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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.

Key points: What you need to know and understand

Sulfonamides: Weak acids structurally similar to PABA

PK: Modest tissue penetration, hepatic metabolism via N-acetylation and CYP pathways, and excretion in urine of both intact drug (high concentration) and acetylated metabolites. Toxic metabolites of the CYP pathways may cause immunological toxicities and direct (non-immunological) toxicities.

Action: Dihydropteroate synthase (DHPS) inhibitors compete with the natural substrate, PABA, in first step of the bacterial folate synthase pathway. Folate is required for purine synthesis.

Antibacterial effect: Bacteriostatic

Selective toxicity: Mammalian cells use exogenous folic acid from dietary sources.

Spectrum: staphylococci (MSSA/MRSA), gram-negative aerobes, and *Nocardia*, and non-bacterial *Pneumocystis jirovecii, Toxoplasma gondii*

Resistance: *widespread resistance to common infective pathogens*
Decreased cellular accumulation of drug (decreased permeation or efflux); enhanced PABA production; modified target
Intrinsic resistance: Enterococci, PCN-resistant *S. pneumoniae*, *P. aeruginosa*, *Rickettsia*, anaerobes, spirochetes, *Mycoplasma*, Mycobacteria

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.

Folate Synthesis Inhibitors

Sulfonamides

Sulfones

(sulfones are not included in this lecture)

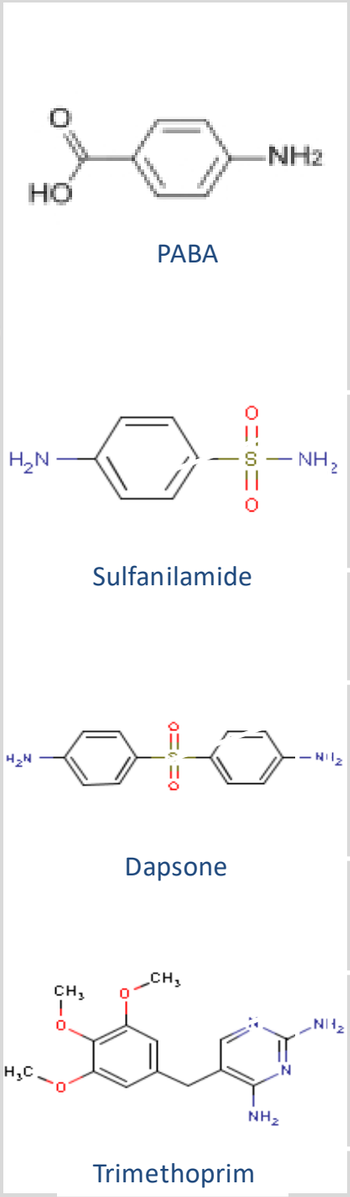
Trimethoprim

Pyrimethamine

(not sulfonamides)

Structure-activity relationship

Sulfur group linked to benzene ring and *para*-NH_2 required for activity



SO_2NH_2 sulfonamide

sulfone (S=S)

structural analog of dihydrofolate

The sulfonamides and trimethoprim are rarely used alone.

Trimethoprim-sulfamethoxazole (TMP-SMX, cotrimazole) fixed combination is frequently used if therapy with a folate synthesis inhibitor is appropriate.

Metabolism of Sulfonamides

- N-acetylation and N-oxidation
- Reactive metabolites of CYP N-oxidation → hypersensitivity reactions

