Al-Mustaqbal University


# Pharmacology I

## 3rd stage

# Folic Acid Antagonists, and Urinary Tract Antiseptics (154- 165)

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## 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.

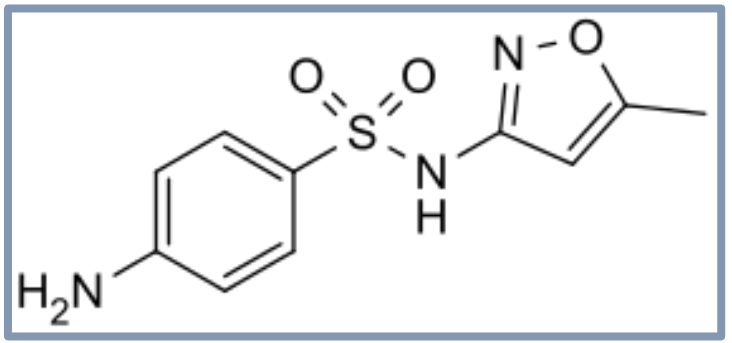
By contrast, many bacteria are impermeable to folate derivatives, and rely on their ability to synthesize folate de novo.

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

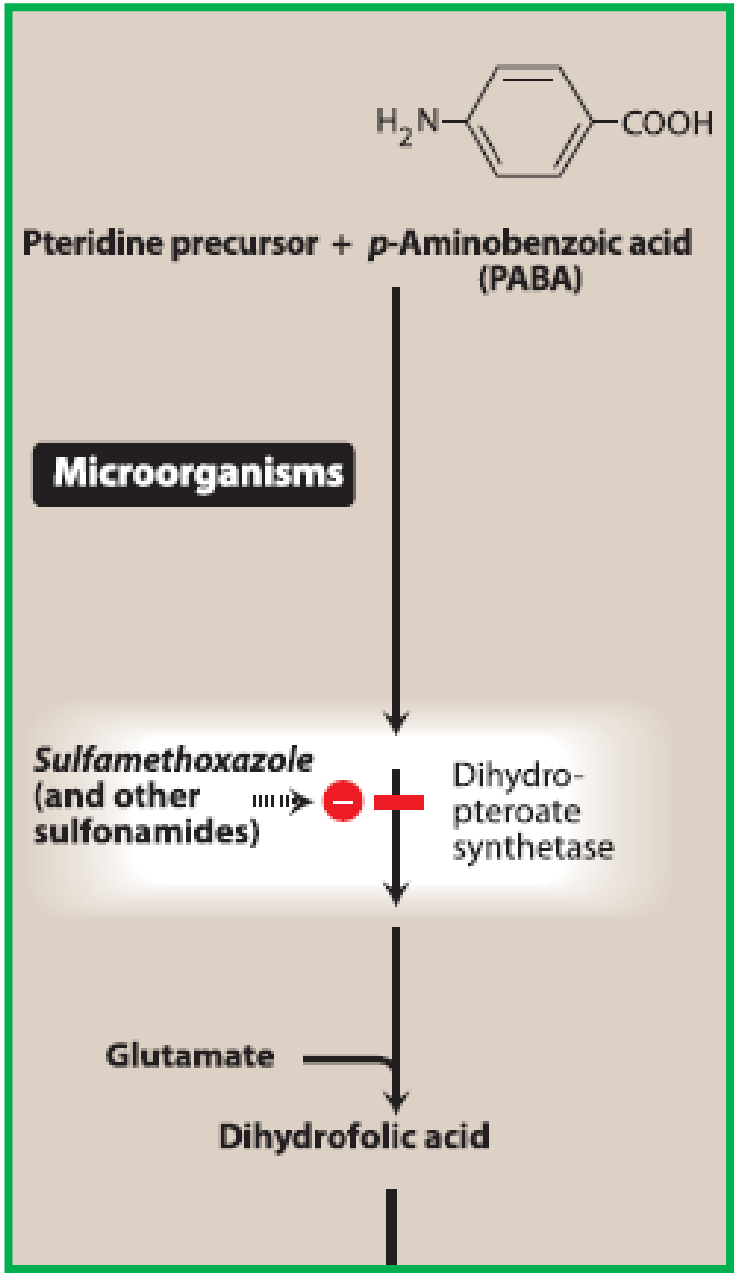
Sulfamethoxazole
sulfadiazine [sul-fa-DYE-a-zeen]
pyrimethamine [py-riMETH-a-meen]
sulfasalazine [sul-faSAL- a-zeen].
sulfapyridine




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

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



**Antibacterial spectrum (have activity against G (-) and G (+) organisms).**

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.

