Al-Mustaqbal University College

Pharmacology I 3rd stage

Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics

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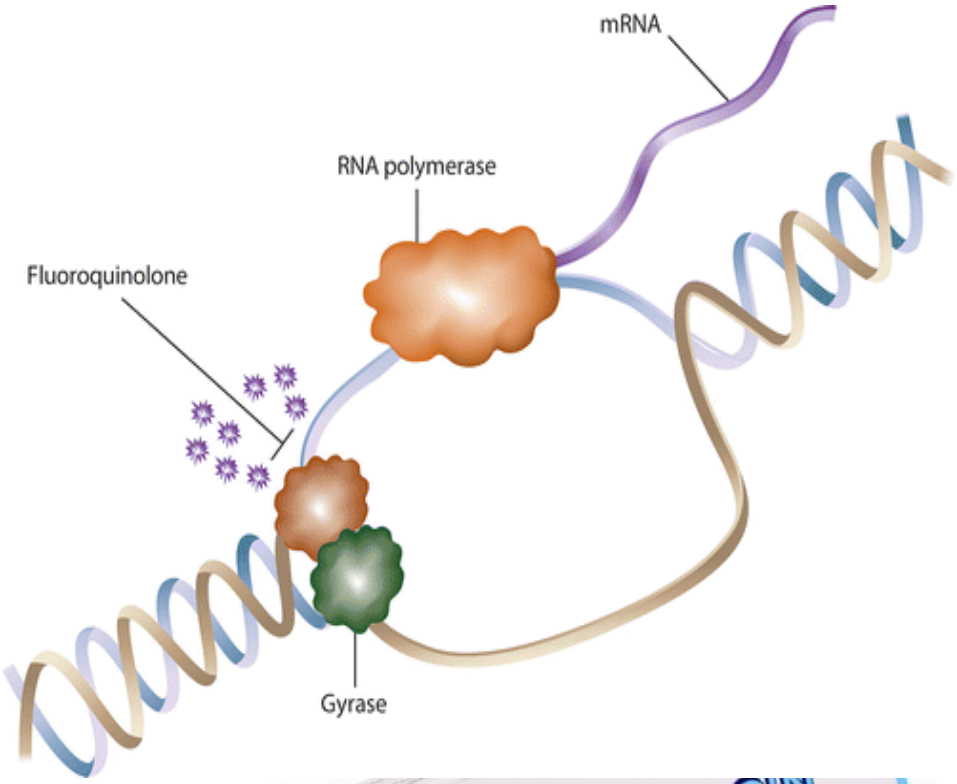
I. Fluoroquinolones

Ciprofloxocin Delofloxocin Gemifloxocin	Levofloxocin Moxifloxocln Ofloxacin

Mechanism of action

fluoroquinolones are gram-negative (DNA gyrase) (topoisomerase II) inhibitors and inhibit gram-positive organisms (topoisomerase IV), resulting in rapid cell death.



Mechanisms of resistance:

1. Altered target binding.
2. Reduction in membrane permeability.
3. Efflux pumps.
4. Fluoroquinolone degradation (acetylate fluoroquinolones).

Antimicrobial Spectrum and Typical Therapeutic Applications of Fluoroquinolones.

ANTHRAX

- *Ciprofloxacin* is the drug of choice for postexposure prophylaxis and for treatment of anthrax. *Levofloxacin* and *doxycycline* are alternative agents.

URINARY TRACT INFECTIONS

- *Ciprofloxacin* and *levofloxacin* are effective in treating uncomplicated and complicated urinary tract infections.

ANAEROBIC INFECTIONS

- *Moxifloxacin* has notable anti-anaerobic activity.

Gram (+) cocci

- S. pneumoniae

Gram (+) bacilli

- Bacillus anthracis

Gram (–) cocci

Gram (–) rods

- Enterobacter species
- E. coli
- H. influenzae
- Klebsiella pneumoniae
- Legionella pneumophila
- Proteus mirabilis
- P. aeruginosa
- Serratia marcescens
- Shigella species

Anaerobic organisms

Spirochetes

Atypical organisms

Other

- M. tuberculosis

RESISTANT RESPIRATORY INFECTIONS

- *Levofloxacin* and *moxifloxacin* are often effective in treating respiratory infections due to their activity against S. pneumoniae.
- *Ciprofloxacin* is not the drug of choice for pneumonia or sinusitis, because it has weak activity against S. pneumoniae, a common causative agent.
- Fluoroquinolones have activity against atypical organisms, such as Legionella, associated with upper and lower respiratory tract infections.

