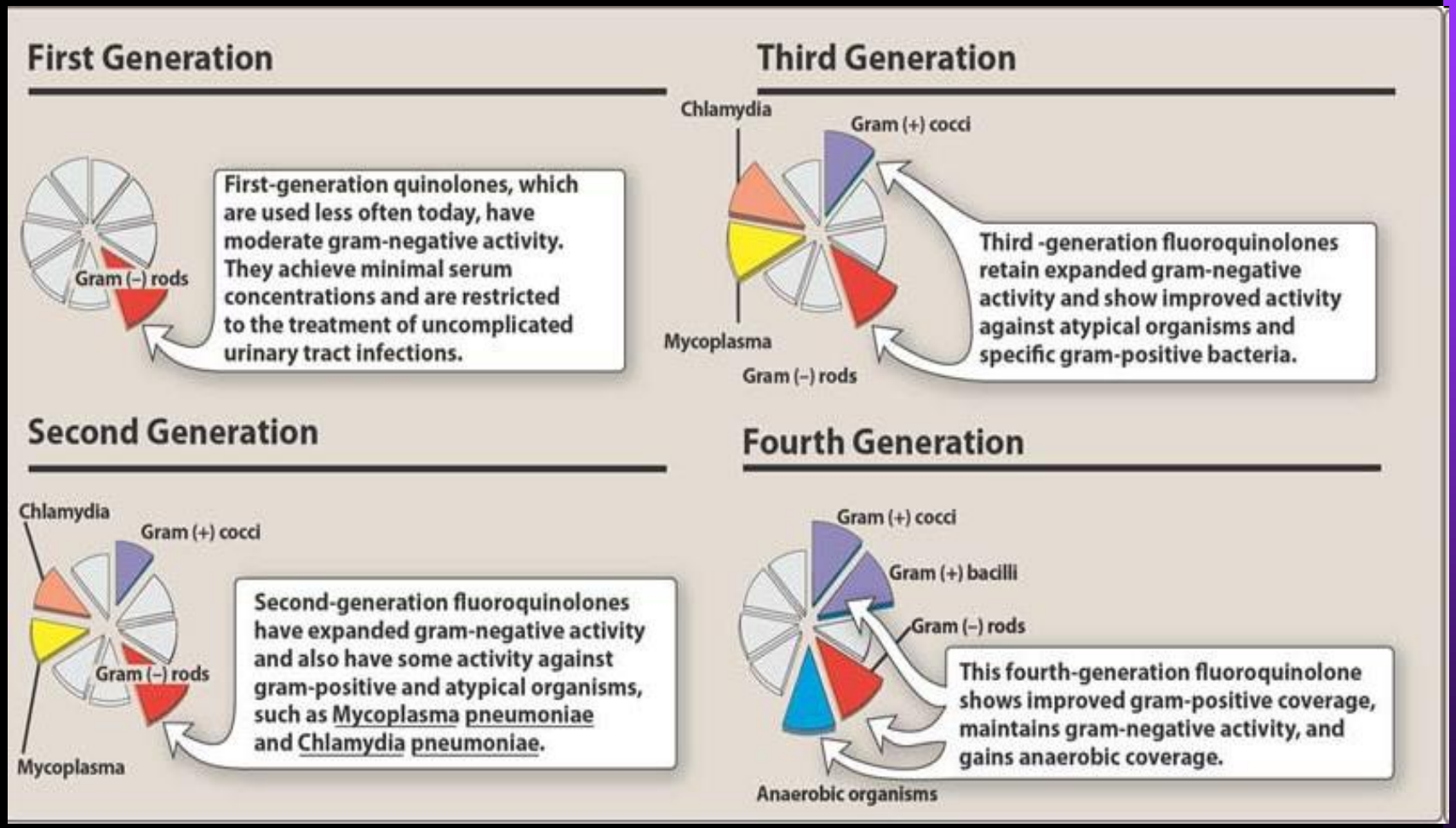
DNA gyrase (TOPO II) – primary target for G-

Topoisomerase IV - primary target for G+

Since DNA gyrase is a bacteriospecific target for antimicrobial therapy, cross-resistance with other antimicrobial drugs is rare, but this is increasing in the case of multidrug-resistant organisms.

