Folate Antagonists

- Enzymes requiring folate-derived cofactors are essential for the synthesis of purines and pyrimidines (precursors of RNA and DNA) and other compounds necessary for cellular growth and replication.
- In the absence of folate, cells cannot grow or divide.
- To synthesize the critical folate derivative, tetrahydrofolic acid, humans must first obtain preformed folate in the form of folic acid from the diet.
- In contrast, many bacteria are impermeable to folic acid and other folates and, therefore, must rely on their ability to synthesize folate de novo.
- **Sulfonamides** (sulfa drugs) are a family of antibiotics that inhibit de novo synthesis of folate.
- **Trimethoprim** a second type of folate antagonist—prevents microorganisms from converting dihydrofolic acid to tetrahydrofolic acid, with minimal effect on the ability of human cells to make this conversion.
- Thus, both sulfonamides and trimethoprim interfere with the ability of an infecting bacterium to perform DNA synthesis.
- Combining the sulfonamide sulfamethoxazole with trimethoprim (the generic name for the combination is cotrimoxazole) provides a synergistic combination.
Sulfonamides

- **Mechanism of action**
  - **Sulfa drugs**
  - All the sulfonamides currently in clinical use are synthetic analogs of PABA.
  - Because of their structural similarity to PABA, the sulfonamides compete with this substrate for the bacterial enzyme, dihydropteroate synthetase.
  - The sulfa drugs, including cotrimoxazole, are bacteriostatic.
Antibacterial spectrum

• Sulfa drugs are active against select Enterobacteriaceae in the **urinary tract** and Nocardia infections.

• **Sulfadiazine** in combination with the dihydrofolate reductase inhibitor pyrimethamine is the preferred treatment for **toxoplasmosis**.

• **Sulfadoxine** in combination with pyrimethamine is used as an **antimalarial** drug.
Resistance

- **Naturally bacterial resistant** to these drugs that can obtain folate from their environment.
- **Acquired bacterial resistance** to the sulfa drugs can arise from *plasmid transfers* or *random mutations*.
- *Organisms resistant to one member of this drug family are resistant to all.*
- Resistance is generally **irreversible** and may be due to:
  - Altered dihydropteroate synthetase.
  - Decreased cellular permeability to sulfa drugs.
  - Enhanced production of the natural substrate, PABA.
Pharmacokinetics

- After **oral** administration, most sulfa drugs are well absorbed except Sulfasalazine is not absorbed when administered orally or as a suppository.
- **Intravenous** sulfonamides are generally reserved for patients who are unable to take oral preparations.
- Because of the risk of **sensitization**, sulfa drugs are not usually applied topically.
- In burn units, creams of **silver sulfadiazine** is effective in reducing burn-associated sepsis because they **prevent colonization of bacteria**.
- Sulfa drugs distribute throughout the bodily fluids and penetrate well into **cerebrospinal fluid**—even in the absence of inflammation.
- They can also pass the **placental barrier** and enter fetal tissues.
• The sulfa drugs are acetylated and conjugated primarily in the liver.
• The acetylated product is devoid of antimicrobial activity but retains the toxic potential to precipitate at neutral or acidic pH crystalluria ("stone formation" and potential damage to the kidney).
• Sulfa drugs are eliminated by glomerular filtration (renal).
• Require dose adjustments for renal dysfunction.
• Sulfonamides may be eliminated in breast milk.
Adverse effects

- **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.
- **Hypersensitivity**.
- **Hematopoietic disturbances**: Hemolytic anemia.
• **Kernicterus**: This disorder may occur in newborns, because sulfa drugs displace bilirubin from binding sites on serum albumin. The bilirubin is then free to pass into the CNS, because the blood–brain barrier is not fully developed.

• **Drug potentiation**: Transient potentiation of the:
  - Anticoagulant effect of **warfarin** results from the displacement from binding sites on serum albumin.
  - Serum **methotrexate** levels may also rise through its displacement.

• **Contraindications**:  
  - **Avoide in newborns** and infants less than 2 months of age,
  - Pregnant women at term.
Trimethoprim

• Potent inhibitor of bacterial dihydrofolate reductase, exhibits an antibacterial spectrum similar to that of the sulfonamides.

• Trimethoprim is most often compounded with sulfamethoxazole producing the combination called cotrimoxazole.
Mechanism of action

✓ The active form of folate is the tetrahydro derivative that is formed through reduction of dihydrofolic acid by dihydrofolate reductase.

✓ Inhibited by trimethoprim, leading to a decreased availability of the tetrahydrofolate cofactors required for purine, pyrimidine, and amino acid synthesis.