GASTROINTESTINAL TRACT INFECTIONS

- *Ciprofloxacin* is highly efficacious in treating acute diarrheal illnesses due to enteric pathogens.

Pharmacokinetics

1. Absorption: Fluoroquinolones are well absorbed after oral administration, with levofloxacin and moxifloxacin having a bioavailability that exceeds 90%.
2. Ingestion of fluoroquinolones with sucralfate, aluminum- or magnesium-containing antacids, or dietary supplements containing iron or zinc can reduce the absorption. Calcium and other divalent cations also interfere with the absorption of these agents.

2. Distribution:

20% to 84% Binding to plasma proteins.

Fluoroquinolones concentrations are high in bone, urine (except moxifloxacin), kidney, prostatic tissue, and lungs as compared to serum.

Penetration into cerebrospinal fluid is good. Accumulation in macrophages and polymorphonuclear leukocytes.

3. Elimination: Most fluoroquinolones are excreted renally. Therefore, dosage adjustments are needed in renal dysfunction.

Moxifloxacin is metabolized primarily by the liver, and while there is some renal excretion, no dose adjustment is required for renal impairment.

A 22-year-old woman presents with a 2-day history of dysuria with increased urinary frequency and urgency.
A urine culture and urinalysis are done. She is diagnosed with a urinary tract infection caused by E. coli. Which agent should be avoided in the treatment of her UTI?

A. Levofloxacin
B. Cotrimoxazole
C. Moxifloxacin
D. Nitrofurantoin

Correct answer = C. Moxifloxacin does not concentrate in the urine and would be ineffective for treatment of a UTI. All other answers are viable alternatives, and the resistance profile for the E. coli can be utilized to direct therapy.

Adverse reactions

Common adverse effects leading to discontinuation are nausea, vomiting, headache, and dizziness.

phototoxicity (avoid excessive exposure to ultraviolet (UV) light.

arthralgia and arthritis in pediatric patients . and should be limited to cystic fibrosis exacerbation).

Hepatotoxicity or blood glucose disturbances.

Fluoroquinolones may prolong the QTc interval.

Ciprofloxacin is enzyme inhibitors.

Choose the ONE best answer.

A 32-year-old man presents to an outpatient clinic with a 5-day history of productive cough, purulent sputum, and shortness of breath. He is diagnosed with community-acquired pneumonia (CAP). It is noted that this patient has a severe ampicillin allergy (anaphylaxis). Which would be an acceptable treatment for this patient?

A. Levofloxacin
B. Ciprofloxacin
C. Penicillin VK
D. Nitrofurantoin

Correct answer = A. Streptococcus pneumoniae is a common cause of CAP, and the respiratory fluoroquinolones levofloxacin and moxifloxacin provide good coverage. Ciprofloxacin does not cover S. pneumoniae well and is a poor choice for treatment of CAP. Penicillin would be a poor choice due to allergy. Nitrofurantoin has no clinical utility for respiratory tract infections.

II- Folate Antagonists:

Folic acid is a coenzyme essential in the synthesis of ribonucleic acid (RNA), DNA, and certain amino acids.

In the absence of folate, cells cannot grow or divide.

Humans use dietary folate to synthesize the critical folate derivative, tetrahydrofolic acid.

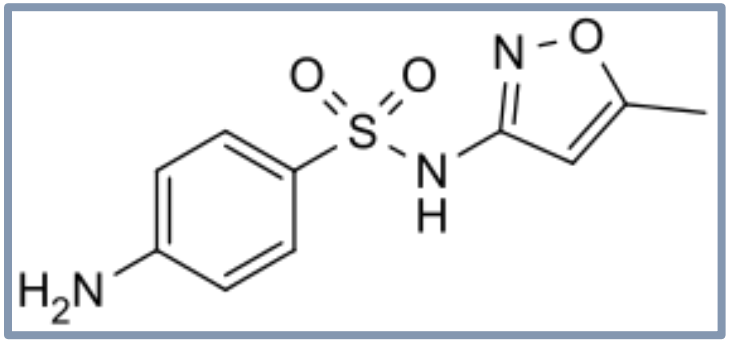
By contrast, many bacteria are impermeable to folate derivatives, and rely on their ability to synthesize folate de novo.

