Pharmacology

Subject :

Lec no : lec-29-pharma

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وَقُل رَّبِّ زِدْنِي عِلْمًا

Folate Antagonists

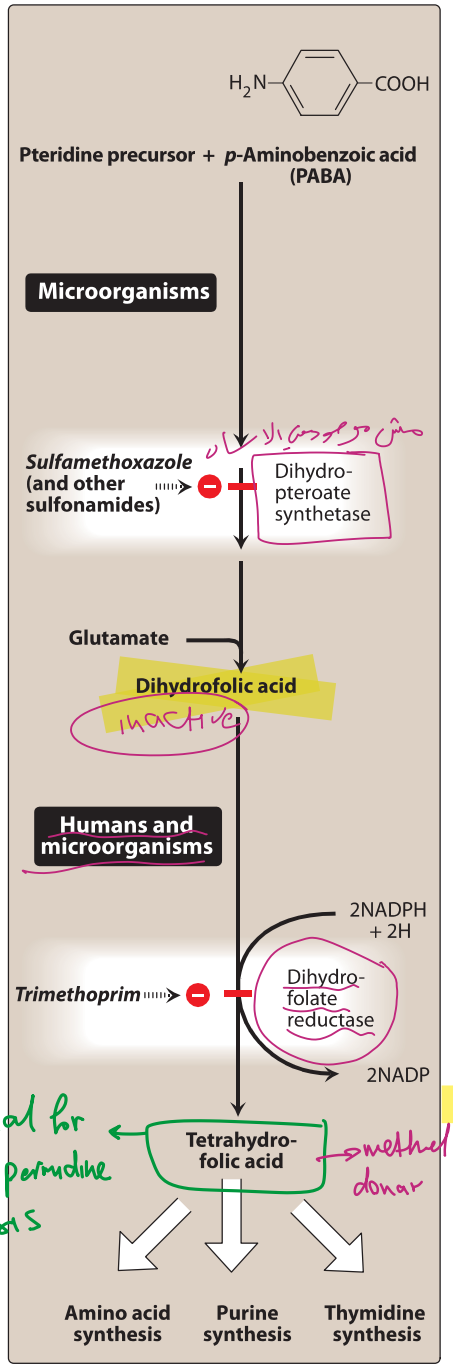


Figure 31.7
Inhibition of tetrahydrofolate synthesis by sulfonamides and *trimethoprim*.

2. **Levofloxacin:** *Levofloxacin* [leev-oh-FLOX-a-sin] has similar activity to *ciprofloxacin* and they are often interchanged when managing gram-negative bacilli, including P. aeruginosa. *Levofloxacin* has enhanced activity against S. pneumoniae and is first-line therapy for community-acquired pneumonia (CAP). It is a second-line agent for the treatment of S. maltophilia.

3. **Moxifloxacin:** *Moxifloxacin* [mox-ee-FLOX-a-sin] has enhanced activity against gram-positive organisms (for example, S. pneumoniae), gram-negative anaerobes, and Mycobacterium spp. The drug may be used for CAP, but not hospital-acquired pneumonia due to poor coverage of P. aeruginosa. It may be considered for mild-to-moderate intra-abdominal infections, but should be avoided if patients have fluoroquinolone exposure within previous three months, due to increasing B. fragilis resistance. *Moxifloxacin* may be considered as a second-line agent for management of drug-susceptible tuberculosis.

4. **Gemifloxacin:** *Gemifloxacin* [gem-ee-FLOX-a-sin] is indicated for management of community-acquired respiratory infections. Unlike the other compounds, it is only available as an oral formulation.

5. **Delafloxacin:** *Delafloxacin* [del-a-FLOX-a-sin] has improved activity against gram-positive cocci, including MRSA and Enterococcus spp. Due to its spectrum of activity, it is an option for managing acute bacterial skin and skin structure infections. It is available as an intravenous and oral formulation.

II. FOLATE ANTAGONISTS

They stop synthesis Folic Acid In the bacteria

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 (Figure 31.7). 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. Thus, both sulfonamides and *trimethoprim* interfere with the ability of an infecting bacterium to perform DNA synthesis and other essential cellular functions. The combination of the sulfonamide *sulfamethoxazole* with *trimethoprim* (the generic name for the combination is *cotrimoxazole*) provides a synergistic effect.

