NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

After completing the preparation materials, students should be able to:

1. Identify the sulfonamides' clinically relevant class and drug-specific pharmacokinetics properties.
2. Differentiate the mechanisms of action, resistance, and cross-resistance for the sulfonamides and trimethoprim.
3. Give examples of the therapeutic applications of each of the clinically used sulfonamides, trimethoprim, and trimethoprim-sulfamethoxazole (TMP-SMX) in relation to their specific spectrums of activity.
4. Explain the mechanisms of potential adverse reactions and drug interactions for the sulfonamides and trimethoprim.
5. Correlate the common and potentially serious adverse effects of each subclass of antifolate antibiotics with their cautions and contraindications for use.

Sulfonamides

Sulfonamides are not used alone for the treatment of systemic infections due to resistance.

Therapeutic uses: Trimethoprim and sulfamethoxazole (TMP-SMX) fixed-combination for a variety of infections; malaria (sulfadoxine and pyrimethamine); toxoplasmosis (sulfadiazine and pyrimethamine); ulcerative colitis and rheumatoid arthritis (sulfasalazine);

Topical: antibacterial ophthalmic drops (sulfacetamide), burn creams/powder (silver sulfadiazine, mafenide acetate)

Toxicities:

- Hypersensitivity reactions with skin rash and fever are common. Severe Stevens-Johnson syndrome and exfoliative dermatitis are rare.
- Nausea, vomiting, and diarrhea are common. Hepatitis occurs rarely.
- Serious hematopoietic disturbances occur rarely – granulocytopenia, thrombocytopenia, and aplastic anemia. Acute hemolysis is a potential in individuals with glucose-6-phosphate-dehydrogenase deficiency.
- Crystalluria can result from sulfonamide precipitation in acidic urine.
- Displacement of unconjugated bilirubin on albumin binding sites can lead the kernicterus (encephalopathy) in neonates.
- HIV/AIDS patients have a high incidence of adverse effects. Poor acetylators are at increased risk of toxicities.

Key points

Trimethoprim: Weak base structurally similar to folic acid

PK: Good tissue penetration, hepatic metabolism (CYP2C9), high concentrations of intact drug excreted in urine; t½ adults 8-12 hours (about the same as sulfamethoxazole that is combined with)

Action: Dihydrofolate reductase (DHFR) inhibitor that blocks the conversion of dihydrofolate to active tetrahydrofolate, the second step in bacterial folate synthesis.

Antibacterial effect: Bacteriostatic

Selective toxicity: Much greater affinity for bacterial DHFR than for mammalian DHFR

Spectrum: Streptococci, staphylococci, MRSA, gram-negative aerobic bacilli
Widespread resistance

Resistance: Production of DHFR with decreased affinity for the drug

Therapeutic uses: Rarely used alone. Clinical applications UTI prophylaxis and *Pneumocystis* pneumonia with dapsone (sulfone)

Toxicities: Megaloblastic anemia, leukopenia, granulocytopenia are predictable adverse effects resulting from inhibition of folate metabolism. Folic acid supplementation reduces these effects.

Key points

Trimethoprim-Sulfamethoxazole: fixed combination for oral and IV administration

PK: Formulated in a 1:5 TMP:SMX ratio, which produces the optimal peak concentration of 1:20 TMP:SMX.

Dual action: By inhibiting DHPS and DHFR, the combination inhibits the first and second step in bacterial folate synthesis, which prevents the synthesis of DNA, RNA and proteins.

Antibacterial effect: Synergistic and bactericidal, broader spectrum than either agent alone

Therapeutic uses: TMP-SMX is effective in the treatment many infections caused by susceptible organisms:

- Urinary tract infections (*E. coli* resistance is common)
- Respiratory, ear, and sinus infections caused by *H. influenzae* and *M. catarrhalis*
- Alternative for Traveler's diarrhea, shigellosis, typhoid fever, MRSA and *Listeria* infections

Drug of choice for:

- Prevention and treatment of *Pneumocystis* pneumonia, which affects HIV/AIDS patients
- Nocardiosis, a disease affecting the brain, lungs, and skin – most common in people with weakened immune systems.

Check your knowledge

1. What is the bacterial enzyme that sulfonamides target?
2. What is the antibacterial spectrum of sulfonamides?
3. What are resistance mechanisms?
4. What organisms are intrinsically resistant to folate synthesis inhibitors?
5. Why are sulfonamides combined with a DHFR inhibitor for treatment of systemic infections?
6. What are the names of the sulfonamide and the DHFR inhibitor in fixed-combination for treatment of bacterial infections?
7. What are the names of the sulfonamides and the DHFR inhibitor used in combination for treatment of certain protozoal infections?
8. TMP-SMX is the drug of choice for which two infections?
9. What is the proposed mechanism of the rashes caused by sulfonamide treatment?
10. What is the reason sulfonamide therapy is not recommended in late pregnancy and infants <2 months old? And the mechanism?
11. What sulfonamides are used topically for burn treatment?
12. What are two adverse effects of mafenide acetate?

