Chapter 46
Sulfonamides, Trimethoprim, & Quinolones
Classification of synthetic antimicrobial agents

I. Antifolate drugs:
   a. Sulfonamides
   b. Trimethoprim

II. DNA gyrase inhibitors:
    Fluoroquinolones
I. Antifolate drugs:
   a. Sulfonamides
   b. Trimethoprim
Sulfonamides

First antimicrobial agent effective against pyogenic bacterial infections

They were developed from prontosil dye- Domagk (1937)

Prontosil $\rightarrow$ sulfanilamide

All sulfonamides are derivatives of sulfanilamide (p-amino benzene sulfonamide)
Chemistry

Sulfanilamide

Sulfadiazine

Sulfisoxazole

$p$-Aminobenzoic acid (PABA)

Sulfamethoxazole

Sulfathalidine (phthalylsulfathiazole)
(1) Sulfonamides have a wide range of antimicrobial activity.

- G+, G- bacteria, Nocardia, Chlamydia trachomatis, etc.
- Enteric bacteria etc. less effective

(2) Sulfonamides exert only bacteriostatic effect.
Mechanism of action

- Structural analogs of para-aminobenzoic acid (PABA)
- Inhibit dihydropteroate synthase - needed for folic acid synthesis
- Prevent normal bacterial utilization of PABA for the synthesis of folic acid
Mechanism of action

1. p-Aminobenzoic acid
2. Dihydropteroate synthase
3. Sulfonamides (compete with PABA)
4. Dihydrofolate reductase
5. Trimethoprim
6. Tetrahydrofolate acid
7. Purines
8. DNA
Mechanism of resistance

- An alternative metabolic pathway for synthesis of an essential metabolite or over-production of PABA
- Lowered affinity of dihydropteroate synthase to sulfonamides
- Decreased bacterial permeability or active efflux of sulfonamides
Pharmacokinetics

(1) **Absorbed** from the stomach and small intestine
(2) **Distributed** widely to tissues and body fluids (CSF), placenta, and fetus. Plasma protein bound 20-95%

- *Sulfadiazine and sulfisoxazole may be effective in meningeal infections.*

(3) **Metabolized** in the liver by acetylation
(4) **Eliminated** mainly in the urine as the unchanged drug and metabolic product

- *In acid urine, the eliminated are insoluble and may precipitate, thus induce renal disturbance.*
Classification

(1) Oral absorbable agents

• **Short-acting agents** (4-9hr): sulfisoxazole
• **Medium-acting agents** (10-17hr): sulfamethoxazole (SMZ)
• **Long-acting agents** (7 days): sulfadoxine

(2) Oral nonabsorbable agents

  Sulfasalazine

(3) Topical agents

  Sulfacetamide, mafenide acetate and silver sulfadiazine
Clinical uses

(1) Systemic infections
- Cerebral meningitis
- Tympanitis
- Uncomplicated urinary tract infections
- Combined with TMP in treating complicated urinary tract infections, respiratory infections, GI infections

(2) Intestinal infections
- Ulcerative colitis, enteritis, other inflammatory bowel disease
  - sulfasalazine

(3) Infections of burn and wound
- Sulfadiazine sliver
**Combination agents**

- Sulfadoxine+pyrimethamine (Fansidar) - malaria second-line
- Sulfadiazine+pyrimethamine – acute toxoplasmosis
- Co-trimoxazole
  
  *Sulfamethoxazole+trimethoprim* – a wide variety of infections

  - Individually they both are **bacteriostatic** but the combination is **bacteroicidal**
Adverse reactions

1. Hypersensitivity
   • Skin rash and fever is common
   • **Stevens-Johnson syndrome** is rare, but is a serious and potentially fatal type of skin and mucous membrane eruption

2. Gastrointestinal effects
   • Nausea, vomiting, and diarrhea is common
   • Mild hepatic dysfunction, hepatitis is uncommon
3. Urinary tract disturbances
   • May precipitate in acid urine
     – Crystalluria and hematuria