III. SULFONAMIDES

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.

A. Mechanism of action

Microorganisms use the enzyme dihydropteroate synthetase to create dihydrofolic acid from the precursor molecule *p*-aminobenzoic acid (PABA). Sulfonamides are synthetic analogs of PABA. Because

of their structural similarity, sulfonamides compete with PABA to inhibit dihydropteroate synthetase and the genesis of bacterial dihydrofolic acid (see Figure 31.7). These agents, including *cotrimoxazole*, are bacteriostatic.

B. Antibacterial spectrum

Sulfa drugs have in vitro activity against gram-negative and gram-positive organisms. Common organisms include Enterobacteriaceae, Haemophilus influenzae, Streptococcus spp., Staphylococcus spp., and Nocardia. Additionally, *sulfadiazine* [sul-fa-DYE-a-zeen] in combination with the dihydrofolate reductase inhibitor *pyrimethamine* [py-ri-METH-a-meen] is the preferred treatment for toxoplasmosis.

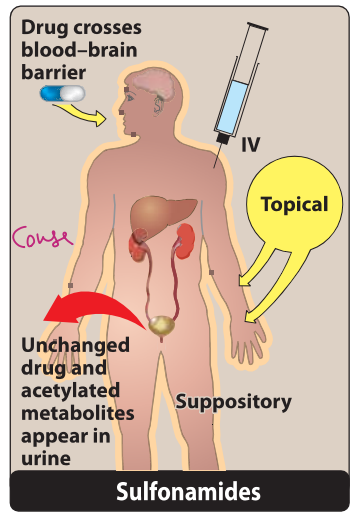


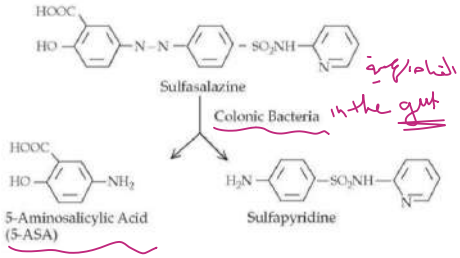
Figure 31.8
Administration and fate of the sulfonamides.

C. Resistance

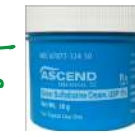
Bacteria that obtain folate from their environment are naturally resistant to sulfa drugs. Acquired bacterial resistance to the sulfa drugs can arise from plasmid transfers or random mutations. Resistance may be due to 1) altered dihydropteroate synthetase, 2) decreased cellular permeability to sulfa drugs, or 3) enhanced production of the natural substrate, PABA. [Note: Organisms resistant to one member of this drug family are resistant to all.]

D. Pharmacokinetics

1. **Absorption:** Most sulfa drugs are well absorbed following oral administration (Figure 31.8). An exception is *sulfasalazine* [sul-fa-SAL-a-zeen]. It is not absorbed when administered orally or as a suppository and, therefore, is reserved for treatment of chronic inflammatory bowel diseases. [Note: Intestinal flora split *sulfasalazine* into sulfapyridine and 5-aminosalicylate, with the latter exerting the anti-inflammatory effect. 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* [sul-fa-DYE-ah-zeen] or *mafenide* [mah-FEN-ide] *acetate* (α-amino-p-toluenesulfonamide) creams have been effective in reducing burn-associated sepsis because they prevent colonization of bacteria. [Note: *Silver sulfadiazine* is preferred because *mafenide* produces pain on application and its absorption may contribute to acid–base disturbances.]



2. **Distribution:** Sulfa drugs are bound to serum albumin in circulation and widely distribute throughout body tissues. Sulfa drugs penetrate well into cerebrospinal fluid (even in the absence of inflammation) and cross the placental barrier to enter fetal tissues.
3. **Metabolism:** 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. This causes crystalluria ("stone formation"; see below) and potential damage to the kidney.
4. **Excretion:** Unchanged sulfa drug and metabolites are eliminated via glomerular filtration and secretion, requiring dose adjustments with renal impairment. Sulfonamides may be eliminated in breast milk.