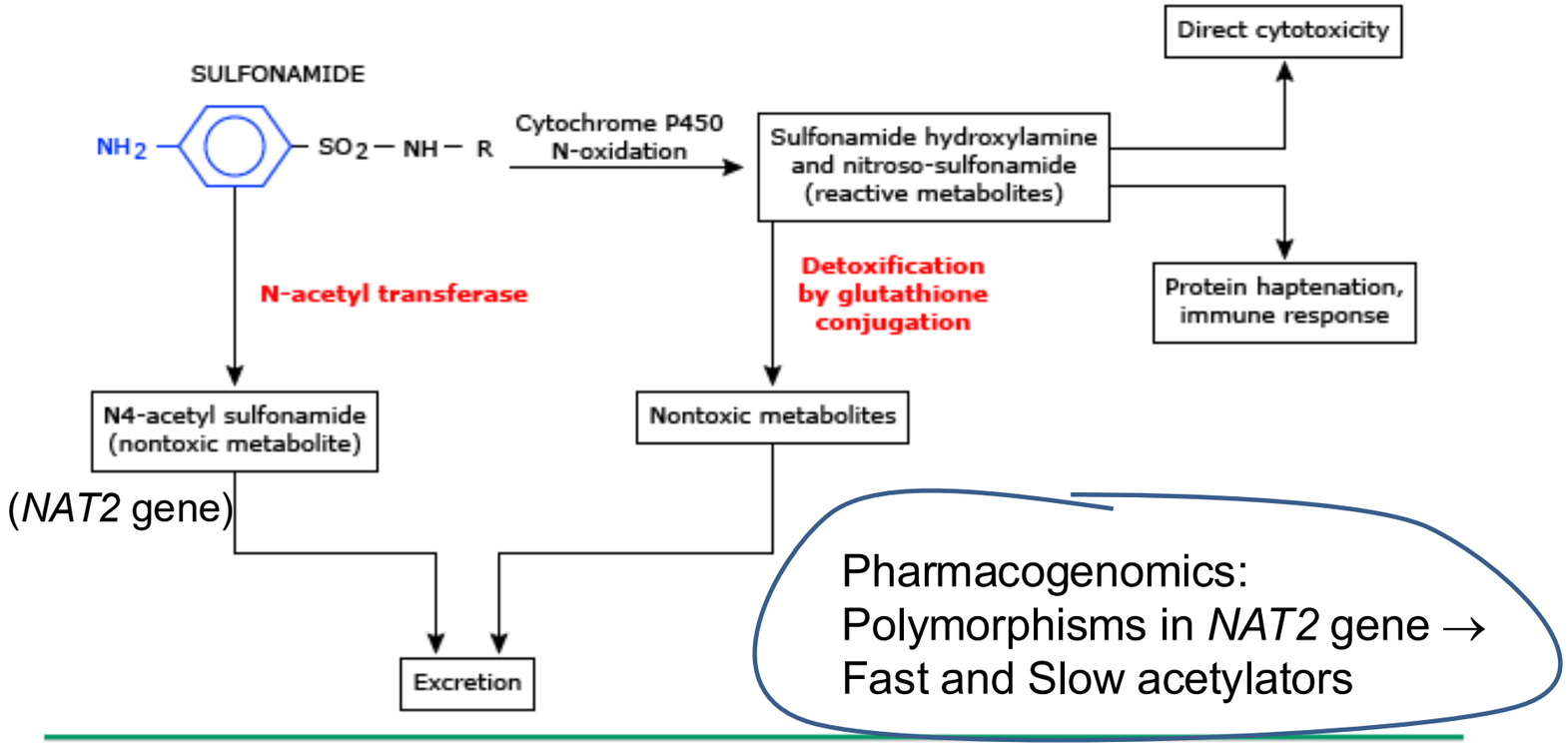
Risk factors:

1. Slow acetylators, and
2. Depleted glutathione stores (*eg* HIV/AIDS)

↓

more prolonged exposure to the reactive metabolites → ↑ risk of hypersensitivity reactions

Sulfonamide metabolic pathways



Sulfonamide antimicrobial drugs are metabolized by oxidation of the arylamine group (shown in blue). Nontoxic metabolites are then excreted. Factors that slow metabolism, such as slow acetylator status or depletion of glutathione stores (in HIV infection), can affect the steps shown in bold red. This may lead to prolonged exposure to reactive metabolites and increased rate of hypersensitivity reactions.

UpToDate®

From: **31 Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics, Figure 31.7**
Lippincott® Illustrated Reviews: Pharmacology, 7e, 2019

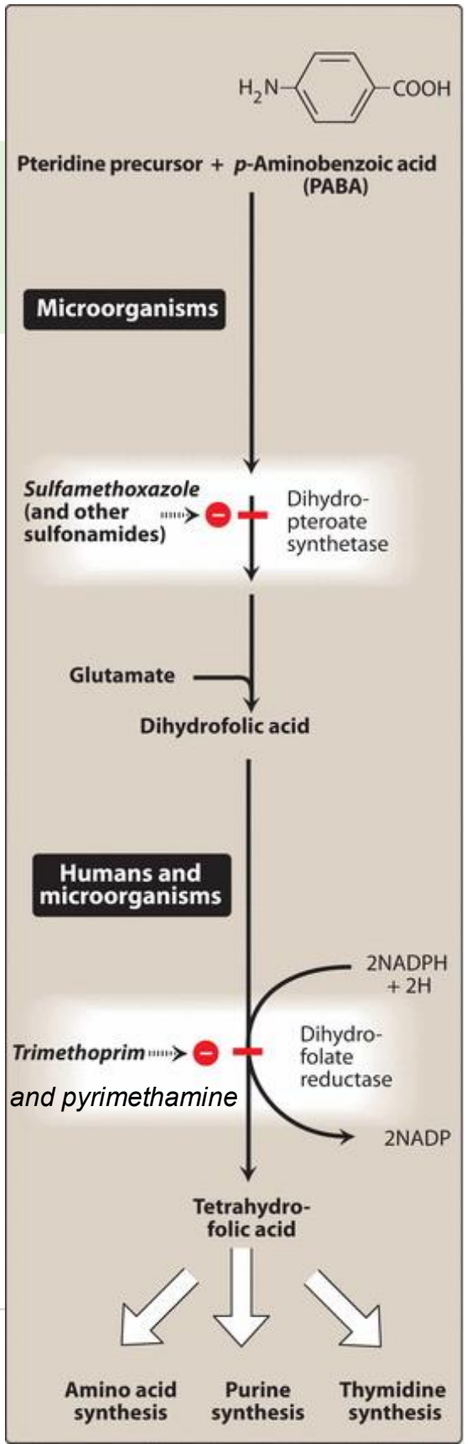
Inhibition of tetrahydrofolate synthesis by sulfonamides and trimethoprim.