4. Hematopoietic disturbances
   • Rare
   • Granulocytopenia, thrombocytopenia, and aplastic anemia
   • Acute hemolysis in G-6PD
   • Kernicterus in newborn
Trimethoprim (TMP)

- TMP inhibits bacterial dihydrofolic acid reductase
- Prevents the formation of active tetrahydro form of folic acid
- 50,000 times less efficient in inhibition of mammalian dihydrofolic acid reductase
- TMP given together with sulfonamides, produces sequential blocking of folic acid synthesis, resulting in marked enhancement (synergism) of the bacteriostatic activity.
Trimethoprim-Sulfamethoxazole (TMP-SMZ)

Mechanism of action

• Sequential interference with folic acid synthesis results in bacterial synergism often with bactericidal activity
• Sulfonamides are structural analogues of para-amino benzoic acid (PABA), competitively inhibiting synthesis of dihydrofolic acid
• Trimethoprim is an analogue of the pteridine portion of dihydrofolic acid inhibiting synthesis of tetrahydrofolic acid
Trimethoprim-Sulfamethoxazole (TMP-SMZ)

Mechanism of resistance

• Resistance is reduced because of the sequential interference with steps involved in folic acid synthesis
• Sulfas: decreased permeability (plasmid mediated), increased production of PABA
• TMP: synthesis of DHFR with decreased affinity for TMP (plasmid-mediated), overproduction of DHFR
• Resistance to both TMP and SMZ has been increasing
Trimethoprim-Sulfamethoxazole (TMP-SMZ)

• Combination antibiotic with 1:5 ratio of TMP to SMZ achieves a serum ratio of 1:20
• Available both orally or parenterally
• Both agents are well distributed achieving good levels in the lungs, kidneys, biliary tree and the central nervous system
• Both are partially metabolized in the liver and are excreted in the urine.
• The serum half-life is 9-11h, however it is prolonged in subjects with renal insufficiency
Trimethoprim-Sulfamethoxazole
(TMP-SMZ)

Spectrum of activity

Excellent broad spectrum activity against a diversity of microorganisms

- Gram positives: staphylococci, streptococci, listeria, not enterococci
- Miscellaneous: pneumocystis, nocardia, chlamydia
Clinical uses

• Urinary tract infections
• Prostatitis
• Treatment of moderately severe to severe pneumocystis pneumonia
• Upper and lower respiratory infections caused by susceptible organisms
• Diarrheal illnesses due to salmonella, shigella and enterotoxigenic *E.coli*
Adverse effects

- Hypersensitive reactions: rash, fever
- GI effects: nausea, vomiting, diarrhea
- Toxicity from TMP-SMZ including fever, rashes, Stevens Johnson syndrome, is dramatically increased in subjects with AIDS. The reason for this is unclear.
II. DNA gyrase inhibitors: Fluoroquinolones
Quinolones

General features

• Bactericidal broad spectrum antibiotics;
• Increasingly used because of their relative safety, their availability both orally and parenterally and their favorable pharmacokinetics;
• Relatively few side effects;
• Microbial resistance to their action does not develop rapidly.
• There is increasing concern about the emergence of resistance to these agents.
Quinolones

Chemistry

•Derived from basic structure of nalidixic acid and have substituents at N-1, C-5, C-7, position 8 and a fluorine atom at position 6.

•Fluorine at position 6 enhances gyrase inhibition and cell penetration.
Antimicrobial activity

(1) Bactericidal and have significant PAE.
(2) Excellent activity against aerobic gram-negative bacteria, some agents have activity against Pesudomonas.
(3) Several newer agents with improved activity against aerobic gram-positive bacteria.
(4) They also are effective against Chlamydia spp., Legionella pneumophila, anaerobic bacteria, mycobacteria
(5) Some agents have limited activity against multiple-resistance strains.
Mechanism of action

Topoisomerases: enzymes that control and modify the topological states of DNA in cells.

- Topoisomerase I, III catalyse merely the relaxation of DNA.
- Topoisomerase II (DNA gyrase) catalyse the supercoiling of DNA.
- Topoisomerase IV involved in the separation process of the DNA daughter chains after chromosome duplication.

