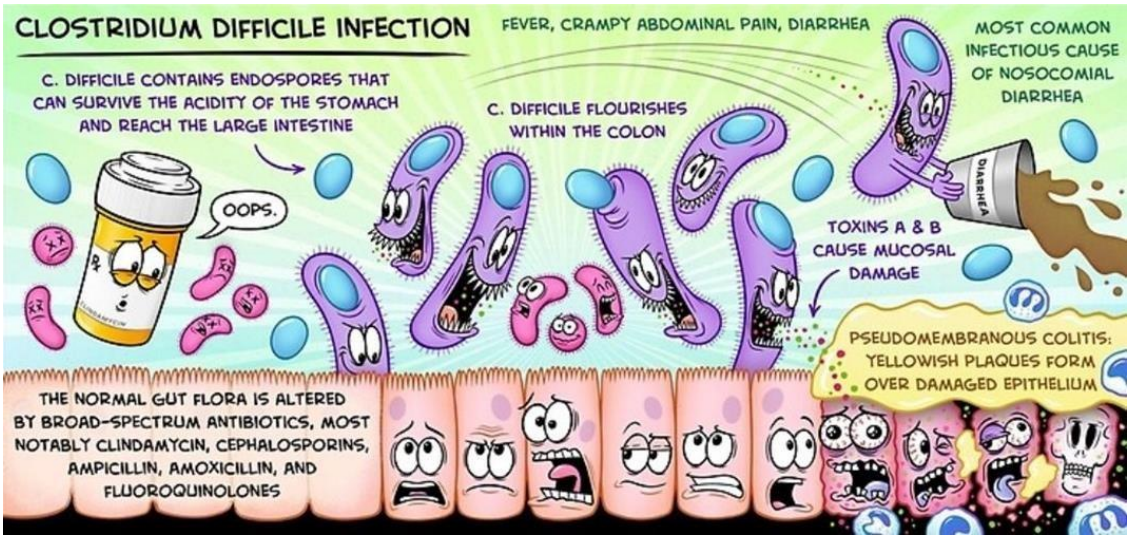
V. Macrocyclic:

***Fidaxomicin*:** is a macrocyclic antibiotic with a structure similar to the macrolides; however, it has a unique mechanism of action that terminate protein synthesis and resulting in cell death in susceptible organisms.

Fidaxomicin has a very narrow spectrum of activity limited to gram-positive aerobes and anaerobes. Following oral administration, fidaxomicin has minimal systemic absorption and primarily remains within the gastrointestinal tract. This is ideal for the treatment of C. difficile infection, which occurs in the gut. - The most common adverse effects include nausea, vomiting, and abdominal pain. Anemia and neutropenia have been observed infrequently. Hypersensitivity reactions including angioedema, dyspnea, and pruritus have occurred.

Fidaxomicin should be used with caution in patients with a macrolide allergy, as they may be at increased risk for hypersensitivity.



VI. Lincosamides:

***Clindamycin*:** has a mechanism of action that is similar to that of the macrolides. Clindamycin is used primarily in the treatment of infections caused by gram-positive organisms, including MRSA and streptococcus, and anaerobic bacteria.

C. difficile is resistant to clindamycin, and the utility of clindamycin for gram negative anaerobes (for example, Bacteroides sp.) is decreasing due to increasing resistance. It distributes well into all body fluids and bones, but exhibits poor entry into the CSF. Low urinary excretion of active drug limits its clinical utility for urinary tract infections. Accumulation has been reported in patients with either severe renal impairment or hepatic failure. In addition to skin rash, the most common adverse effect is diarrhea, which may represent a serious pseudomembranous colitis caused by overgrowth of C. difficile.

Oral administration of either metronidazole or vancomycin is usually effective in the treatment of C. difficile infection.

Ueses of clindamycin:

Anaerobic infections caused by Bacteroids, Staphylococcal joint and bone infections such as osteomyelitis, staphylococcal conjunctivitis (eye drops), diabetic foot infections, acne, penetrating wounds, prophylaxis of endocarditis and toxoplasmosis of AIDS.

VII. Oxazolidinones:

Linezolid and *tedizolid* are synthetic oxazolidinones developed to combat gram positive organisms, including resistant isolates such as methicillin-resistant Staphylococcus aureus, VRE, and penicillin-resistant streptococci.

Linezolid and tedizolid are well absorbed after oral administration. IV formulations are also available.

These drugs distribute widely throughout the body.

The most common adverse effects are gastrointestinal upset, nausea, diarrhea, headache, and rash.

Thrombocytopenia has been reported, usually in patients taking the drug for longer than 10 days.

Linezolid and tedizolid are weak nonspecific inhibitors of MAO and may lead to serotonin syndrome (e.g., palpitations, headache, hypertensive crisis) if given concomitantly with large quantities of tyraminecontaining foods, selective serotonin reuptake inhibitors, or monoamine oxidase inhibitors. The condition is reversible when the drug is discontinued.