Sulfonamides / sulfones compete with p-aminobenzoic acid (PABA) for dihydropteroate synthase → prevents conversion of PABA to dihydrofolic acid

Trimethoprim: Inhibits dihydrofolate reductase (DHFR) → prevents conversion of dihydrofolic acid to active tetrahydrofolic acid

Spectrum of activity: Trimethoprim-Sulfamethoxazole (TMP-SMX)
(sulfonamides are not used alone for systemic infections)

- many aerobic gram-positive and gram-negative bacteria
- non-bacteria *Pneumocystis jirovecii* and some protozoa
- caMRSA generally susceptible



Acquired Resistance

Widespread resistance limits use of folate synthesis inhibitors.

Plasmid transfer or random mutation under selective pressure:

1. Decreased intracellular concentration of drug
   - ↓ Cellular permeability to the drugs
   - Drug efflux
2. Increased PABA production → outcompetes the drug
3. Modified targets → low affinity for the drug
   - Altered dihydropteroate synthase (sulfonamides)
   - Altered dihydrofolate reductase (trimethoprim)

Formerly susceptible but now resistant bacteria:

- *S. pneumoniae*
- Group A *Streptococcus*
- *N. gonorrhoeae*
- *N. meningitidis*

Increasing resistance

- *E. coli; Klebsiella*

Intrinsic resistance:

Anaerobes, Enterococci, *P. aeruginosa*, spirochetes, Mycoplasma, Mycobacteria

Sulfonamides **STIMULATE** growth of *Rickettsia.*

Therapeutic Uses of Sulfonamides

(Uses of TMP-SMX combination are listed after the section on trimethoprim.)

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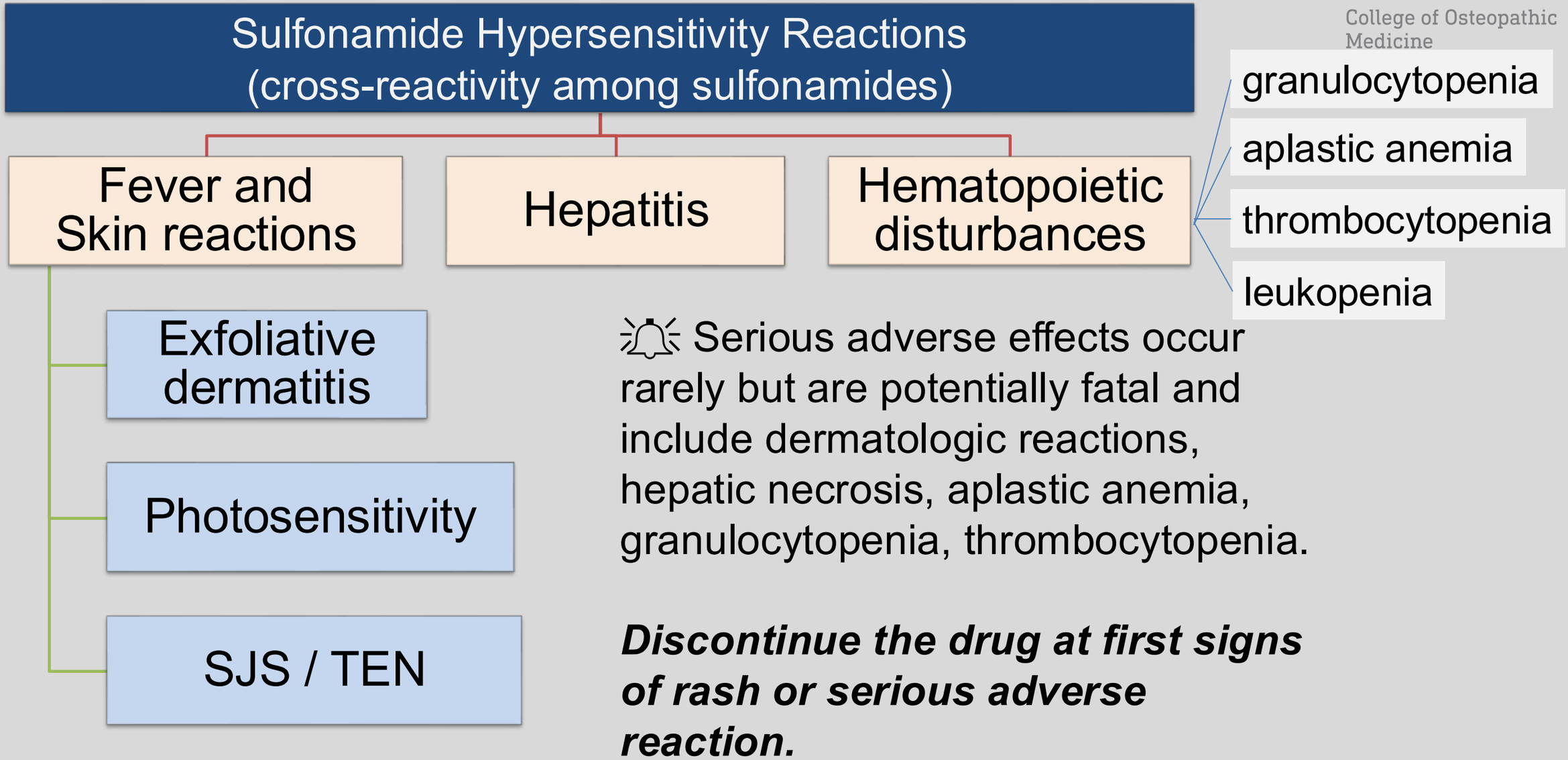
Sulfadiazine + pyrimethamine (+ leucovorin = active folate)	Acute toxoplasmosis first-line treatment	Pyrimethamine is a potent inhibitor of parasitic DHFR. It is combined with a sulfonamide for synergy.
Sulfadoxine + pyrimethamine (+ leucovorin)	*Plasmodium falciparum* malaria treatment (widespread resistance)	
Sulfasalazine	Inflammatory bowel disease; rheumatoid arthritis	