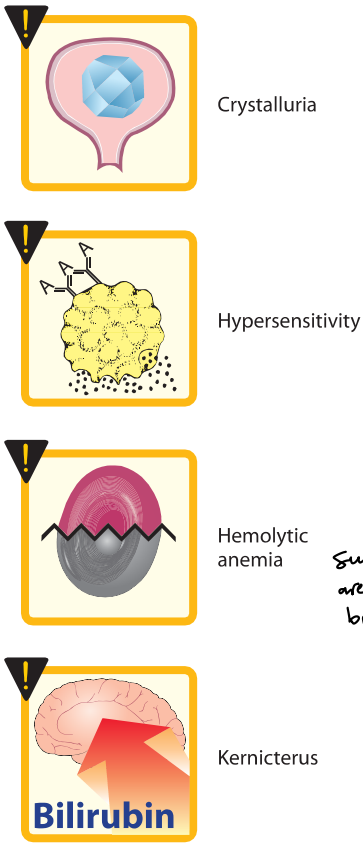


Figure 31.9
Some adverse reactions to sulfonamides.

E. Adverse effects

1. **Crystalluria:** Nephrotoxicity may develop as a result of crystalluria (Figure 31.9). Adequate hydration and alkalinization of urine can prevent the problem by reducing the concentration of drug and promoting its ionization.

2. **Hypersensitivity:** Hypersensitivity reactions, such as rashes, angioedema, or Stevens-Johnson syndrome, may occur. When patients report previous sulfa allergies, it is paramount to acquire a description of the reaction to direct appropriate therapy.

3. **Hematopoietic disturbances:** Hemolytic anemia is encountered in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Granulocytopenia and thrombocytopenia can also occur. Fatal reactions have been reported from associated agranulocytosis, aplastic anemia, and other blood dyscrasias.

4. **Kernicterus:** Bilirubin-associated brain damage (kernicterus) 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.

5. **Drug potentiation:** *Sulfamethoxazole* potentiates the anticoagulant effect of *warfarin* due to inhibition of CYP2C9, resulting in reduced clearance of *warfarin*. Sulfonamides may also displace *warfarin* from binding sites on serum albumin. Serum *methotrexate* levels may rise through protein binding displacement. Other CYP2C9 substrates, such as *phenytoin*, may have increased concentrations when given with sulfonamides.

6. **Contraindications:** Due to the danger of kernicterus, sulfa drugs should be avoided in newborns and infants less than 2 months of age, as well as in 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.

IV. TRIMETHOPRIM

Trimethoprim [try-METH-oh-prim], a potent inhibitor of bacterial dihydrofolate reductase, was initially available in combination with the sulfonamide *sulfamethoxazole* [sul-fa-meth-OX-a-zole], and later approved for use as a single agent. Today, *trimethoprim* is most commonly used in combination with *sulfamethoxazole*.

A. Mechanism of action

Trimethoprim is a potent inhibitor of bacterial dihydrofolate reductase (see Figure 31.7). Inhibition of this enzyme prevents the formation of the metabolically active form of folic acid, tetrahydrofolic acid, and thus, interferes with normal bacterial cell functions. *Trimethoprim* binds to bacterial dihydrofolate reductase more readily than it does to human dihydrofolate reductase, which accounts for the selective toxicity of the drug.

B. 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).

Antibacterial spectrum
- Similar to sulfa drugs e.g., sulfamethoxazole
- More potent as a single agent
- Can be used alone. For what? ... but not very often...

C. 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.

Mechanisms of resistance
- Altered dihydrofolate reductase
- Efflux pumps

D. 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* undergoes some O-demethylation, but 60% to 80% is renally excreted unchanged.

E. Adverse effects

Trimethoprim can produce the effects of folic acid deficiency. These effects include megaloblastic anemia, leukopenia, and granulocytopenia, especially in pregnant patients and those with nutrient-poor diets. These blood disorders may be reversed by simultaneous administration of *folinic acid* (also known as *leucovorin*), which does not enter bacteria. *Trimethoprim* has a potassium-sparing effect and may cause hyperkalemia, especially at higher doses and when administered with other medication that causes hyperkalemia (for example, angiotensin converting enzyme inhibitors).