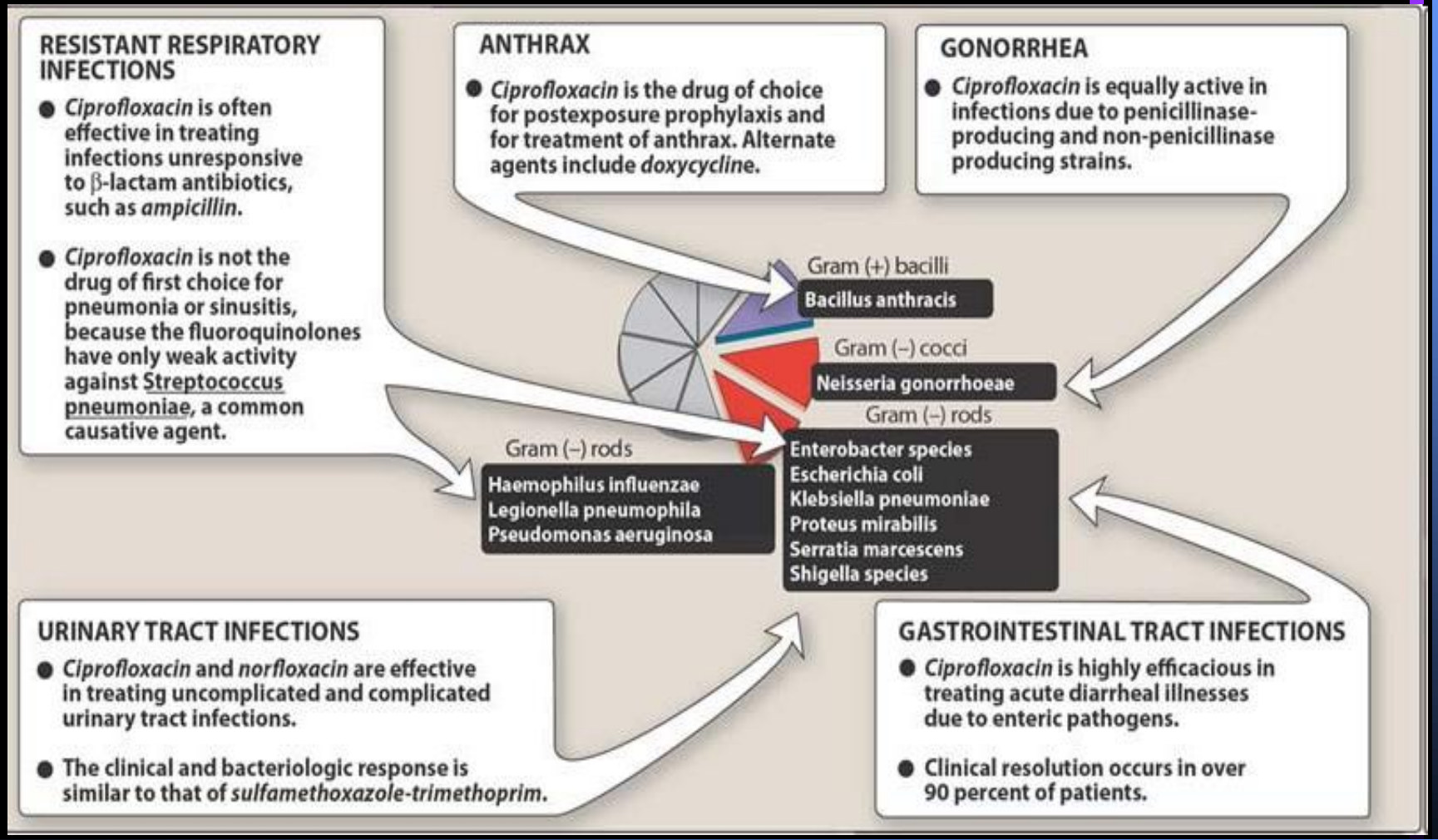
Bactericidal

Antimicrobial spectrum



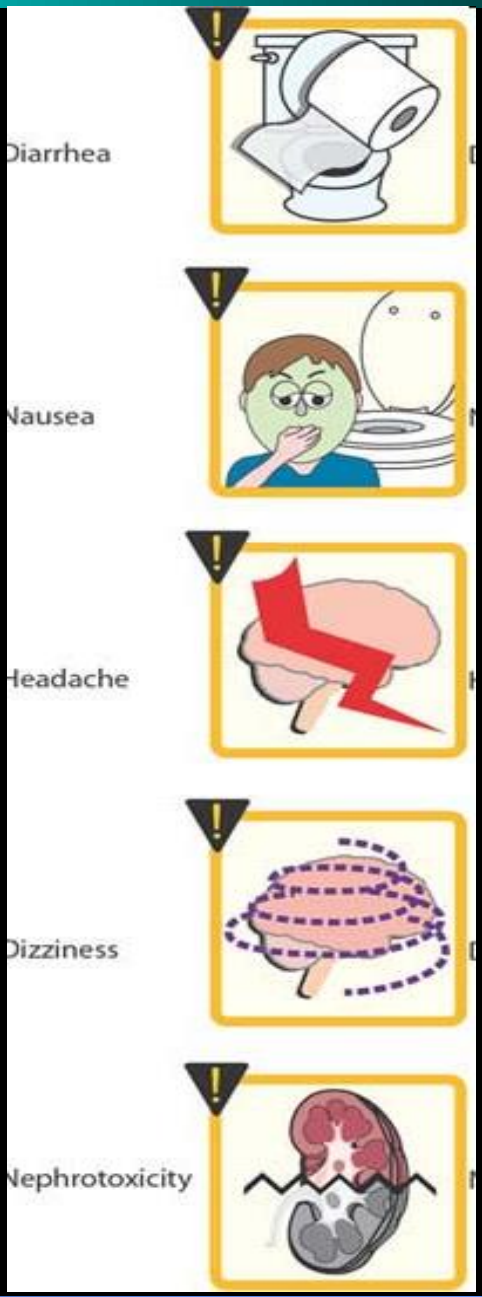
C. Examples of clinically useful fluoroquinolones

Ciprofloxacin - frequently used.



F. Adverse reactions - well tolerated

Connective tissue problems: They should be avoided in pregnancy, in nursing mothers, and in children under 18 years - because articular cartilage erosion (arthropathy)



SULFONAMIDES (SA)

Structurally related to p-aminobenzoic acid (PABA).

Seldom use alone. The introduction of trimethoprim in combination with sulfamethoxazole led to a renewed interest in sulfonamides.

The SA inhibit the synthesis of folic acid.

A. Mechanism of action

Folic acid - synthesized from PABA, pteridine, and glutamate.

- SA - analogs of PABA

- SA compete with PABA for the bacterial enzyme, dihydropteroate synthetase – inhibition of the synthesis of bacterial FA

All sulfa drugs are bacteriostatic.

B. Antibacterial spectrum

-selected enterobacteriaceae, chlamydia, and nocardia.

- SULFADIAZINE + pyrimethamine (dihydrofolate reductase inhibitor) is the preferred form of treatment for toxoplasmosis and chloroquine-resistant malaria.