Topical sulfonamides

Sulfacetamide sod.	Ophthalmic; dermatologic uses
Silver sulfadiazine minimal absorption	Burns Silver is slowly released → toxic to the bacteria.
Mafenide readily absorbed from burn area	Burns Causes intense pain on application Caution: Can cause **metabolic acidosis** (carbonic anhydrase inhibitor)

Sulfonamides: Adverse Effects



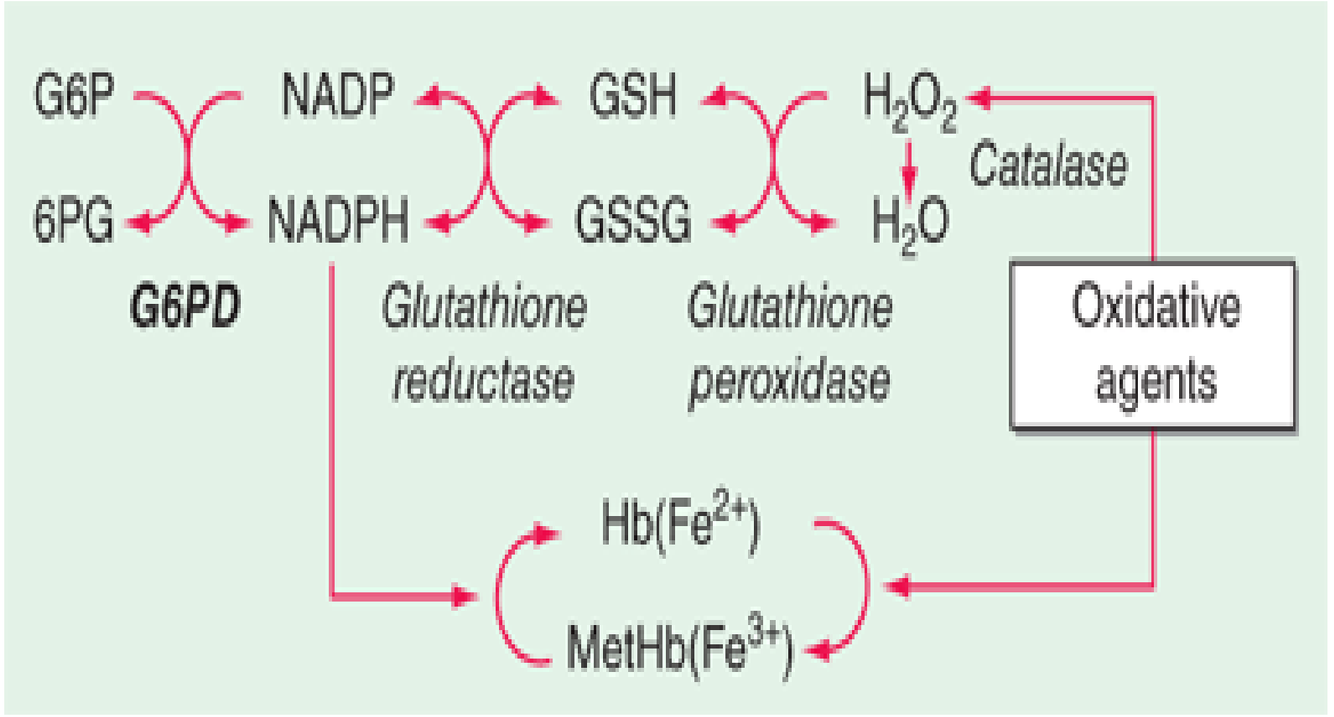
Serious adverse effects occur rarely but are potentially fatal and include dermatologic reactions, hepatic necrosis, aplastic anemia, granulocytopenia, thrombocytopenia.

Discontinue the drug at first signs of rash or serious adverse reaction.