Sulfonamides (sulfa drugs) are a family of antibiotics that inhibit de novo synthesis of folate.

A second type of folate antagonist, trimethoprim, prevents microorganisms from converting dihydrofolic acid to tetrahydrofolic acid.

Sulfonamides

Sulfamethoxazole
sulfadiazine [sul-fa-DYE-a-zeen]
pyrimethamine [py-riMETH-a-meen]
sulfasalazine [sul-faSAL- a-zeen].
sulfapyridine

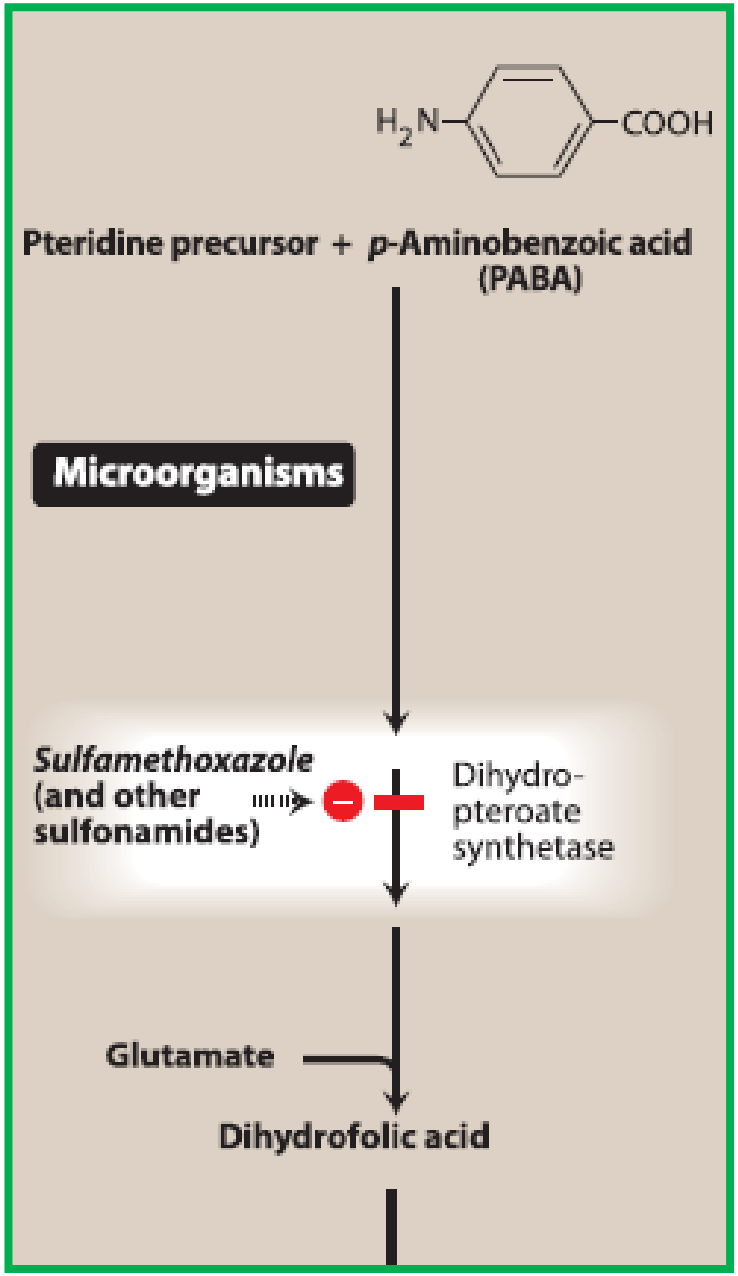


Sulfa drugs were among the first antibiotics used in clinical practice. Today, they are seldom prescribed alone except in developing countries, where they are employed because of low cost and efficacy.