Trimethoprim

Adverse effects
- can produce the effects of folic acid deficiency.
  -megaloblastic anemia
  -leukopenia
  -granulocytopenia,
  ***Reversed by administration of folinic acid, which does not enter bacteria.
- Hyperkalemia

V. COTRIMOXAZOLE

The combination of *trimethoprim* with *sulfamethoxazole*, called *cotrimoxazole* [co-try-MOX-a-zole], shows greater antimicrobial activity than equivalent quantities of either drug used alone (Figure 31.10). The combination was selected because of the synergistic activity and the similarity in the half-lives of the two drugs.

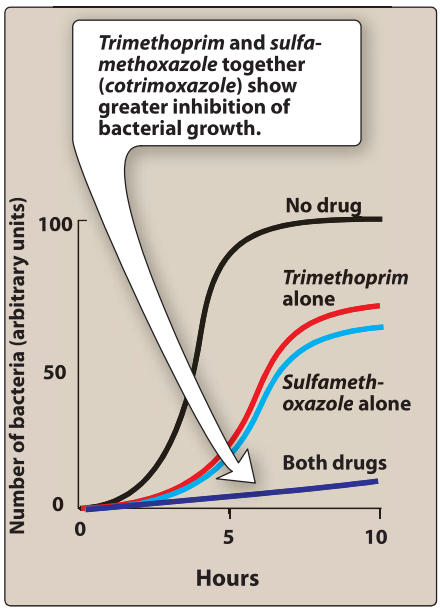


Figure 31.10
Synergism between *trimethoprim* and *sulfamethoxazole* inhibits growth of E. coli.

A. Mechanism of action

The synergistic antimicrobial activity of *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 (Figure 31.7).

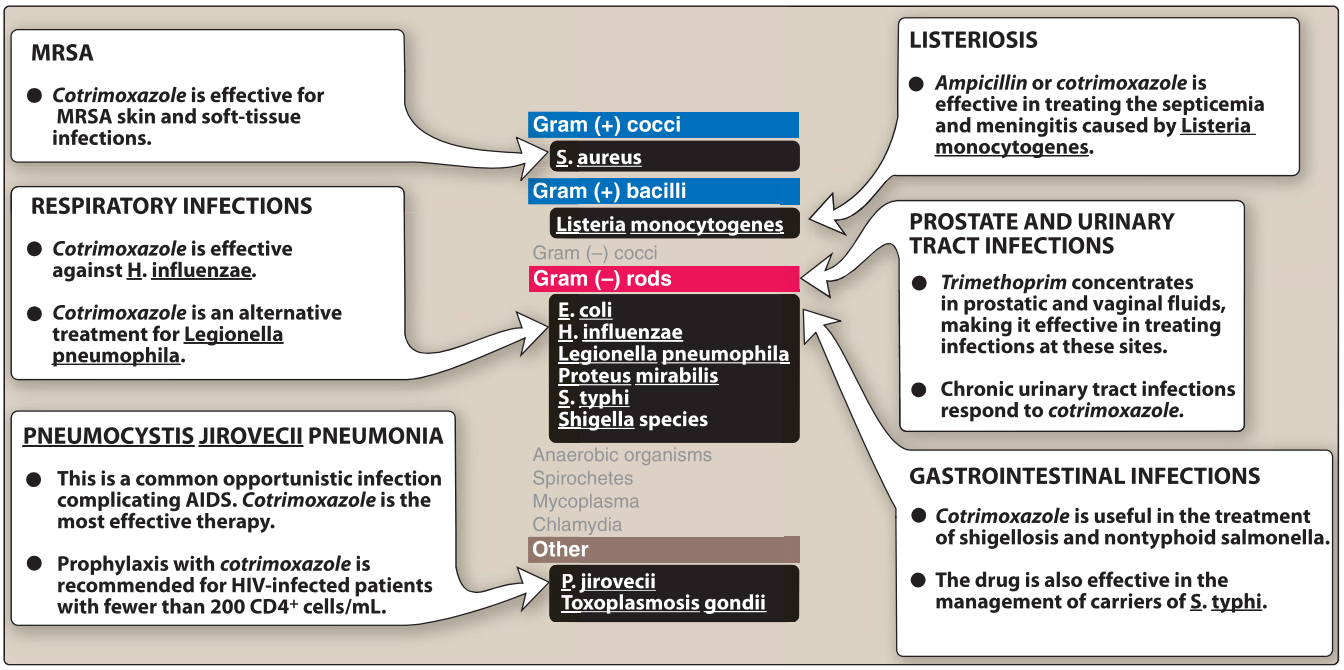


Figure 31.11
Typical therapeutic applications of *cotrimoxazole* (*sulfamethoxazole* plus *trimethoprim*).