Sulfonamides: Cautious use in patients with…

Glucose-6-phosphate dehydrogenase deficiency	Hemolytic anemia (G6PD deficiency is a common X-linked disorder.)
Bone marrow suppression	Agranulocytosis; aplastic anemia More common in pts with limited reserve Use caution in patients with folate deficiency
Crystalluria risk factors High sulfonamide dose Acidic urine	Sulfadiazine and sulfamethoxazole may precipitate in acidic urine Practice point: Drink lots of water (all sulfa drugs)
Newborn infants	**Kernicterus** Sulfonamides displace bilirubin from albumin binding sites $\rightarrow \uparrow$plasma levels of unconjugated bilirubin
Pregnancy / Lactation	Kernicterus concern: Avoid in LATE pregnancy Nursing is contraindicated for infants $\leq$2 months old
Plus like all ABX, they can cause *C. difficile* infection	Diarrhea; dehydration; pseudomembranous colitis; toxic megacolon

Erythrocytes are vulnerable to oxidative stress in patients with G6PD deficiency. Sulfonamides can induce oxidative stress by creating reactive oxygen species (ROS).



G6PD maintains the body's supply of reduced NADPH.

In red cells, G6PD is critical.

It is the only source of NADPH, which directly and via glutathione (GSH) defends these cells against oxidative stress.

G6PD deficiency makes red cells more vulnerable to oxidative stress.

NADPH is also necessary for reduction of methemoglobin to $Hb(Fe^{2+})$. $MetHb(Fe^{3+})$ is unable to bind oxygen.

Solubility of the older sulfonamides is decreased in acidic urine.

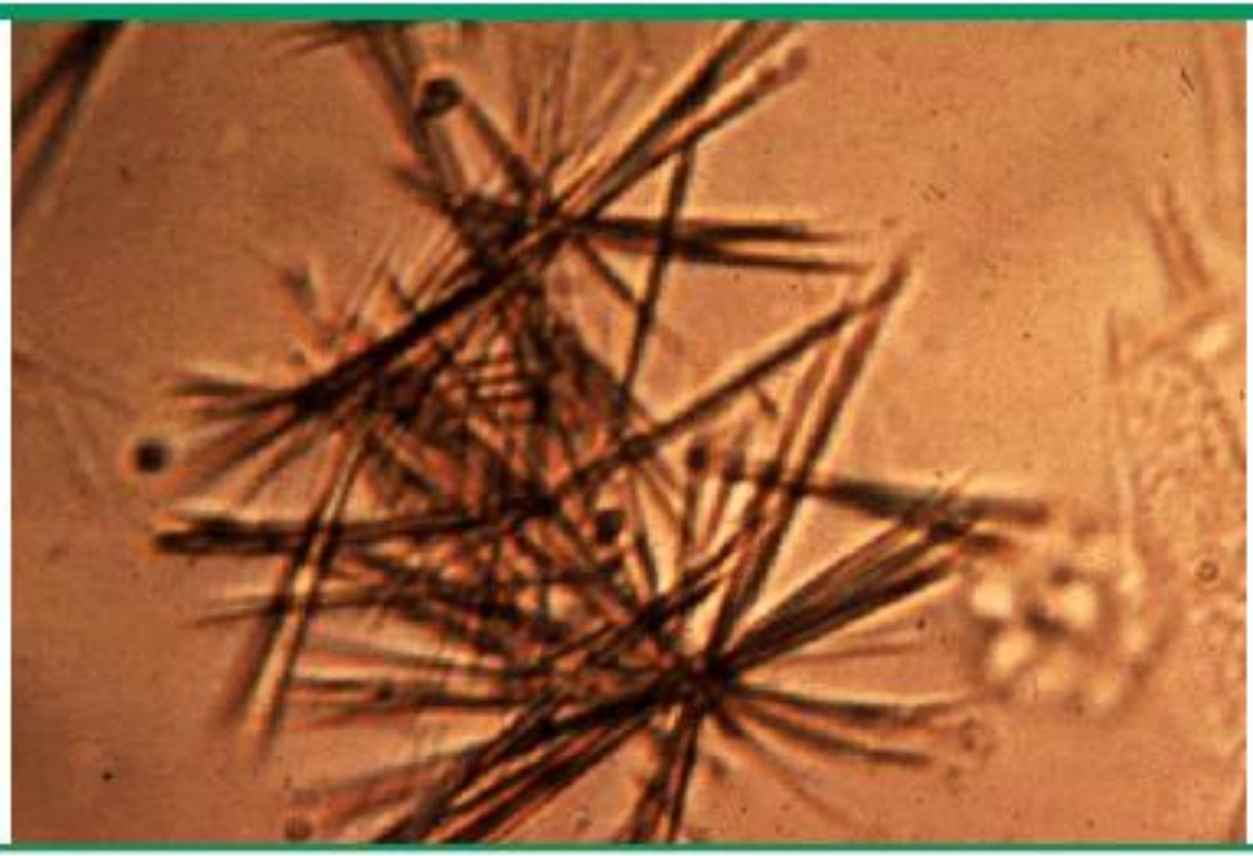
- Crystals are more likely to form in acidic urine.
- Intratubular precipitation of crystals can lead to hematuria, obstruction, and acute kidney injury

Drug-drug interaction:

✳**Methenamine** is a urinary antiseptic for the prophylaxis or suppression of recurrent urinary tract infections. Methenamine is hydrolyzed to formaldehyde and ammonia in acidic urine.