The quinolone antibiotics target bacterial DNA gyrase (gram-negative bacteria)
- Topoisomerase IV (gram-positive bacteria).
Inhibition of topoisomerase IV → interferes with separation of replicated chromosomal DNA into the respective daughter cells during cell division.

Inhibition of DNA gyrase → prevents the relaxation of positively supercoiled DNA that is required for normal transcription and replication.
Structure of nalidixic acid and some fluoroquinolones

Nalidixic Acid 1962

Norfloxacin 1978

Ciprofloxacin 1983

Levofloxacin 1987

Moxifloxacin 1994

Gemifloxacin 1994
Interfere with bacterial DNA synthesis
Inhibit topoisomerase II (DNA gyrase) and topoisomerase IV
Block the relaxation of supercoiled DNA catalyzed by DNA gyrase
  Step required for normal transcription and duplication
Bactericidal
Exhibit postantibiotic effects
Classification

**Norfloxacin (1\textsuperscript{st} group)**

- Least active against gram (-) and gram (+)
- Derived from nalidixic acid
- Common pathogens that cause UTI
Ciprofloxacin, levofloxacin, ofloxacin, enoxacin, lomefloxacin and pefloxacin (2nd group)

- Excellent activity against gram (-) cocci and bacilli
  - *S. aureus* (systemic infections)
- Greater activity against gram (+) cocci
  - Streptococci
- *S. pneumoniae*
  - Staphylococci
- MRSA
- Mycobacteria

Ciprofloxacin remains the quinolone most active against *Pseudomonas aeruginosa*
Gatifloxacin, gemifloxacin and moxifloxacin (3rd group)*

Improved activity against gram (+)

*S. pneumoniae
Some staphylococci

• Enhanced activity against *anaerobes*
Resistance

- Emerged rapidly for 2nd group
  - C. jejuni and gonococci
  - Gram (+) cocci (MRSA)
  - Pseudomonas and Serratia

- Changes in sensitivity of the enzyme via point mutations in the antibiotic binding regions
- Changes in permeability of the organism
Pharmacokinetics

- Good oral bioavailability (80-95%)
- Penetrate most body tissues
- Serum half-lives range from 3 to 10 hours
- Elimination through the kidneys via active tubular secretion
  - Blocked by probenecid
- Dosage reduction needed in renal dysfunction
Pharmacokinetics cont.

Norfloxacin
- Does not achieve adequate plasma levels for use in systemic infections
Moxifloxacin, sparfloxacin, travofloxacin
- Eliminated partly by hepatic metabolism and biliary excretion
Clinical uses

• Complicated **urinary tract infection**: chlamydial urethritis, cervicitis, prostatitis. The 1st choice is ciprofloxacin, gatifloxacin and ofloxacin

• **Respiratory tract infections:**
  Levofloxacin, gatifloxacin, gemifloxacin and moxifloxacin

• **Intestinal infections and typhus**

• **Therapy for multidrug-resistant tuberculosis**

• **Soft tissue, bone and joints infections**
Current Uses of Fluoroquinolones

Ciprofloxacin: wide range of infections
  pneumonias, bone infections, diarrhea, skin infections and urinary tract infections. Not good for methicillin resistant \textit{Staphylococcus aureus}

Norfloxacin: better for UTI
  effective against Gram-negative (including \textit{Pseudomonas aeruginosa}) and Gram-positive UTIs and prostatitis, but not in systemic infections

Levofloxacin:
  Community-acquired pneumonia
  Atypical pneumonia (\textit{M. pneumoniae})

Moxifloxacin – overcomes the problems with \textit{S. pneumoniae}
  Acute bacterial sinusitis; mild to moderate community-acquired pneumonia
Adverse effects

• Quinolones are among the most well tolerated antimicrobial agents
• Gastrointestinal distress is most common
• Skin rashes
• Dizziness
• Abnormal liver function tests
• Headache
• Insomnia
• Phototoxicity