B. Antibacterial spectrum

Antibacterial spectrum
- Effective in treating UTIs and RTIs
- Effective against *Pneumocystis jirovecii* pneumonia
- Skin and soft tissue MRSA infections
- Drug of choice for infections caused by Nocardia spp.

Cotrimoxazole has a broader spectrum of antibacterial action than the sulfa drugs alone (Figure 31.11). It is effective in treating UTIs and respiratory tract infections, as well as Pneumocystis jirovecii, toxoplasmosis, Listeria monocytogenes, and Salmonella infections. It has activity against *methicillin*-resistant S. aureus and can be particularly useful for skin and soft tissue infections caused by this organism. It is the drug of choice for infections caused by susceptible Nocardia spp. and Stenotrophomonas maltophilia.

C. Resistance

Resistance to the *trimethoprim–sulfamethoxazole* combination is encountered less frequently than resistance to either of the drugs alone, because it requires bacterium to maintain simultaneous resistance to both drugs. Significant resistance has been documented in a number of clinically relevant organisms, including E. coli.

D. Pharmacokinetics

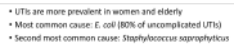
Pharmacokinetics
- Administered orally (IV reserved for severe cases of PCP)
- Crosses BBB
- Excreted in the urine

Cotrimoxazole is generally administered orally (Figure 31.12). Intravenous administration may be utilized in patients with severe pneumonia caused by Pneumocystis jirovecii. Both agents distribute throughout the body. *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.

• Administered orally (IV reserved for severe cases of PCP)

E. Adverse effects

Adverse reactions and drug interactions related to *cotrimoxazole* are similar to those expected with each of the individual components, *sulfamethoxazole* and *trimethoprim* (Figure 31.13). The most common adverse reactions are nausea and vomiting, skin rash, hematologic toxicity, and hyperkalemia.



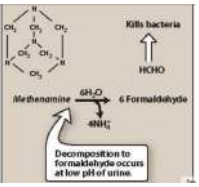
VI. URINARY TRACT ANTISEPTICS/ANTIMICROBIALS

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* (see Chapter 29) can be considered for treatment or suppression of recurrence, due to their efficacy against common pathogens and high concentrations in the urine.

Most frequently used agents:
1. Cotrimoxazole
2. Nitrofurantoin
3. Fluoroquinolones
4. Methenamine

Simple UTI

A. Methenamine



1. **Mechanism of action:** *Methenamine* [meth-EN-a-meen] salts are hydrolyzed to ammonia and formaldehyde in acidic urine (pH ≤ 5.5). Formaldehyde denatures proteins and nucleic acids, resulting in bacterial cell death. *Methenamine* is combined with a weak acid (for example, hippuric acid) to maintain urine acidity and promote production of formaldehyde (Figure 31.14).

2. **Antibacterial spectrum:** *Methenamine* is primarily used for chronic suppressive therapy to reduce the frequency of UTIs. *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. The main benefit of *methenamine* is the lack of selection for resistant organisms.

3. **Pharmacokinetics:** *Methenamine* is orally absorbed, with up to 30% decomposing in gastric juices, unless protected by enteric coating. It reaches the urine through tubular secretion and glomerular filtration. Concentrations are sufficient to treat susceptible organisms. Due to ammonia formation, use should be avoided in hepatic insufficiency.

4. **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. [Note: 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.]

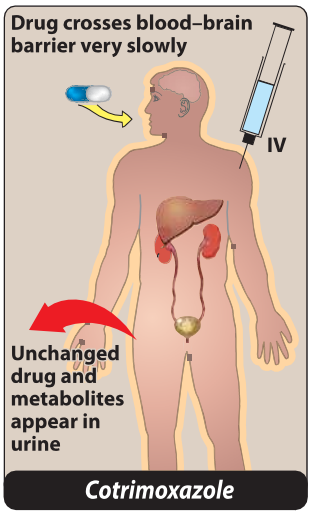


Figure 31.12
Administration and fate of *cotrimoxazole*.