Combination with sulfonamide is contraindicated.

Photomicrograph showing urine sediment of a patient with sulfonamide crystalluria

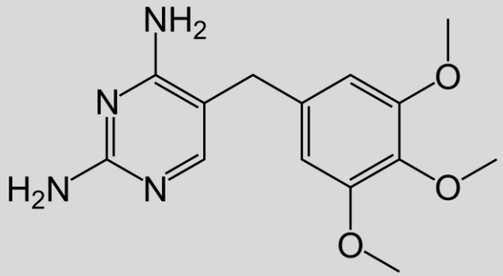


Urine sediment showing sulfonamide crystals with a needle-shaped appearance. Other forms that may be seen include rosettes and a shock of wheat appearance.

Courtesy of Harvard Medical School.

Trimethoprim

Pyrimethamine



Trimethoprim Properties

PK	Oral, well-absorbed; widely distributed in fluids and tissues; some hepatic metabolism; excreted in urine, unchanged drug; t½ 8-10 h adults w. normal renal fx
MOA	Inhibits bacterial DHFR, which inhibits nucleic acid synthesis and DNA Resistance mechanisms as for the sulfonamides, specifically DHFR with reduced sensitivity
TU	Trimethoprim monotherapy: Treatment of acute, uncomplicated urinary tract infection (UTI) and Prophylaxis of UTI
AEs	Megaloblastic anemia, leukopenia, granulocytopenia (rare) (hematopoietic effects of folate synthesis inhibition) Hyperkalemia
DDIs	Other drugs that may enhance the neutropenic or hyperkalemic effects

Trimethoprim-sulfamethoxazole is effective in a wide variety of infections – if the pathogens have not developed resistance.

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The 2 drugs have a similar half-life. The fixed TMP-SMX combination is in a 1 to 5 ratio that provides peak plasma concentration in the optimal 1:20 ratio

UTIs, Prostatitis	*E. Coli, Klebsiella, Proteus*
Traveler's diarrhea	Enterotoxigenic *E. coli*
Gastroenteritis	Shigella
Acute otitis media	Susceptible *S. pneumoniae, H. influenzae, M. catarrhalis*
Skin infections	Susceptible community-acquired MRSA
Nocardia (gram-positive)	**TMP-SMX is drug of choice**
Listeria	Ampicillin combo if gentamicin cannot be used
Pneumocystis pneumonia	***Pneumocystis jirovecii* (yeast) TMP-SMX drug of choice**
Some protozoa	*Toxoplasma gondii* (TMP-SMX or sulfadiazine and pyrimethamine) Malaria (sulfadoxine-pyrimethamine)

Enterobacterales resistance is common

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?

- **Sulfonamides** are weak acids structurally similar to PABA. They are competitive inhibitors of dihydropteroate synthase (DHPS). DHPS is a selective drug target because we do not synthesize folic acid but take it in folic acid in our diet.
- **Trimethoprim** is a weak base structurally similar to folic acid that inhibits dihydrofolate reductase (DHFR), blocking the conversion of dihydrofolate to active tetrahydrofolate, the second step in bacterial folate synthesis. Trimethoprim has lower affinity of human DHFR, accounting for its relative selectivity.
- Used alone, sulfonamides and trimethoprim are bacteriostatic. Together, they have synergistic and bactericidal activity and a broader spectrum than either agent alone. Trimethoprim and sulfamethoxazole are formulated in fixed combination for oral and IV administration.
- They have broad spectrums of activity against streptococci, staphylococci, and aerobic gram-negative bacilli. Resistance is widespread and especially common among the Enterobacterales, limiting the use of the folate inhibitors.
- The mechanisms of resistance to sulfonamides are reduced intracellular concentration of drug (decreased permeability or drug efflux), increased PABA production that outcompetes the drug at DHPS, and decreased affinity of DHPS for the drugs.
- A common mechanism of trimethoprim resistance is production of DHFR with decreased affinity for the drug.

- The sulfonamides and trimethoprim are rarely used as single drug therapy.
- Clinical applications for sulfonamides are antibacterial ophthalmic drops, topical burn preparations, ulcerative colitis/rheumatoid arthritis (sulfasalazine), malaria and toxoplasmosis in combination with pyrimethamine.
- Trimethoprim may be used for prophylaxis of urinary tract infection or *Pneumocystis* pneumonia with dapsone.
- Trimethoprim-sulfamethoxazole (TMP-SMX) has many therapeutics uses for aerobic gram-positive and gram-negative infection caused by susceptible bacteria.
- Hypersensitivity reactions with skin rash and fever are common with sulfonamides. Serious but rare toxicities include hepatitis, blood dyscrasias, hemolytic anemia in people with G6PD deficiency, crystalluria, and kernicterus in the neonate. Trimethoprim can cause megaloblastic anemia due to its antifolate action.
- Pharmacokinetic features of sulfonamides are modest tissue penetration, hepatic metabolism involving mainly N-acetyltransferase and CYPs, with excretion of active drug and acetylated metabolites in the urine. The drugs tend to precipitate in acidic urine. Patients should be advised to drink lots of water when taking these drugs.
- Pharmacokinetic features of trimethoprim are extensive absorption, minor hepatic metabolism, excretion of unchanged drug in urine, and a half-life similar to that of sulfamethoxazole, 10-12 hours.