✓ The bacterial reductase has a much stronger affinity for trimethoprim than does the mammalian enzyme, which accounts for the selective toxicity of the drug.
Pteridine precursor + p-Aminobenzoic acid (PABA)

Microorganisms

Sulfamethoxazole (and other sulfonamides) → Dihydropteroate synthetase

Glutamate → Dihydrofolic acid

Humans and microorganisms

Trimethoprim → Dihydrofolate reductase

2NADPH + 2H → 2NADP

Tetrahydrofolate acid

Amino acid synthesis, Purine synthesis, Thymidine synthesis
Antibacterial spectrum

- The antibacterial spectrum of trimethoprim is similar to that of sulfamethoxazole.
- Trimethoprim is 20- to 50-fold more potent than the sulfonamides.
- Trimethoprim may be used alone in the treatment of UTIs and in the treatment of bacterial prostatitis (although fluoroquinolones are preferred).

**Resistance**

- Resistance in gram-negative bacteria is due to the presence of an altered dihydrofolate reductase that has a lower affinity for trimethoprim.
- Efflux pumps and decreased permeability to the drug may play a role.
Pharmacokinetics

- Trimethoprim is rapidly absorbed following oral administration.
- Because the drug is a weak base, higher concentrations of trimethoprim are achieved in the relatively acidic prostatic and vaginal fluids.
- The drug is widely distributed into body tissues and fluids, including penetration into the cerebrospinal fluid.
- Trimethoprim: 60% to 80% is renally excreted unchanged.

- Adverse effect: folic acid deficiency effects.
  - Megaloblastic anemia, leukopenia, and granulocytopenia,
  - Especially in pregnant patients and those having very poor diets.
  - Reversed by the simultaneous administration of folicin acid, which does not enter bacteria.
Cotrimoxazole

- **Mechanism of action**
  - Synergistic antimicrobial.
  - Cotrimoxazole results from its inhibition of two sequential steps in the synthesis of tetrahydrofolic acid.
  - Sulfamethoxazole inhibits the incorporation of PABA into dihydrofolic acid precursors, and trimethoprim prevents reduction of dihydrofolate to tetrahydrofolate.
  - Cotrimoxazole has a **broader spectrum** of antibacterial action than the sulfa drugs alone.

**Figure 40.11**
Synergism between *trimethoprim* and *sulfamethoxazole* inhibits growth of *E. coli*.
Resistance to the trimethoprim–sulfamethoxazole combination is less frequently encountered than resistance to either of the drugs alone, because it requires that the bacterium have simultaneous resistance to both drugs.
Figure 40.13
Administration and fate of cotrimoxazole.
Adverse effects

Skin rash

Nausea

Hematologic toxicities

Figure 40.14
Some adverse reactions to cotrimoxazole.
Urinary tract antiseptic/antimicrobial

• UTIs are prevalent in **women of child-bearing age** and in the **elderly** population.

• *E. coli* is the most common pathogen, causing about 80% of uncomplicated upper and lower UTIs.

• cotrimoxazole and the quinolones

• UTIs may be treated with any one of a group of agents called **urinary tract antiseptics**, including methenamine, nitrofurantoin, and the quinolone nalidixic acid

• These drugs do not achieve antibacterial levels in the circulation, but because they are concentrated in the urine, microorganisms at that site can be effectively eradicated.
Methenamine

• Decomposes at an acidic pH of 5.5 or less in the urine, thus producing formaldehyde, which acts locally and is toxic to most bacteria
• Bacteria do not develop resistance to formaldehyde, which is an advantage of this drug.
• Methenamine is primarily used for chronic suppressive therapy to reduce the frequency of UTIs.
Pharmacokinetics

- Methenamine is administered orally.
- In addition to formaldehyde, ammonium ions are produced in the bladder.
- Contraindicated in patients with hepatic insufficiency, because the liver rapidly metabolizes ammonia to form urea.
- As ammonia can accumulate. Methenamine is distributed throughout the body fluids, but no decomposition of the drug occurs at pH 7.4. Thus, systemic toxicity does not occur.
- The drug is eliminated in the urine.
Adverse effects:

• The major side effect is gastrointestinal distress
• contraindicated in patients with renal insufficiency, because mandelic acid may precipitate.
• Sulfonamides, such as cotrimoxazole, react with formaldehyde and must not be used concomitantly with methenamine.
• The combination increases the risk of crystalluria and mutual antagonism
Nitrofurantoin

- Sensitive bacteria reduce the drug to a highly active intermediate that inhibits various enzymes and damages bacterial DNA.
- It is useful against E. coli
- The drug should not be used in patients with significant renal impairment or pregnant women.