Mechanism of action

Microorganisms use the enzyme dihydropteroate synthetase to create dihydrofolic acid from the precursor molecule p-aminobenzoic acid (PABA). Sulfonamides are synthetic analogs of PABA.

Because of their structural similarity, sulfonamides compete with PABA to inhibit dihydropteroate synthetase and the synthesis of bacterial dihydrofolic acid. These agents, including cotrimoxazole, are bacteriostatic.



Antibacterial spectrum

Common organisms include Enterobacteriaceae, Haemophilus influenzae, Streptococcus spp., Staphylococcus spp., and Nocardia.

Additionally, sulfadiazine in combination with the dihydrofolate reductase inhibitor pyrimethamine is the preferred treatment for toxoplasmosis.

Resistance

Resistance may be due to:

1) altered dihydropteroate synthetase.
2) decreased cellular permeability to sulfa drugs.
3) enhanced production of the natural substrate, PABA.

Pharmacokinetics

1. Absorption: Most sulfa drugs are well absorbed by GIT.

An exception is sulfasalazine. It is not absorbed when administered orally or as a suppository and, therefore, is reserved for treatment of chronic inflammatory bowel diseases.

Absorption of sulfapyridine can lead to toxicity in patients who are slow acetylators.

Intravenous sulfonamides are generally reserved for patients who are unable to take oral preparations or have severe infections.

Because of the risk of sensitization, sulfa drugs are not usually applied topically.

However, in burn units, silver sulfadiazine creams have been effective in reducing burn-associated sepsis because they prevent colonization of bacteria.

2. Distribution: Sulfa drugs are bound to serum albumin in circulation and widely distribute throughout body tissues.

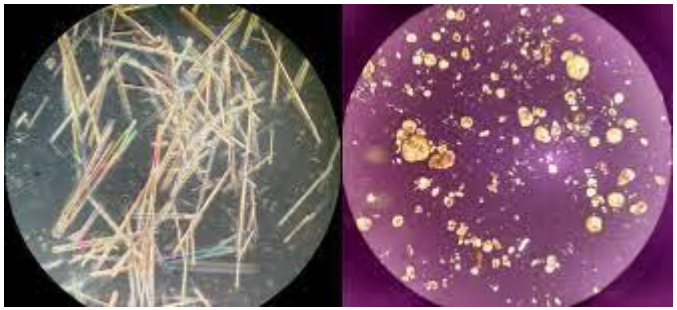
Sulfa drugs penetrate well into cerebrospinal fluid (even in the absence of inflammation) and cross the placental barrier to enter fetal tissues.

3. Metabolism: Sulfa drugs are acetylated. The acetylated product is devoid of antimicrobial activity but retains the toxic potential to precipitate at neutral or acidic pH. This causes crystalluria ("stone formation and potential damage to the kidney.

4. Excretion: eliminated via kidney, requiring dose adjustments with renal impairment. Sulfonamides may be eliminated in breast milk.

Adverse effects

1. **Crystalluria:** Nephrotoxicity may develop as a result of crystalluria. Adequate hydration and alkalinization of urine can prevent the problem by reducing the concentration of drug and promoting its ionization.



1. **Hypersensitivity.**
2. **Hemolytic anemia**.

3. **Kernicterus:** Bilirubin-associated brain damage (kernicterus) may occur in newborns, because sulfa drugs displace bilirubin from binding sites on serum albumin.

Drug interaction: Sulfamethoxazole inhibits of CYP2C9, resulting in reduced clearance of warfarin.

Sulfonamides may also displace warfarin from binding sites on serum albumin.

Contraindications:

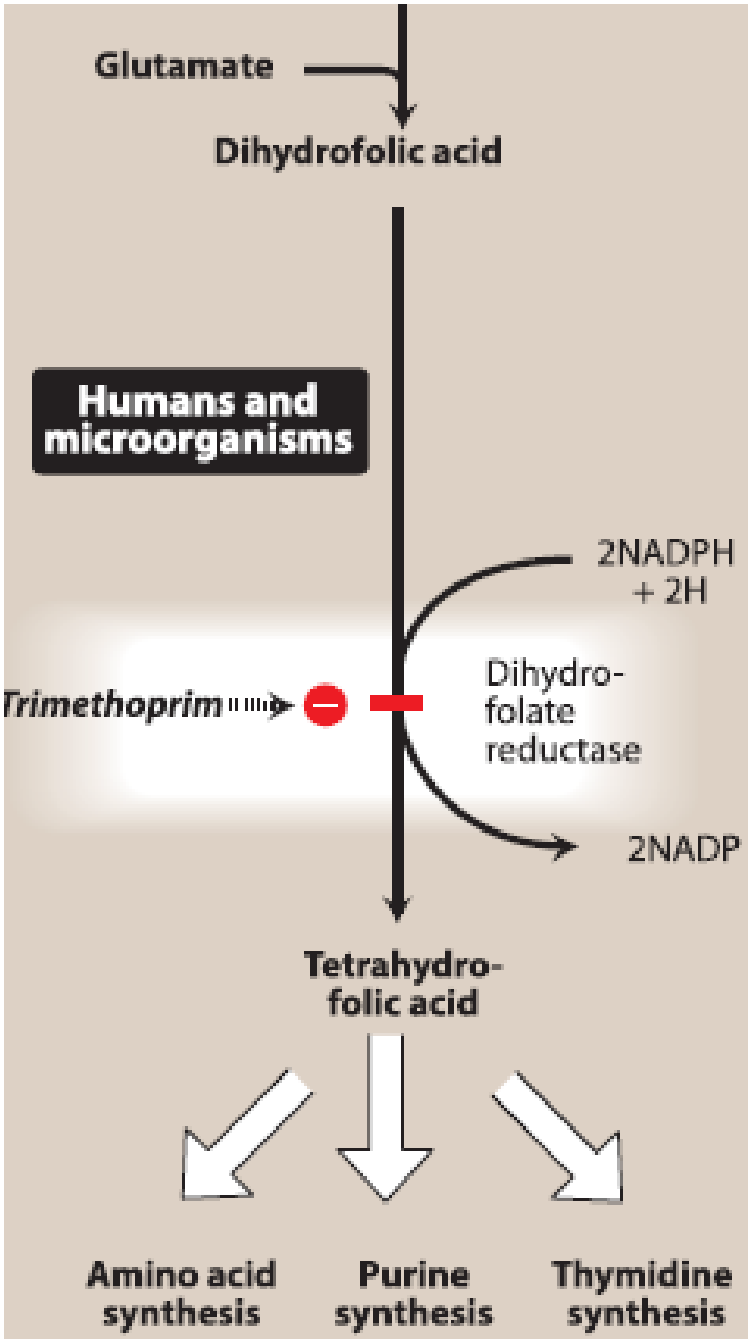
- Newborns and infants less than 2 months of age.
- Pregnant women at term.
- Sulfonamides should not be given to patients receiving methenamine, since they can crystallize in the presence of formaldehyde produced by this agent.

Trimethoprim

Trimethoprim [try-METH-oh-prim], a potent inhibitor of bacterial dihydrofolate reductase (more readily than it does to human dihydrofolate reductase). Today, trimethoprim is most commonly used in combination with sulfamethoxazole.