Check your knowledge Answers

1. Sulfonamides bind dihydropteroate synthase and compete with PABA in the first step of bacterial folate synthesis.
2. The sulfonamides and TMP-SMX are active against many susceptible aerobic gram-negative and gram-positive organisms including community-acquired MRSA (caMRSA).
3. Resistance arises by ↓ intracellular accumulation of drug (efflux or decrease permeability), increased PABA production that outcompetes the drug at DHPS), and modified targets (DHPS and DHFR) with low affinity for the drugs.
4. Anaerobes, enterococci, *P. aeruginosa*, spirochetes, *Mycoplasma*, *Mycobacterium* spp are intrinsically resistant. Sulfonamides stimulate growth of *Rickettsia.* There is widespread resistance to common infections that were once susceptible.
5. Sulfonamides are bacteriostatic. Trimethoprim is bacteriostatic. Together they are bactericidal and synergistic. Sulfonamides are combined with pyrimethamine for synergy against certain protozoal infections.

Check your knowledge Answers

6. Sulfamethoxazole / Trimethoprim
7. Pyrimethamine (DHFR inhibitor) with sulfadoxine for malaria (high-level resistance). Pyrimethamine with sulfadiazine for toxoplasmosis.
7. TMP-SMX is the drug of choice for drug of choice for prevention and treatment of *Pneumocystis* pneumonia, which affects AIDS patients, and nocardiosis, a disease affecting the brain, lungs, and skin – most common in people with weakened immune systems.
8. Reduced function of NAT2 and reduced glutathione levels increase concentrations of sulfonamides' toxic reactive metabolites.
9. Kernicterus (encephalopathy) in the newborn by displacement of unconjugated bilirubin by sulfonamide on albumin, increasing free bilirubin which deposits in brain tissue.
10. Silver sulfadiazine and mafenide acetate.
11. Mafenide acetate in large quantities can cause metabolic acidosis by inhibition of carbonic anhydrase and pain on application.

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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.

Fluoroquinolones

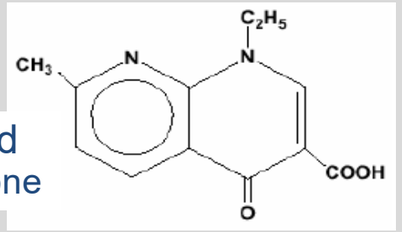
Inhibit bacterial DNA gyrase and topoisomerase IV

FQs available in the U.S.
for systemic use:

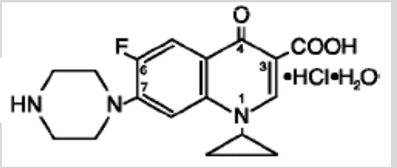
Older FQ	Respiratory FQs
✳Ciprofloxacin	✳Levofloxacin
	✳Moxifloxacin
	✳Delafloxacin
	Ofloxacin

Respiratory FQ: Activity against *S. pneumoniae*

Nalidixic acid
the first quinolone



Ciprofloxacin



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.

Fluoroquinolones PK-PD Profile

- **Cmax/MIC:** concentration-dependent bacterial killing (in vitro)