Irreversible peripheral neuropathies and optic neuritis causing blindness have been associated with greater than 28 days of use, limiting utility for extended-duration treatments.

VIII. Others:

Chloramphenicol:

The use of chloramphenicol, a broad-spectrum antibiotic, is restricted to life-threatening infections for which no alternatives exist..

Because of some similarity of mammalian mitochondrial ribosomes to those of bacteria, protein and ATP synthesis in these organelles may be inhibited at high circulating chloramphenicol concentrations, producing bone marrow toxicity.

Chloramphenicol is administered intravenously and is widely distributed throughout the body. It reaches therapeutic concentrations in the CSF.

Chloramphenicol primarily undergoes hepatic metabolism to an inactive glucuronide, which is secreted by the renal tubule and eliminated in the urine. Dose reductions are necessary in patients with liver dysfunction or cirrhosis.

Chloramphenicol is also secreted into breast milk and should be avoided in breastfeeding mothers.

Adverse effects

1.Anemias: Patients may experience dose-related anemia, hemolytic anemia (observed in patients with glucose-6phosphate dehydrogenase deficiency), and aplastic anemia. [Note: Aplastic anemia is independent of dose and may occur after therapy has ceased.]

2. Gray baby syndrome: Neonates have a low capacity to glucuronidate the antibiotic, and they have underdeveloped renal function, which decreases their ability to excrete the drug. This leads to drug accumulation to concentrations that preventing the interfere with the function of mitochondrial ribosomes, causing poor feeding, depressed breathing, cardiovascular collapse, cyanosis (hence the term “gray baby”), and death. Adults who have received very high doses of chloramphenicol may also exhibit this toxicity.

3. Drug interactions:

Chloramphenicol inhibits some of the hepatic mixed-function oxidases, metabolism of drugs such as warfarin and phenytoin, which may potentiate their effects.

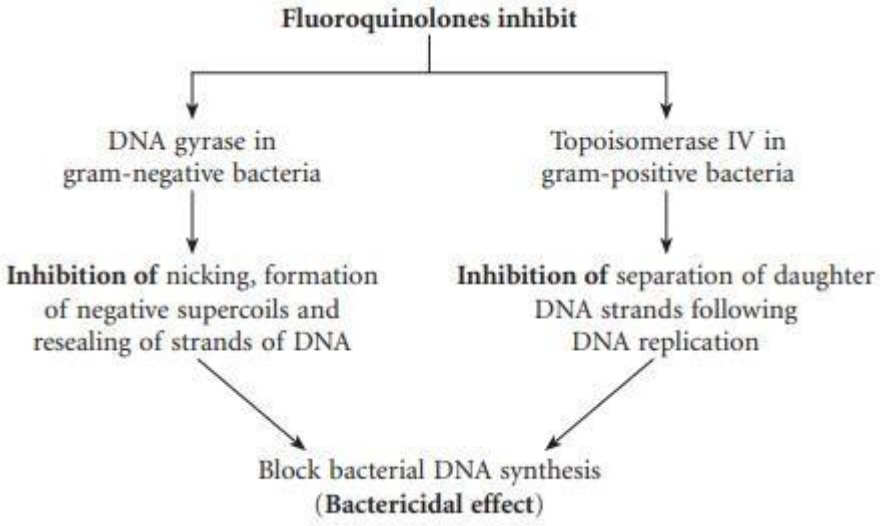
Quinupristin/Dalfopristin:

Due to significant adverse effects, this combination drug is normally reserved for the treatment of severe infections caused by vancomycin-resistant Enterococcus faecium (VRE) in the absence of other therapeutic options.

The combination drug has bactericidal activity.

Quinolones

Fluoroquinolones are DNA gyrase inhibitors.



First-generation quinolones (nalidixic acid) are active against Gram-negative organisms and used to treat urinary tract infections. They are not commonly used.
Second-generation quinolones (ciprofloxacin, levofloxacin, norfloxacin) are active against Gram-negative organisms, Gram-positive cocci, and some others.

Third-generation quinolones like sparfloxacin and gatifloxacin have an even broader spectrum.

Fourth-generation quinolone trovofloxacin has activity against anaerobes and Gram-negative and Grampositive organisms. These newer fluoroquinolones are not used as first-line drugs, and many have been removed from the U.S. market due to their toxicity.

Both oral and intravenous administration is effective, and the drugs distribute widely in the body. As with tetracyclines, fluoroquinolones should not be taken with milk, antacids, or iron supplements.

Elimination is by renal secretion of the active drug.

Erosion of cartilage by the quinolones can lead to tendinitis and tendon rupture.

They can also cause GI upset, CNS problems, and phototoxicity. Trovofloxacin can cause liver toxicity. Fluoroquinolones may prolong the QTc interval, and these agents should be avoided in patients predisposed to arrhythmias or taking medication associated with QT prolongation.