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After completing the preparation materials, students should be able to:

1. Identify the fluoroquinolones' (FQs) clinically relevant class and drug-specific pharmacokinetics properties.
2. Differentiate the mechanisms of action, resistance, and cross-resistance for the fluoroquinolones.
3. Give examples of the therapeutic applications of each of the clinically used fluoroquinolones in relation to their specific spectrums of activity.
4. Explain the mechanisms of potential adverse reactions and drug interactions for the fluoroquinolones.
5. Correlate the common and potentially serious adverse effects of the fluoroquinolones class with their cautions and contraindications for use.

Fluoroquinolones Key Points

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- Fluoroquinolones (FQs) are broad-spectrum antibiotics highly effective in the management of many different bacterial infections caused by aerobic gram-negative and gram-positive infections.
- FQs interfere with DNA synthesis by forming a FQ-enzyme-DNA ternary complex, which inhibits the actions of DNA gyrase (primary target in gram negative bacteria) and topoisomerase IV (especially in gram positive bacteria).
- DNA gyrase: The FQ-topoisomerase-DNA complex interrupts the replication fork, prevents re-ligation of the DNA, and promotes breakage of double-stranded DNA, leading to cell death.
- Topoisomerase IV: The FQ-topo-DNA complex interferes with separation of the replicated chromosomal DNA (decatenation) during cell division.
- FQs are bactericidal.
- Resistance to FQs may arise during therapy by chromosomal mutations in genes 1) encoding DNA gyrase or topoisomerase IV, 2) mutations leading to increased expression of efflux pumps, or 3) under-expression of porins. Plasmid transfer of genes encoding topo protection protein (Qnr) or acetyltransferase that modifies the FQ structure and inactivates the drug lead to low-level resistance.
- FQ resistance is common and widespread.

Fluoroquinolones Key Points

- FQs class pharmacokinetic properties: oral and parenteral administration, large volumes of distribution, low to moderate plasma protein binding, minor hepatic metabolism, high bioavailability, mainly renal excretion, drug-specific half-lives.
- Parameters associated with efficacy (PK-PD profile): concentration-dependent effects and AUC_{24}/MIC ratio with organism-specific post-antibiotic effect. C_{max}/MIC and AUC_{24}/MIC goals are listed in the drug monographs.
- Nausea, vomiting, and diarrhea are common side effects. FQs are associated with higher rates of *C. difficile* infection compared to other antibiotics.
- A range of serious adverse effects are reported with FQ use. Included are tendon rupture, peripheral neuropathy, exacerbation of myasthenia gravis (muscle weakness), QT interval prolongation, aortic aneurysm/dissection, dysglycemia (hypo-/hyperglycemia), and phototoxicity. Older patients are at increased risk of adverse effects.
- The FDA has issued several US Boxed Warnings and recommended against the use of FQs for uncomplicated infections. Expert recommendation is to weigh benefits vs risks before prescribing FQs.
- Drug interactions: Oral absorption is reduced by the presence of di- and trivalent cations. Ciprofloxacin inhibits CYP1A2 and increases blood levels of theophylline. Glucocorticoids increase the risk of tendon rupture. Avoid administration with other drugs that cause QT interval prolongation.

What is the meaning of clinical relevant pharmacokinetics?

A treatment is clinically relevant if it provides a positive benefit in how the patient feels, functions, and/or survives – the perception of benefit by the patient – and outweighs potential harm = optimization of therapy.

Knowing the pharmacokinetic properties enables prescribing the right drug for the individual patient at the right dose by the right route of administration and the right duration for optimal efficacy (benefit to the patient) and minimal harm.

ADME:

- correct route of administration for desired effect and patient adherence to therapy,
- distribution to site of action in therapeutic concentration (correct dose) but not excessive concentration, which would increase the risk of adverse effects
- hepatic function $\rightarrow$ drug metabolizing capacity
- potential for metabolism/transport drug interactions
- function of drug eliminating organs (renal and hepatic function)

Application of knowledge can give the prescriber the ability to anticipate and mitigate potential PK-related adverse effects and drug interactions.

Chromosomal and plasmid mediated resistance mechanisms.

Resistance to fluoroquinolones is common and rates are growing.

Chromosomally-mediated mechanisms

The main mechanisms are target modification and reduced permeability to the drug.

- **Target modification:** One or more point mutations in chromosomal genes encoding the binding region of DNA gyrase and topoisomerase IV
- **Reduced accumulation of drug:**
  - Active transport (efflux) of the drug out of the bacteria or
  - changes in porin structures

Plasmid-mediated mechanisms

These confer low-level resistance, unless they accumulate or occur with chromosomal resistance mutations.