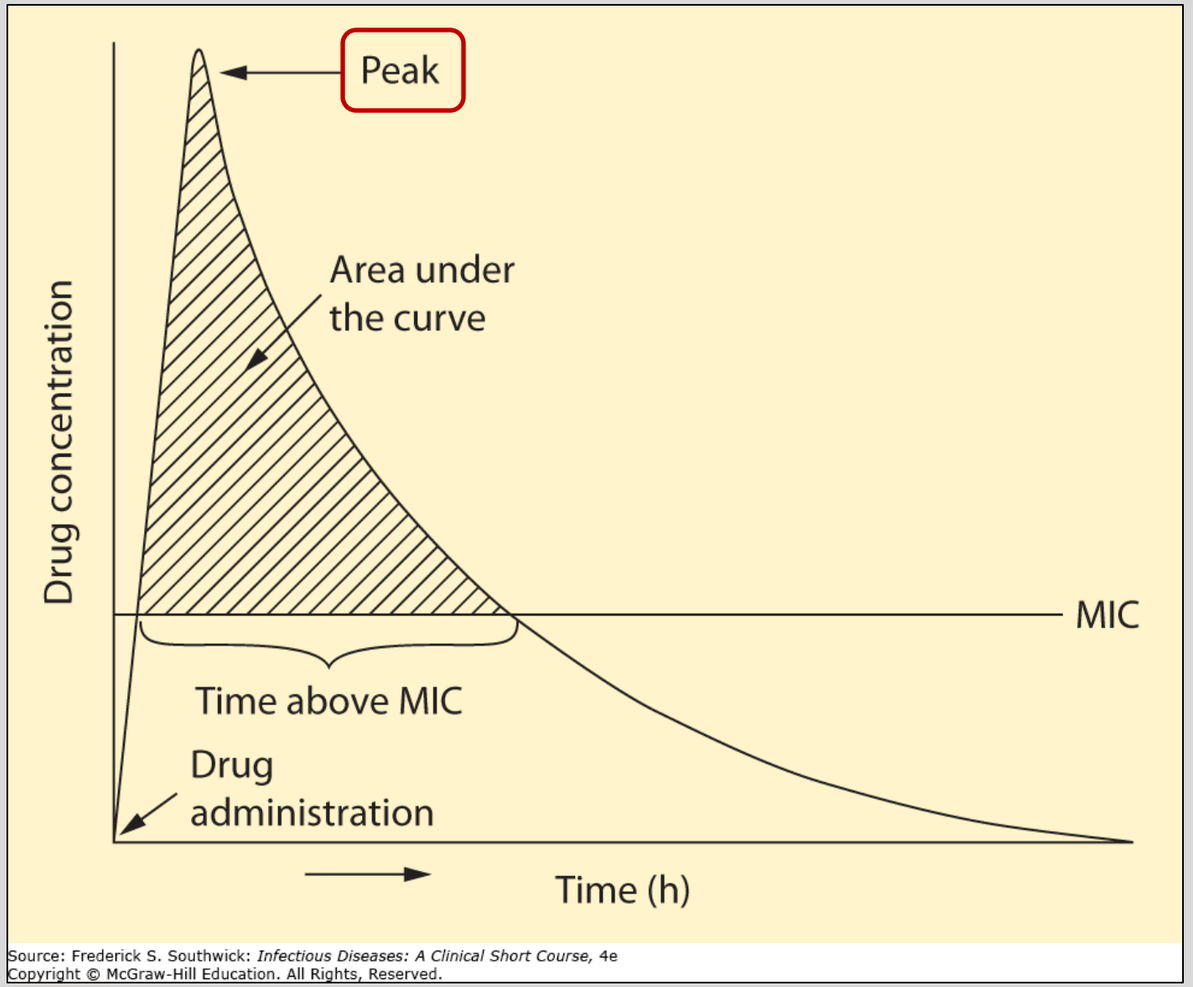
  – the greater the concentration, the greater the rate and extent of bacterial killing –

- **Post-antibiotic effect:** moderate persistent bacterial suppression
- **24h-AUC/MIC Ratio:** Efficacy correlates with total amount of drug (at steady state)

The ideal dosing regimen maximizes the total amount of drug administered over a 24-hour period.

Organism-dependent values predictive of clinical success are available in the literature.

- **Killing effect: Bactericidal**



Chapter 1 Anti-Infective Therapy, Southwick FS. *Infectious Diseases: A Clinical Short Course, 4e*

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.

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?

PK: Good oral bioavailability (antacids containing multivalent cations may interfere with absorption); penetrate most body tissues. High concentrations in urine (except moxifloxacin – hepatic and biliary elimination)

Efficacy is associated with: 24h AUC/MIC and Cmax/MIC; post-antibiotic effects

Action: Inhibit bacterial DNA gyrase and topoisomerase IV → DNA strand breaks / cell death; inhibition of topo IV prevents separation of daughter cells (decatenation)

Antibacterial effect: Bactericidal

Chomosomally-mediated resistance:

Spontaneous point mutations in the genes encoding the topoisomerases

Reduced intracellular accumulation of the drug (efflux or decreased influx through porins)

Plasmid-mediated resistance → low-level resistance:

Qnr protein protects topoisomerase binding site

FQ-modifying enzymes

Resistance can develop during therapy.

Ciprofloxacin:

Active against gram-negative aerobic bacteria including *P. aeruginosa*

Moderate activity against gram-positive organisms

Levofloxacin: Respiratory FQ

Enhanced gram-positive activity, including *S. pneumoniae* and other respiratory pathogens

Aerobic gram-negative bacteria, including *Pseudomonas*

Many therapeutic uses

Moxifloxacin: Respiratory FQ

Improved gram-positive activity and reduced activity against gram-negative bacteria.

The only FQ with anaerobic activity: anaerobic lung infections, ie abscess, aspiration pneumonia.

Delafloxacin: Respiratory FQ

Aerobic gram-negative bacteria, including *P. aeruginosa*; Improved gram-positive activity, including MRSA

For treatment of acute bacterial skin and skin structure infections in adults caused by aerobic gram-positive, including MRSA, and community acquired pneumonia

Toxicities: FDA safety alerts:

CNS effects, peripheral neuropathy, tendinitis/tendon rupture, worsening of myasthenia gravis muscle weakness, QTc interval prolongation, hypersensitivity reactions.

Pregnancy: MDR tuberculosis, inhalation anthrax and serious infection if benefit outweighs risk

Pediatrics: Infants ≥6 months old and children if benefit outweighs risk

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

Drug interactions:

Ciprofloxacin: CYP1A2 (theophylline toxicity risk), 3A4- and OAT-mediated

All FQs: drugs prolong QTc interval; glucocorticoids (tendon rupture); di-, trivalent cations reduce absorption (separate by 2 hours)

Check your knowledge:

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?

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.