Ciprofloxacin inhibits P450 1A2- and 3A4-mediated metabolism.

Fluoroquinolones are contraindicated during pregnancy.

Fluoroquinolones should be avoided in athletes as there is an increased incidence of tenosynovitis and tendon rupture.

Uses of fluoroquinolones:

1. Urinary tract infections.
2. Bacterial diarrheas.
3. Typhoid fever: Ciprofloxacin (750 mg orally b.d. for 10 days) is the preferred drug for the treatment of typhoid. Multidrug-resistant cases are treated with ceftriaxone.
4. Sexually transmitted diseases: Fluoroquinolones are effective for chancroid and gonococcal infections.
5. Respiratory infections: Newer fluoroquinolones (levofloxacin and moxifloxacin) are highly effective for community-acquired pneumonias and chronic bronchitis.
6. Others: Skin, soft tissue, and bone infection; fluoroquinolones are used in combination with other antimicrobial agents in multidrug-resistant (MDR) tuberculosis and leprosy.

Folate Antagonists

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.

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.

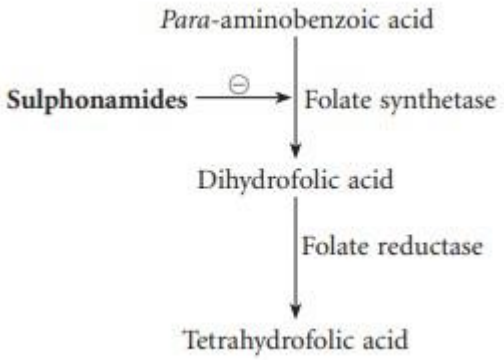
Thus, both sulfonamides and trimethoprim interfere with the ability of an infecting bacterium to perform DNA synthesis and other essential cellular functions. The combination of the sulfonamide sulfamethoxazole with trimethoprim (the generic name for the combination is cotrimoxazole) provides a synergistic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

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. Para-aminobenzoic acid (PABA) is a precursor of folic acid, which is essential for the growth and multiplication of many bacteria. Sulphonamides, being structurally similar to PABA, competitively inhibit folate synthetase enzyme and prevent the formation of folic acid, thereby producing bacteriostatic effect.

Sulphonamides are not effective in the presence of pus (?)

Mammalian cells do not synthesize folic acid, but utilize folic acid present in the diet, hence are unaffected by sulphonamides.



All systemic acting sulphonamides are well absorbed from the gut. They are bound to plasma proteins, particularly albumin. Sulphonamides are distributed in almost all the tissues of the body including CSF even in the absence of inflammation. They cross placental barrier and reach fetal circulation; they are metabolized in 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" and potential damage to the kidney.

Adverse effects

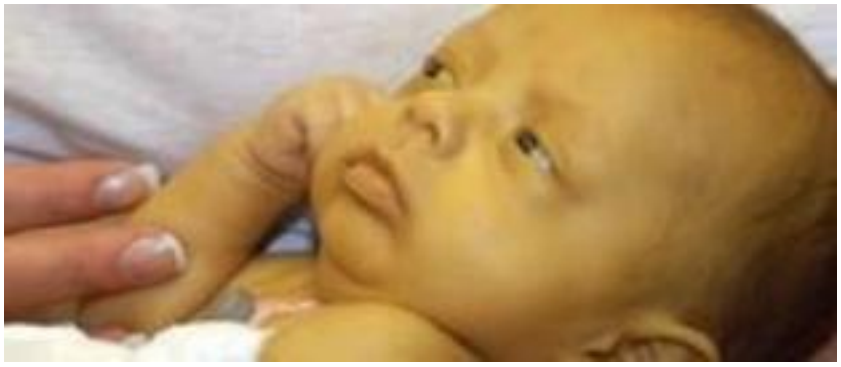
The acetylated products of sulphonamides are poorly soluble in acidic urine and may cause crystalluria, haematuria or even obstruction to urinary tract. This may be avoided by taking plenty of water and alkalinizing the urine.

Hypersensitivity reactions include skin rashes, itching, drug fever and exfoliative dermatitis. Stevens–Johnson syndrome is the most severe type of hypersensitivity reaction characterized by fever, erythema multiforme and ulceration of mucous membranes.

In patients with G6PD deficiency, sulphonamides may cause acute haemolytic anaemia.

Rarely cause hepatitis and suppression of bone marrow.

Use of sulphonamides in neonates, especially in premature babies, may cause displacement of bilirubin from plasma proteins. The free bilirubin can cross the blood–brain barrier and get deposited in the basal ganglia resulting in kernicterus.



Drug interactions

Sulphonamides potentiate the effect of phenytoin, methotrexate, oral anticoagulants and oral hypoglycaemic agents (sulfonylureas) by inhibiting their metabolism and displacing them from plasma protein binding sites.

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.