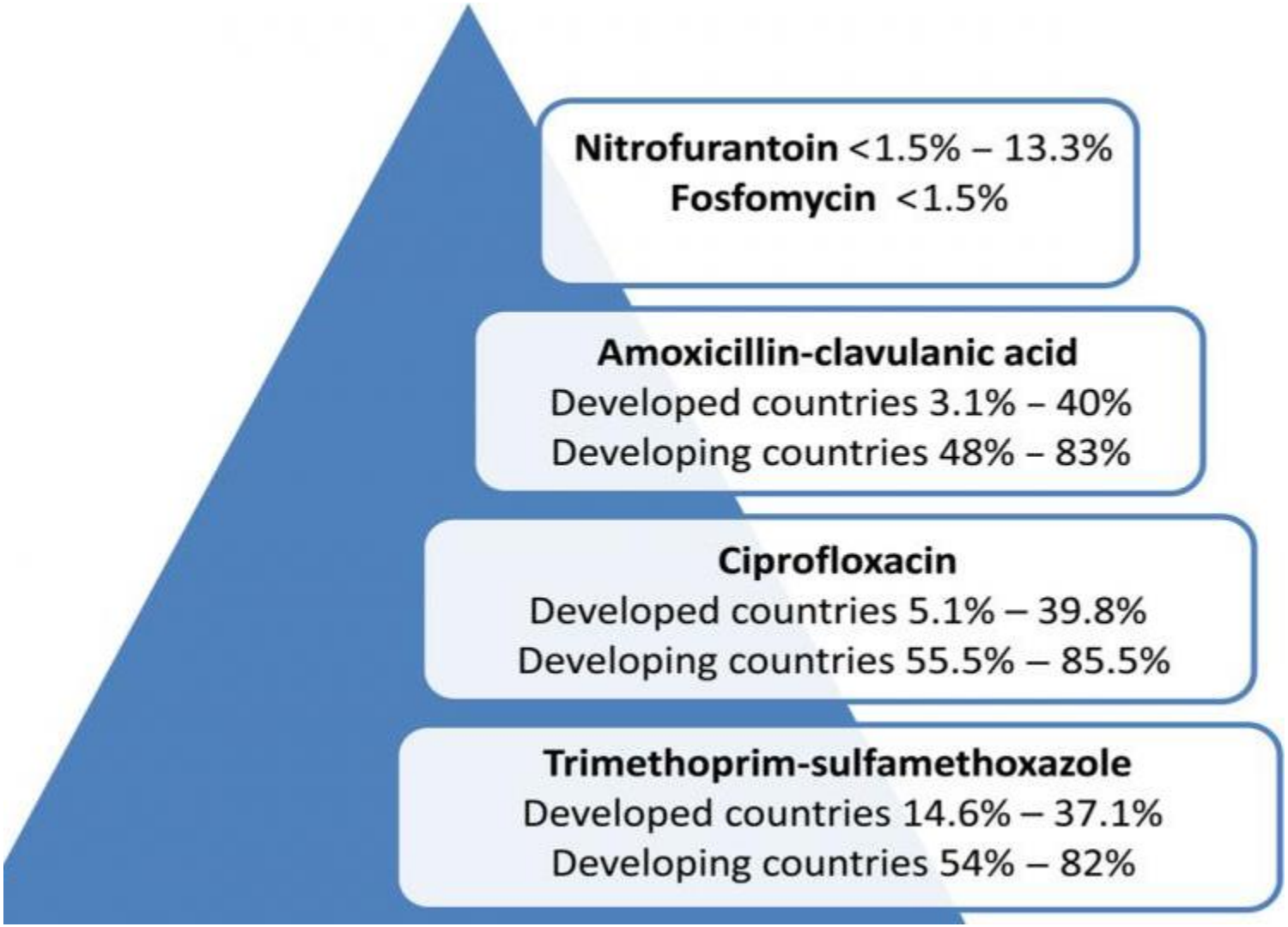
Antibacterial spectrum

The antibacterial spectrum of trimethoprim is similar to that of sulfamethoxazole.
However, trimethoprim is 20- to 50-fold more potent than the sulfonamides.



Resistance

- Altered dihydrofolate reductase.
- Efflux pumps and decreased permeability to the drug.