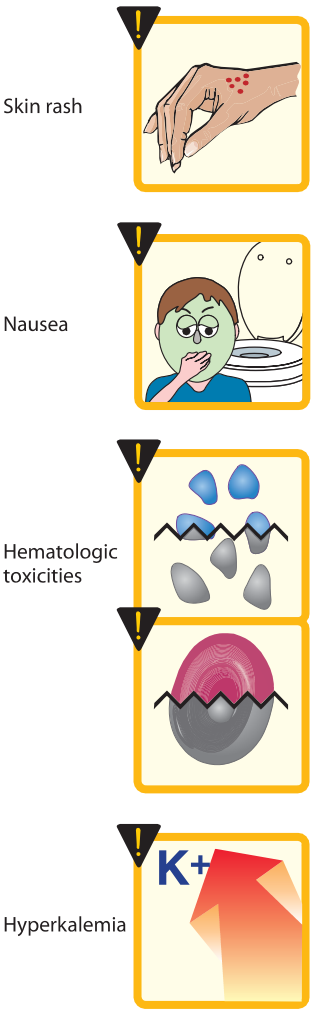


Figure 31.13
Some adverse reactions to *cotrimoxazole*.

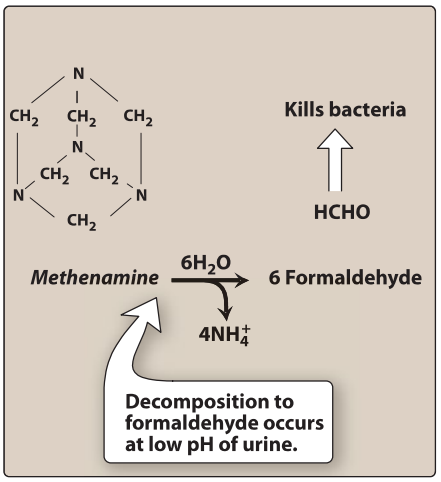


Figure 31.14
Formation of formaldehyde from *methenamine* at acid pH.

B. Nitrofurantoin

Nitrofurantoin [NYE-troe-fue-RAN-toin] was introduced into clinical practice for the management of cystitis in the early 1950s. For decades, it was rarely used, but was resurrected due to increasing antibiotic resistance among Enterobacteriaceae and 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. Use of the microcrystalline formulation decreases the incidence of gastrointestinal toxicity. Rare complications of therapy include pulmonary fibrosis, neuropathy, and autoimmune hepatitis. These events are observed with prolonged exposure greater than 1 month. Additionally, patients with impaired renal function should not receive *nitrofurantoin* due to an increased risk of adverse events.

- Nitrofurantoin is now first-line for uncomplicated cystitis
- **MOA**: Major inhibitor of DNA and RNA synthesis
- Useful against *E.coli*
- Can also cause hemolytic anemia in patients with G6PD
- Should not be used in patients with renal impairment or term pregnant women

Study Questions

Choose the ONE best answer.

31.1 A 32-year-old man presents to an outpatient clinic with a 5-day history of productive cough, purulent sputum, and shortness of breath. He is diagnosed with community-acquired pneumonia (CAP). It is noted that this patient has a severe ampicillin allergy (anaphylaxis). Which would be an acceptable treatment for this patient?

A. Levofloxacin
B. Ciprofloxacin
C. Penicillin VK
D. Nitrofurantoin

Correct answer = A. Streptococcus pneumoniae is a common cause of CAP, and the respiratory fluoroquinolones levofloxacin and moxifloxacin provide good coverage. Ciprofloxacin does not cover S. pneumoniae well and is a poor choice for treatment of CAP. Penicillin would be a poor choice due to allergy. Nitrofurantoin has no clinical utility for respiratory tract infections.

31.2 A 22-year-old woman presents with a 2-day history of dysuria with increased urinary frequency and urgency. A urine culture and urinalysis are done. She is diagnosed with a urinary tract infection caused by E. coli. Which agent should be avoided in the treatment of her UTI?

A. Levofloxacin
B. Cotrimoxazole
C. Moxifloxacin
D. Nitrofurantoin

Correct answer = C. Moxifloxacin does not concentrate in the urine and would be ineffective for treatment of a UTI. All other answers are viable alternatives, and the resistance profile for the E. coli can be utilized to direct therapy.