Individual sulfonamides:

1) Well absorbed orally, short-acting: Sulfadiazine, Sulfadimidine, Sulfisoxazole, Sulfamethoxazole

2) Well absorbed orally, long-acting: Sulfamethopyrazine

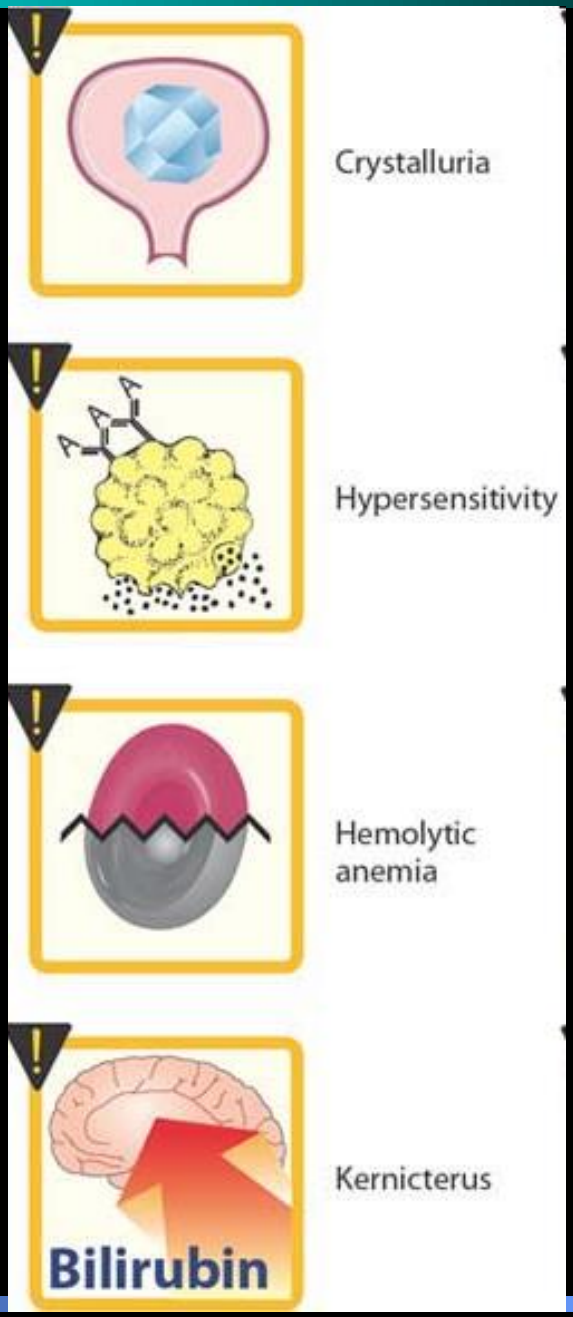
3) Poorly absorbed in GIT: Sulfasalazine

4) Used topically: Silver sulfadiazine

E. Adverse effects

Adequate hydration and alkalization of urine is necessary and prevent the crystalluria.

Note: It is contraindicated to use acidic drugs (salicylates) or food (oranges etc.) which may lead to acidic pH of urine during therapy with sulfonamides !!!



TRIMETHOPRIM

inhibitor of bacterial dihydrofolate reductase antibacterial spectrum similar to SA. Mostly compounded with sulfamethoxazole = co-trimoxazole.