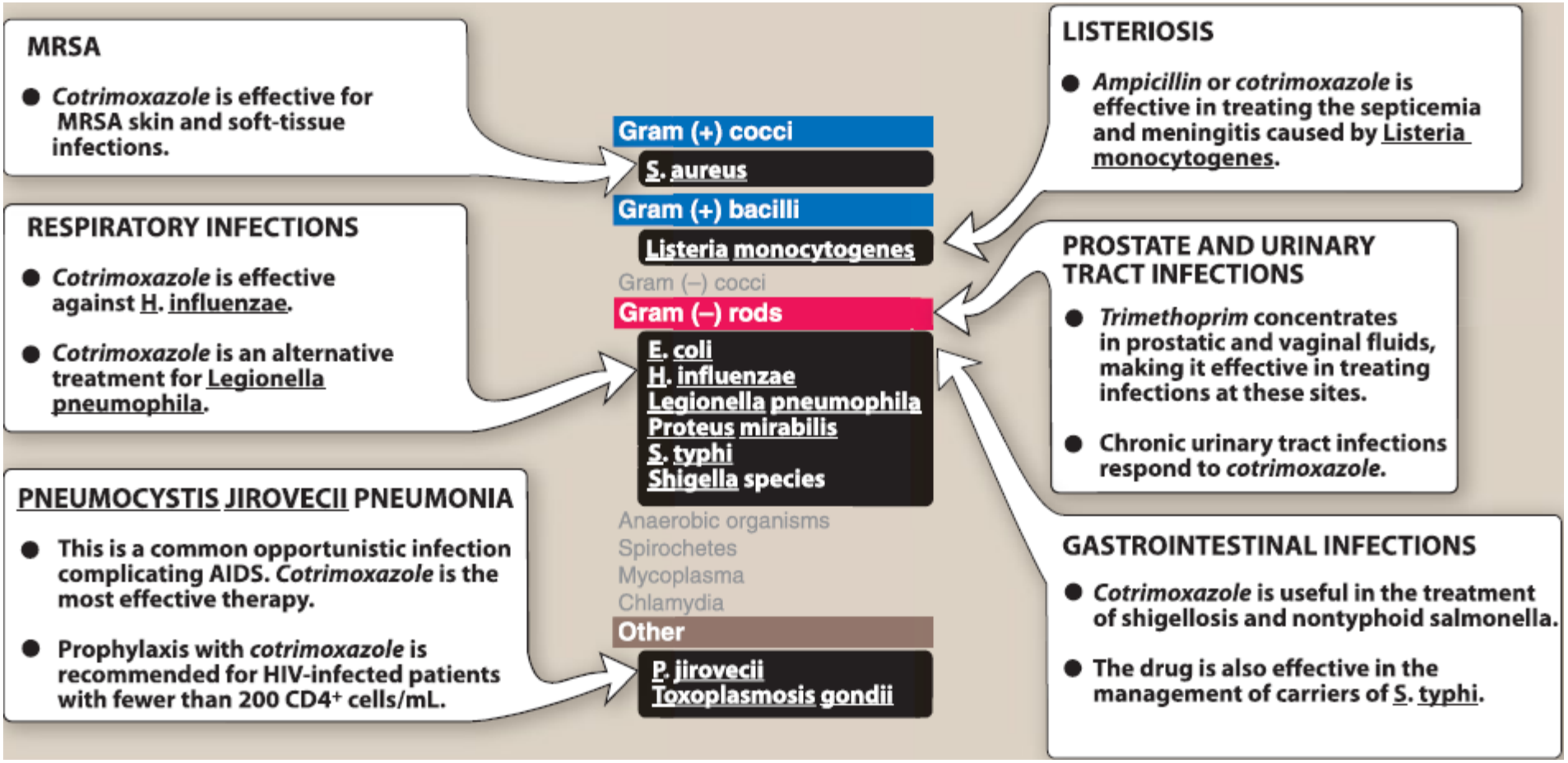
Cotrimoxazole

The combination of trimethoprim with sulfamethoxazole, called cotrimoxazole [co-try-MOX-a-zole], shows greater antimicrobial activity than equivalent quantities of either drug used alone.

The combination was selected because of the synergistic activity and the similarity in the half-lives of the two drugs.

Mechanism of action

The synergistic antimicrobial activity of cotrimoxazole results from its inhibition of two sequential steps in the synthesis of tetrahydrofolic acid.



Typical therapeutic applications of *cotrimoxazofe (sulfamethoxazofe* plus *trimethoprim).*

Resistance

Significant resistance has been documented in a number of clinically relevant organisms, including. E. coli.

Pharmacokinetics

Cotrimoxazole is generally administered orally.

Intravenous administration may be utilized in patients with severe pneumonia caused by Pneumocystis jirovecii.

Trimethoprim concentrates in the relatively acidic milieu of prostatic fluids, and this accounts for the use of trimethoprim sulfamethoxazole in the treatment of prostatitis.