31.3 Which drug is correctly matched with the appropriate adverse effect?

A. Levofloxacin—hyperkalemia
B. Nitrofurantoin—pulmonary fibrosis
C. Cotrimoxazole—hepatic encephalopathy
D. Methenamine—nystagmus

Correct answer = B. Hyperkalemia may be caused by cotrimoxazole, not fluoroquinolones. Hepatic encephalopathy may be related to therapy with methenamine in patients with hepatic insufficiency. Nystagmus is not associated with methenamine therapy.

31.4 Cotrimoxazole provides activity against which organism?

A. MRSA
B. Pseudomonas aeruginosa
C. Anaerobes
D. Mycoplasma

Correct answer = A. Cotrimoxazole is effective against MRSA. It does not have activity against Pseudomonas, anaerobes, or Mycoplasma.

31.5 A 55-year-old man presents to primary care clinic with an erythematous and tender abscess on his left thigh. He has a history of MRSA skin infections. Which is an appropriate antibiotic for empiric treatment?

A. Ciprofloxacin
B. Cotrimoxazole
C. Pyrimethamine
D. Cephalexin

Correct answer = B. Cotrimoxazole is the only agent with reliable activity against MRSA. Ciprofloxacin does have some minor activity, but resistance has readily increased and it is no longer a valid recommendation. The other agents do not have activity against MRSA.

31.6 Which is a common adverse effect of cotrimoxazole?

A. Hyperkalemia
B. Pulmonary fibrosis
C. Tendon rupture
D. Blood glucose disturbances

Correct answer = A. Trimethoprim acts as a potassium-sparing agent, resulting in an increase in serum potassium concentrations. Pulmonary fibrosis is an adverse effect of nitrofurantoin. Tendon rupture and blood glucose disturbances are adverse effects of fluoroquinolones.

31.7 A 21-year-old marathon runner reports to the clinic with acute Achilles tendon rupture. The nurse noted that the patient recently took an antibiotic for community-acquired pneumonia. Which antibiotic may have contributed to tendon rupture?

A. Amoxicillin/clavulanate
B. Cefdinir
C. Levofloxacin
D. Minocycline

Correct answer = C. Levofloxacin is associated with tendon ruptures and tendinopathy. The other agents are not associated with this adverse effect.

31.8 A 70-year-old woman with acute cystitis presents to the Family Medicine clinic for assessment. She has a past medical history of hypertension and chronic kidney disease. The team recommends initiation of nitrofurantoin for cystitis. After reviewing her antimicrobial therapy, which actions should be taken prior to clinic discharge?

A. Continue current therapy and counsel on gastrointestinal effects of nitrofurantoin.
B. Change nitrofurantoin to alternative agent due to chronic kidney disease.
C. Reduce nitrofurantoin dose due to impaired renal function.
D. Counsel patient regarding neuropathy associated with short-term therapy.

Correct answer = B. The key issue with the antibiotic recommendation is that nitrofurantoin should not be administered in patients with poor kidney function. Adjusting the dose and continuing the current regimen are not acceptable modifications. Neuropathy is more common with therapy greater than 1 month.

31.9 Which recommendation should be provided to avoid phototoxicity associated with fluoroquinolone therapy?

A. Use sunscreen and avoid excessive exposure to UV light.
B. Take the medication at night to avoid high drug concentrations during the day.
C. Take with food.
D. Drink with 1 L of water per day to minimize drug buildup in skin tissue.

Correct answer = A. Patients taking a fluoroquinolone should apply sunscreen and take precautions to minimize risk of phototoxicity. Adjusting the timing of the dose or taking with food or additional water does not change the risk of an event.

31.10 What is the main benefit for prescribing methenamine for treatment of a urinary tract infection?

A. Safe to use in patients with hepatic failure.
B. Available in intravenous and oral formulations.
C. Broad spectrum of activity.
D. Minimal development of resistance.

Correct answer = D. Methenamine does not select for resistance. Due to its conversion to formaldehyde, this compound is the least likely compound to select for resistant isolates. Methenamine should be avoided in patients with hepatic failure. This agent is only available as an oral formulation, and it has a narrow spectrum of activity.