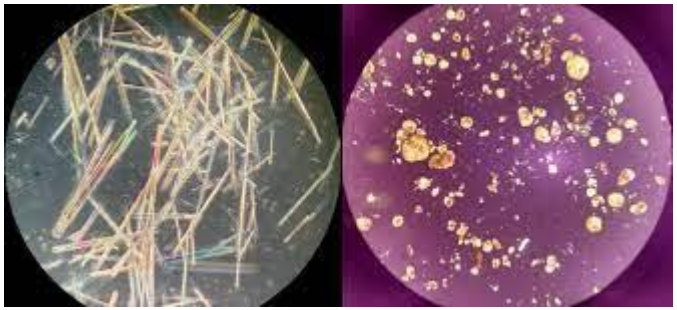
Sulfa drugs penetrate well into cerebrospinal fluid and cross the placental barrier to enter fetal tissues.

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.



**2- Hypersensitivity.**

**3- Hemolytic anemia**.

**4- 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:**

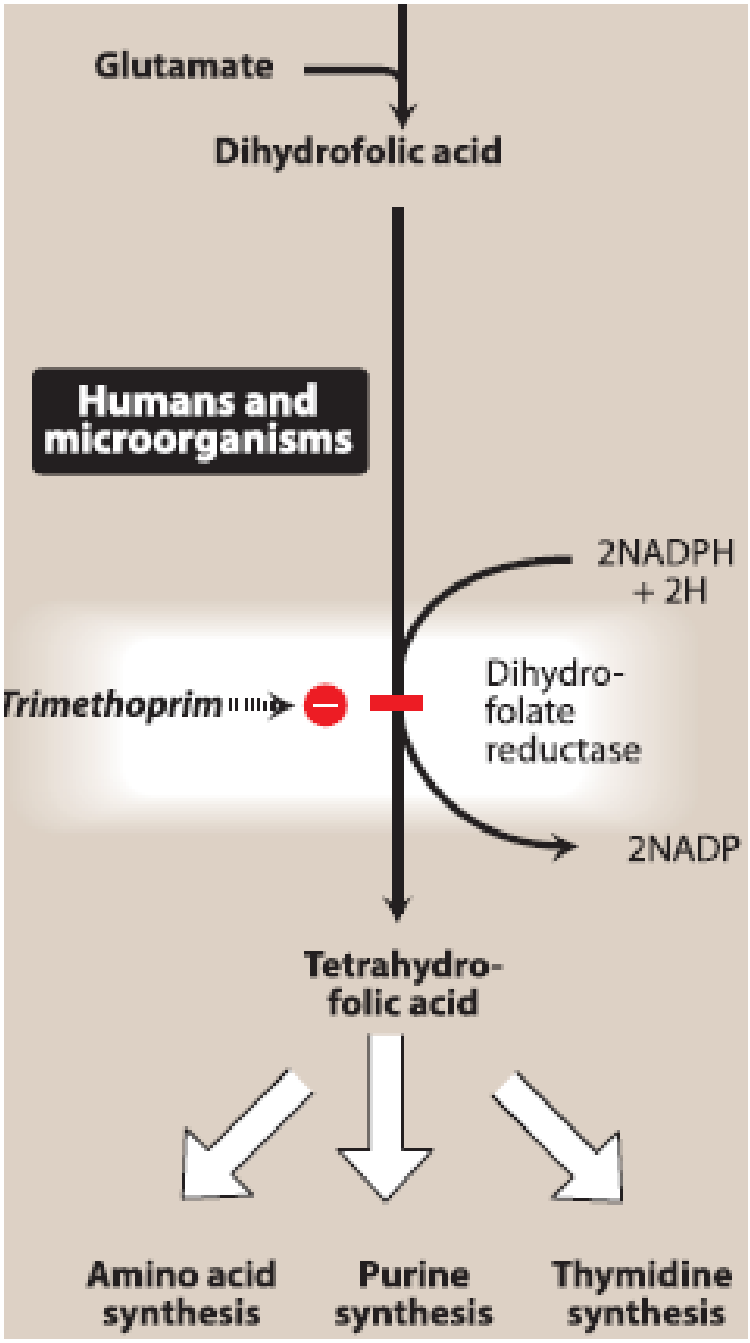
- Newborns and infants less than 2 months of age.
- Pregnant women at term.
- Sulfonamides should not be given to patients receiving methenamine, since they can crystallize in the presence of formaldehyde produced by this agent.