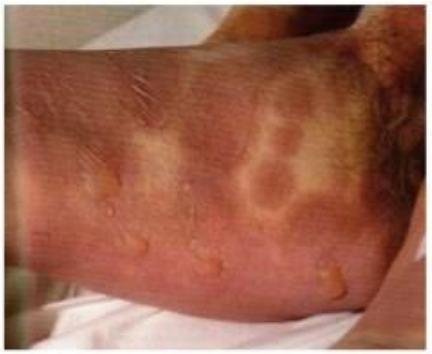
Cotrimoxazole readily crosses the blood-brain barrier. Both parent drugs and their metabolites are excreted in the urine.

Adverse effects

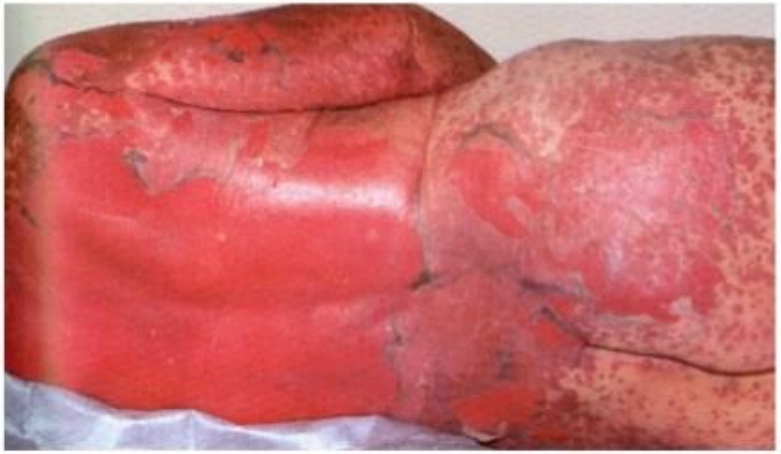
The most common adverse reactions are:
nausea and vomiting,
hematologic toxicity,

skin rash,

and
hyperkalemia
(Trimethoprim
has a potassium-
sparing effect
and may cause
Hyperkalemia).



Stevens–Johnson syndrome after oral intake of Co-trimoxazole
(Color Atlas and Synopsis of Clinical Dermatology, 1999)



Lyell syndrome after oral intake of Co-trimoxazole

Urinary tract Antiseptics/Antimicrobials

UTIs are one of the most common bacterial infections in the world, primarily impacting women and the elderly.

Historically, fluoroquinolones and cotrimoxazole have been first-line therapy for the treatment of UTIs.

Unfortunately, resistance has increased among common pathogens (for example, .E. coli).

As a result, methenamine, nitrofurantoin, and fosfomycin can be considered for treatment or suppression of recurrence, due to their efficacy against common pathogens and high concentrations in the urine.

Methenamine

1. Mechanism of action: Methenamine [meth-EN-a-meen] salts are hydrolyzed to ammonia and formaldehyde in acidic urine (pH ≤ 5.5).

Formaldehyde denatures proteins and nucleic acids, resulting in bacterial cell death.

indication: Methenamine is primarily used for chronic suppressive therapy to reduce the frequency of UTIs.

The main benefit of methenamine is the lack of selection for resistant organisms.

Pharmacokinetics: Methenamine is orally absorbed. It reaches the urine through tubular secretion and glomerular filtration.
Due to ammonia formation, use should be avoided in hepatic insufficiency.

Adverse effects:
The major adverse effect of methenamine is gastrointestinal distress, although at higher doses, albuminuria, hematuria, and rashes may develop.

Methenamine mandelate is contraindicated in patients with renal insufficiency, because mandelic acid may precipitate. The methenamine hippurate formulation
should be used instead.

Nitrofurantoin

Nitrofurantoin [NYE-troe-fue-RAN-toin] is considered first-line therapy for uncomplicated cystitis.

Nitrofurantoin works by inhibiting DNA and RNA synthesis. Susceptible organisms include
.E. coli, Klebsiella spp., Enterococcus spp., and Staphylococcus spp.

Following oral administration, it is rapidly absorbed, with nearly 40% excreted unchanged in the urine. Overall, nitrofurantoin is well tolerated.
Common adverse events include nausea, vomiting, and diarrhea. Rare complications of therapy include pulmonary fibrosis, neuropathy, and autoimmune hepatitis. greater than 1 month. Additionally, patients with impaired renal function should not receive nitrofurantoin due to an increased risk of adverse events.


Thank
you!