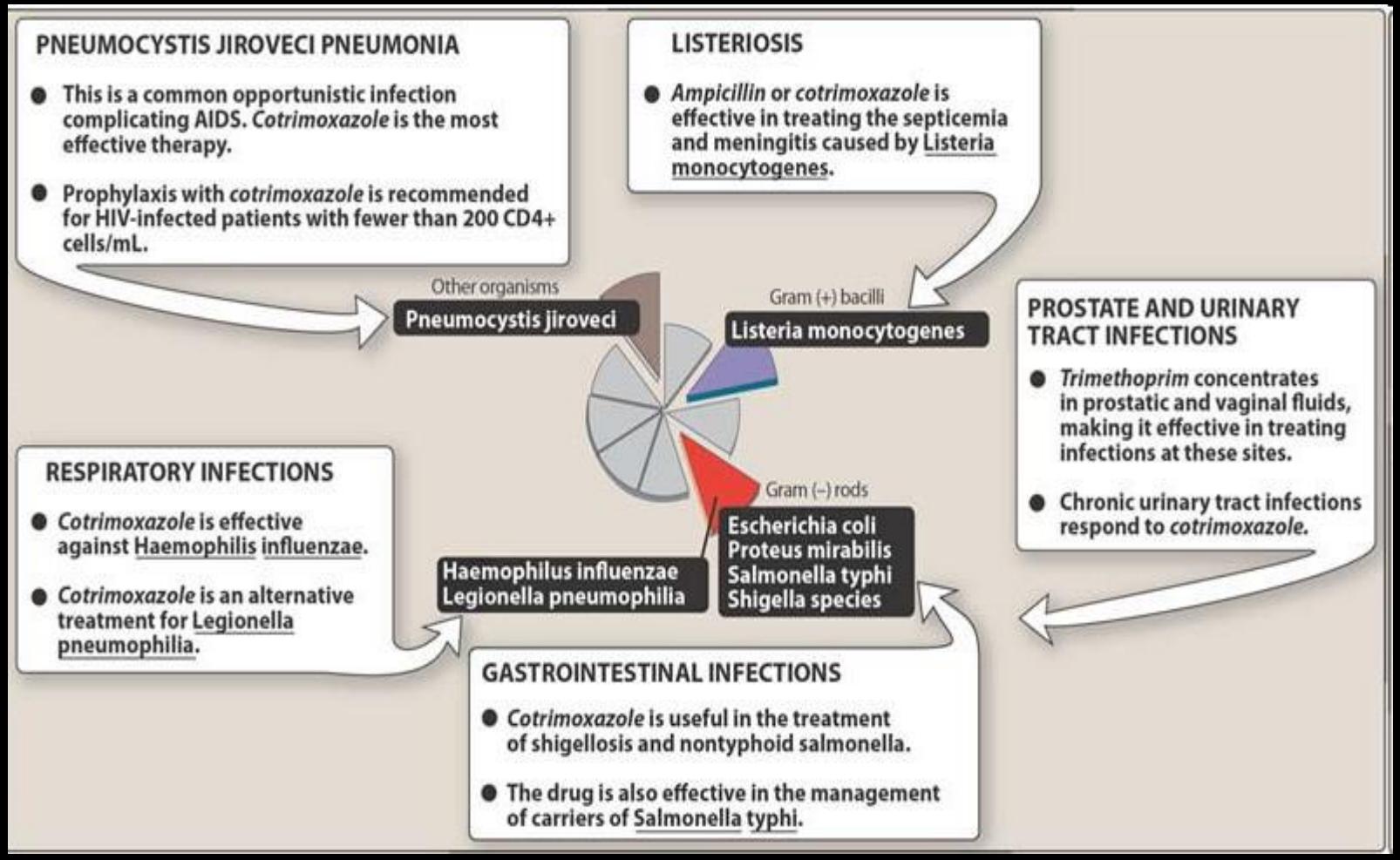
A. Mechanism of action

The active form of folate - tetrahydroderivative (formed by reduction of dihydrofolate by dihydrofolate reductase). This enzymatic reaction is inhibited by trimethoprim - decreased availability of the tetrahydrofolate coenzymes required for purine, pyrimidine, and amino acid synthesis.