## 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.



Trimethoprim may be used alone in the treatment of urinary tract infections (UTIs) and in the treatment of bacterial prostatitis (although fluoroquinolones and cotrimoxazole are preferred).

**Resistance**

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

## Pharmacokinetics

drug is a weak base, higher concentrations of trimethoprim are achieved in acidic prostatic and vaginal fluids. It penetrats into the cerebrospinal fluid.

Trimethoprim undergoes 60% to 80% is renally excreted unchanged.

## Adverse effects

- folic acid deficiency leads to megaloblastic anemia, leukopenia, and granulocytopenia, especially in pregnant. (reversed by administration of folinic acid (also known as leucovorin), which does not enter bacteria.
- Trimethoprim : hyperkalemia, especially at higher doses and when administered with other medication that causes hyperkalemia (for example, angiotensin-converting enzyme inhibitors).

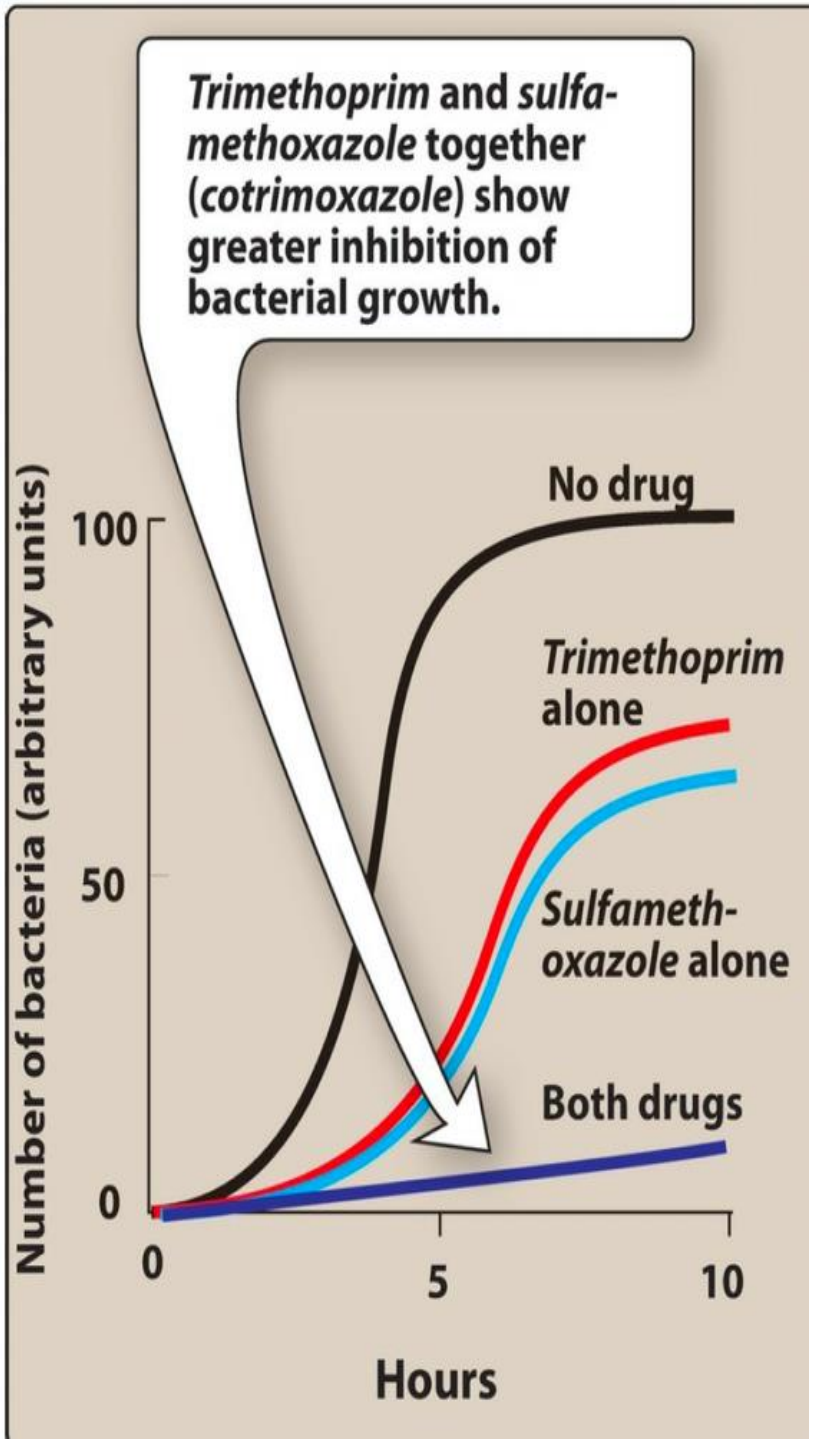
## Cotrimoxazole

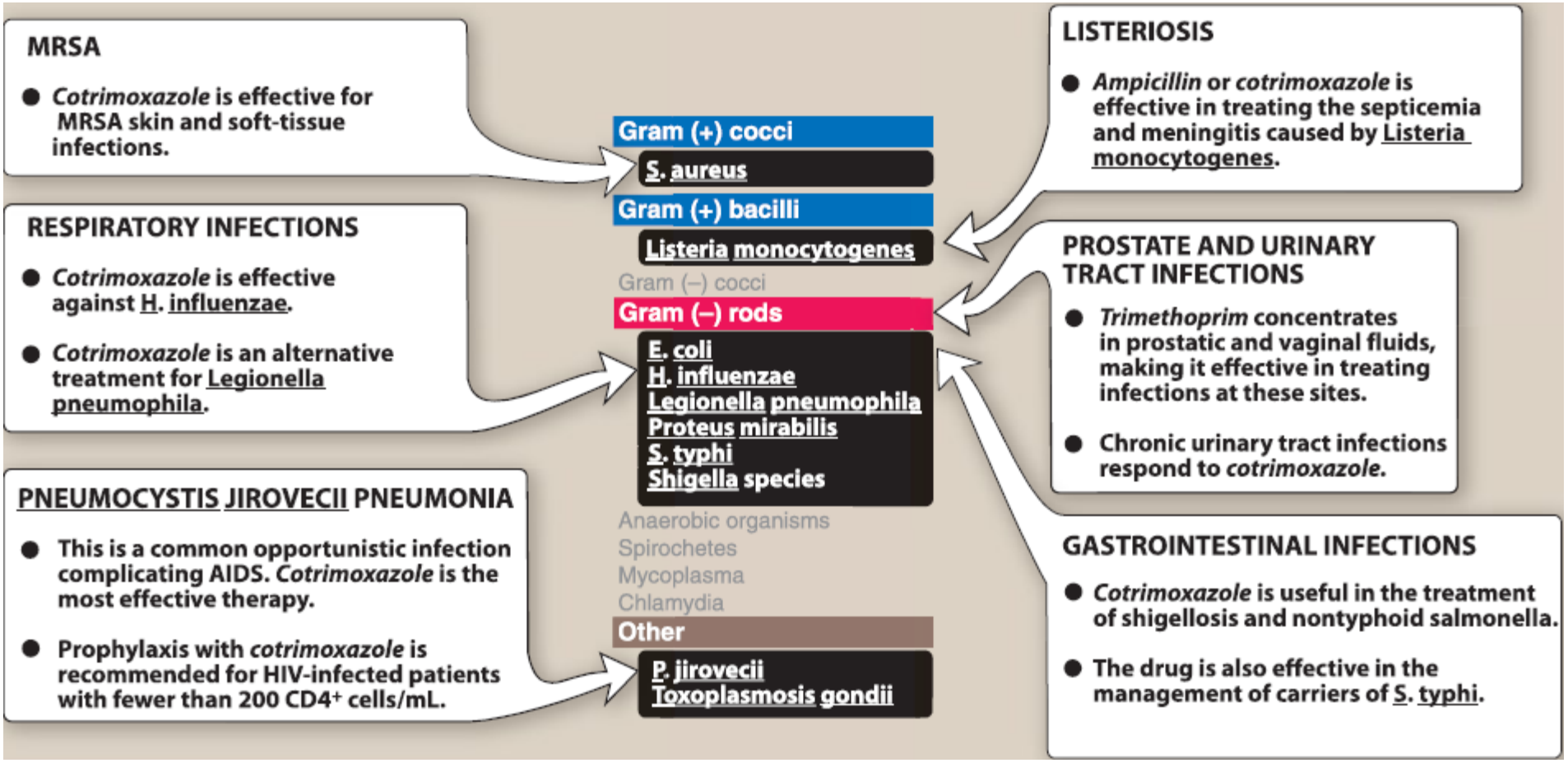
The combination of trimethoprim with sulfamethoxazole, called cotrimoxazole, shows greater antimicrobial activity than equivalent quantities of either drug used alone.