- **Topo protection:** Topoisomerase binding site protection proteins (Qnr proteins)
- **Drug modification:** Acetylation by acetyltransferase that inactivates the drug

Low-level resistance unless mutations accumulate or combined with chromosomal resistance mechanisms.

➢ **Resistance can emerge during therapy**, especially among:
E. coli and other enteric bacteria, *Pseudomonas*, *N. gonorrhoeae*, and staphylococci
Cross-resistance: High-level resistance to one FQ confers resistance to the others.
(Delafloxacin appears to retain activity.)

Adverse Effects of Fluoroquinolones

Fluoroquinolones are associated with ***potentially permanent and disabling adverse effects*** of the tendons, muscles, joints, nerves, and CNS that may occur together in the same patient and may occur soon after initiation of therapy.

➢ Consider patients' risk factors and weigh benefit vs risk when considering FQ therapy.

US Boxed Warnings

- CNS:

Seizures (rare), ↑intracranial pressure, headache, dizziness, insomnia, nightmares, depression, psychosis

- Peripheral neuropathy

  (can be irreversible)
- Tendon rupture
- Myasthenia gravis exacerbation

Additional potential AEs

- Nausea/vomiting/diarrhea
- QT interval prolongation
- Glucose dysregulation (serious hypoglycemia/hyperglycemia in diabetic patients)
- Aneurysm / aortic dissection
- *C. difficile* or *Candida* infection
- Phototoxicity
- Hypersensitivity reactions

Special Populations

Pregnancy

- FQs Cross the placenta and can be found in cord blood
- No specific teratogenic effect or increased pregnancy risk has been identified.
- May be used in the treatment of multidrug resistant tuberculosis, inhalational anthrax, and plague (*Yersinia pestis*) during pregnancy.

Older patients: Adverse effects may be increased in the elderly.

Pediatrics

- Dosing recommendations are available for infants ≥6 months old and children

➢ FQs are not first-line agents in pediatric patients. A FQ may be considered after assessment of risks and benefits and no safe alternatives are available.

- Arthralgias and joint pain during therapy are more common among children receiving FQs relative to comparators, studies have not noted long-term joint abnormalities or growth inhibition among children exposed to FQs.

FQ Drug Interactions

Ciprofloxacin:

CYP1A2, 3A4 inhibitor, OAT substrate

Classic example of ciprofloxacin DDI:

- Theophylline is a substrate of CYP1A2 and inhibited by ciprofloxacin.
- Theophylline has the potential to cause seizures at higher concentrations.
- Theophylline as a narrow therapeutic window.

Ciprofloxacin + Theophylline

↓

Increased theophylline levels

↓

Increased seizure risk

- Ciprofloxacin may increase levels of CYP3A4 substrates and OAT substrates

All FQs:

- **QTc prolongation: Examples**
  - antiarrhythmics
  - macrolides
  - azole antifungals
  - antipsychotics
  - tricyclic, SSRI antidepressants
  - many more
- **Glucocorticoids:**
  - Concomitant use may →↑risk of **tendon rupture**
- **Antacids and other divalent cations** → ↓FQ absorption

Check your knowledge:

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1. How is gaining knowledge about class and drug-specific PK properties relevant to optimizing drug therapy for the individual patient?
2. What parameters are associated with clinical efficacy (and provide dosing guidance)?
3. What are the bacterial targets of the FQs?
4. What are the chromosomal and plasmid-mediated resistance mechanisms?
5. Which mechanisms confer low-level resistance ?
6. What risks must be weighed against the benefit when considering therapy with a FQ?

Check your knowledge:

1. How is gaining knowledge about class and drug-specific PK properties relevant to optimizing drug therapy for the individual patient?
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1. **Right drug | Right patient | Right dose | Right route | Right time**

The ability to **anticipate and mitigate** potential PK-related adverse effects and drug interactions.

2. Concentration-dependent Cmax/MIC; AUC24/MIC; post-antibiotic effect

3. DNA gyrase (main target in gram-negatives); topo IV (main target in gram-positives)

4. Chromosomal mutations in genes of FQ binding regions, efflux pumps, porins. Plasmid transfer of genes for topo protection protein (Qnr) and drug inactivation by acetylation.

5. Plasmid transfer of genes for topo protection protein (Qnr) and drug inactivation by acetylation confer low-level resistance, unless they accumulate or are coupled with chromosomal resistance mutations.

6. Significant toxicities, including peripheral neuropathy, tendon rupture, QT prolongation, and CNS effects. Patient factors at increased risk of experiencing adverse effects: older patients, pediatric patients, pregnant patients, myasthenia gravis patients, diabetic patients.