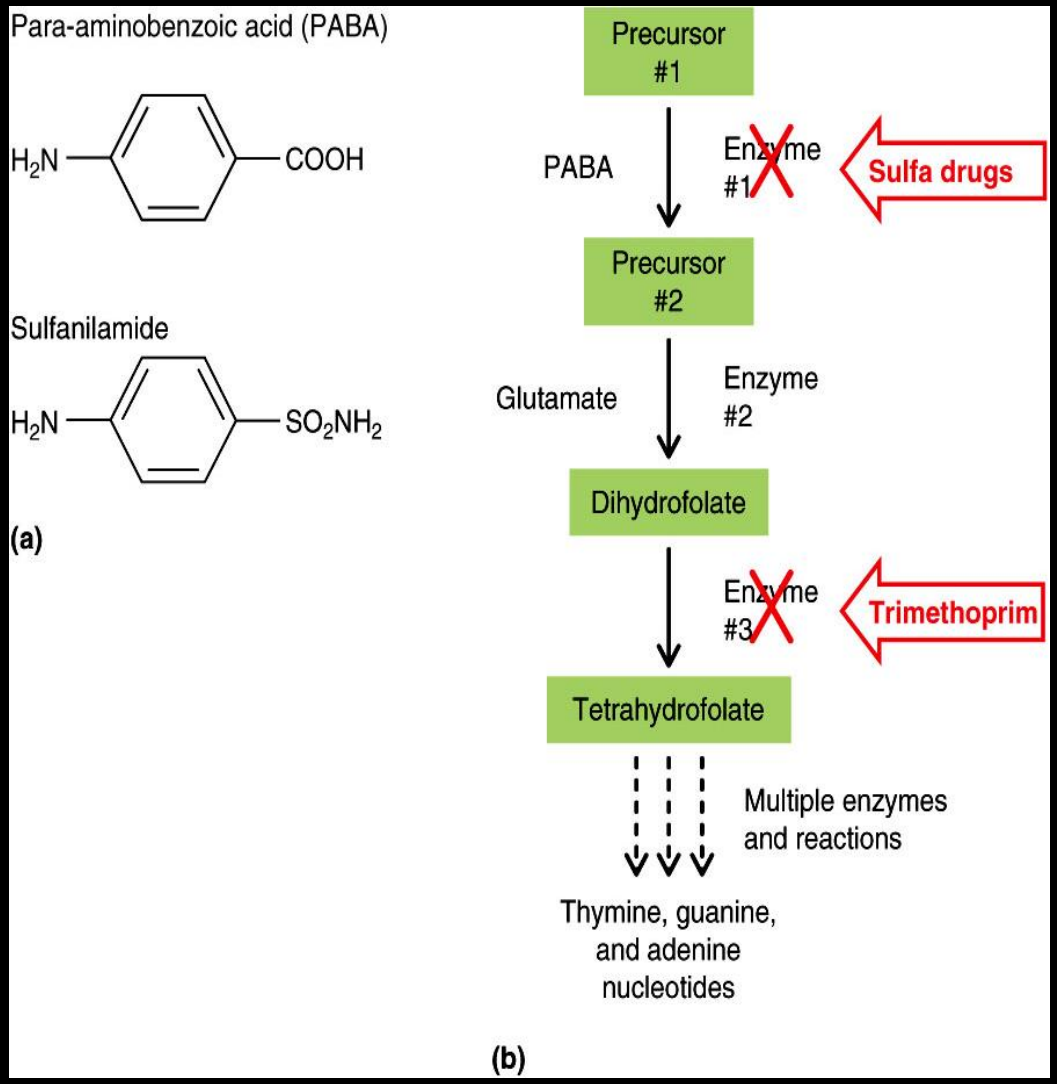
Action of trimethoprim - much stronger for the bacterial reductase than for the mammalian enzyme

CO-TRIMOXAZOLE

Trimethoprim – mostly compounded with sulfamethoxazole.



Sequential Blockade



E. Adverse effects

Dermatological: Reactions involving the skin are very common and may be severe in the elderly.

GIT: Nausea, vomiting, glossitis, stomatitis - not unusual.

Hematological: Megaloblastic anemia, leukopenia, thrombocytopenia - may be reserved by administration of FA.

Hemolytic anemia - in patients with G6-PD

Immunocompromised patients with pneumocystis pneumonia - frequently drug-induced fever, rashes, diarrhea, and/or pancytopenia.