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.

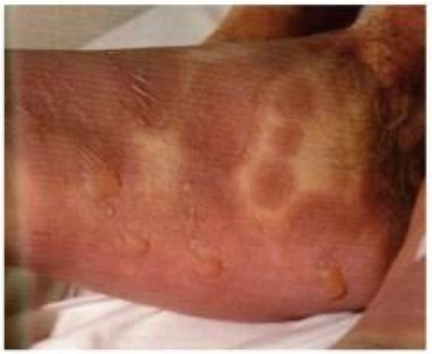
Cotrimoxazole readily crosses the blood-brain barrier. Both parent drugs and their metabolites are excreted in the urine.

## Adverse effects

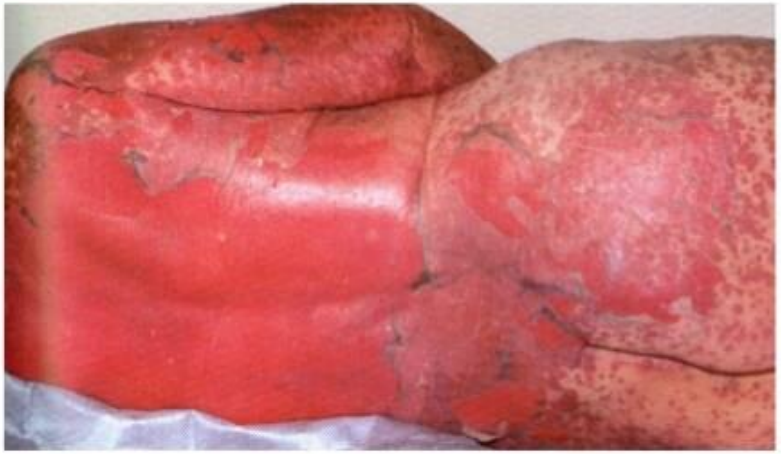
The most common adverse reactions are:
nausea and vomiting,
hematologic toxicity,

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 salts are hydrolyzed to ammonia and formaldehyde in acidic urine (pH $\leq$ 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.

**Antibacterial spectrum:** Methenamine is active against E. coli, Enterococcus spp., and Staphylococcus spp. It has some activity against Proteus spp. and Pseudomonas aeruginosa, but urine pH must be kept acidic to achieve bactericidal activity.

**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 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.

## References

Lippincott Illustrated Reviews: Pharmacology. 7TH ed, Wolters Kluwer.