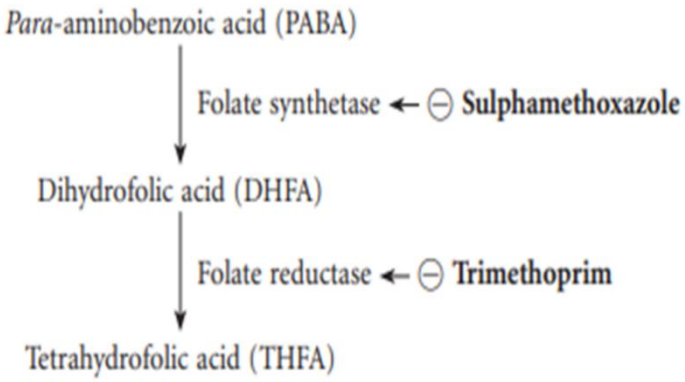
Trimethoprim: is a competitive inhibitor of dihydrofolate reductase. This enzyme synthesizes tetrahydrofolate, the active form of folic acid. This inhibitory action leads to effects on folic acid synthesis that are similar to the sulfonamides, although the onset is more rapid.
Selective toxicity occurs because the bacterial reductase is 20,000 times as sensitive as the human reductase.



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).
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 60% to 80% is renally excreted unchanged.

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).

Cotrimoxazole:

The combination of trimethoprim with sulfamethoxazole, called cotrimoxazole, shows greater antimicrobial activity than equivalent quantities of either drug used alone.
The combination was selected because of the synergistic activity and the similarity in the half-lives of the two drugs.
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.
Cotrimoxazole has a broader spectrum of antibacterial action than the sulfa drugs alone.
Adverse reactions and drug interactions related to cotrimoxazole are similar to those expected with each of the individual components, sulfamethoxazole and trimethoprim. The most common adverse reactions are nausea and vomiting, skin rash, hematologic toxicity, and hyperkalemia.

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

Antimycobacterial Drugs:

Overview

Mycobacteria are rod-shaped aerobic bacilli that multiply slowly, every 18 to 24 hours in vitro.
Their cell walls contain mycolic acids, which give the genus its name. Mycolic acids are long-chain, β-hydroxylated fatty acids. Mycobacteria produce highly lipophilic cell walls that stain poorly with Gram stain. Once stained, the bacilli are not decolorized easily by acidified organic solvents. Hence, the organisms are called "acid-fast bacilli." Mycobacterial infections classically result in the formation of slow-growing, granulomatous lesions that cause tissue destruction anywhere in the body.
Mycobacterium tuberculosis can cause latent tuberculosis infection (LTBI) and the disease known as tuberculosis (TB). [Note: In LTBI, the patient is infected with M. tuberculosis without signs or symptoms of active TB disease.]

Chemotherapy for Tuberculosis:

M. tuberculosis is slow growing and requires treatment for months to years. LTBI can be treated for 9 months with isoniazid (INH) monotherapy or with 12 once-weekly higher doses of INH and rifapentine.
In contrast, active TB disease must be treated with several drugs. Treatment for drug-susceptible TB lasts for at least 6 months, while treatment of multidrug-resistant TB (MDR-TB) typically lasts for about 2 years.
Multidrug therapy is employed to suppress the resistant organisms. The first-line drugs isoniazid, rifampin, ethambutol, and pyrazinamide are preferred because of their high efficacy and acceptable incidence of toxicity.
Standard short-course chemotherapy for tuberculosis includes isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months (the intensive phase), followed by isoniazid and rifampin for 4 months (the continuation phase).

Isoniazid: acts by inhibiting mycolic acid syntheis leading to a disruption in the bacterial cell wall.
Isoniazid, along with rifampin, is one of the two most important TB drugs.
Isoniazid is readily absorbed after oral administration. Absorption is impaired if isoniazid is taken with food, particularly high-fat meals.
The drug diffuses into all body fluids, cells, and caseous material (necrotic tissue resembling cheese that is produced in tuberculous lesions).

Adverse effects

Hepatitis is the most serious adverse effect associated with isoniazid. If hepatitis goes unrecognized, and if isoniazid is continued, it can be fatal. The incidence increases with age (greater than 35 years old), among patients who also take rifampin, or among those who drink alcohol daily.

Peripheral neuropathy, manifesting as paresthesia of the hands and feet, appears to be due to a relative pyridoxine deficiency caused by isoniazid. This can be avoided by daily supplementation of pyridoxine (vitamin B6). Central nervous system (CNS) adverse effects can occur, including convulsions in patients prone to seizures. Hypersensitivity reactions with isoniazid include rashes and fever. Because isoniazid inhibits the metabolism of carbamazepine and phenytoin, isoniazid can potentiate the adverse effects of these drugs (for example, nystagmus and ataxia).

Rifamycins: rifampin, rifabutin & rifapentine

They are first-line oral agents for tuberculosis.

Absorption is adequate after oral administration.

Rifampin: inhibits mycobacterial DNA-dependent RNA polymerase. It can induce hepatic cytochrome P450 enzymes and transporters, leading to numerous drug interactions. Because rifampin induces a number of phase I cytochrome P450 enzymes and phase II enzymes, it can decrease the half-lives of coadministered drugs that are metabolized by these enzymes This may necessitate higher dosages for coadministered drugs, a switch to drugs less affected by rifampin, or replacement of rifampin with rifabutin.

Hepatitis and death due to liver failure are rare. However, the drug should be used judiciously in older patients, alcoholics, or those with chronic liver disease.

Elimination of rifampin and its metabolites is primarily through the bile and into the feces; a small percentage is cleared in the urine. [Note: Urine, feces, and other secretions have an orange-red color, so patients should be forewarned. Tears may even stain soft contact lenses orange-red.]

Rifabutin: is preferred for TB patients coinfected with the human immunodeficiency virus (HIV) who are receiving protease inhibitors or several of the nonnucleoside reverse transcriptase inhibitors. Rifabutin is a less potent inducer (approximately 40% less) of cytochrome P450 enzymes, thus lessening drug interactions. Rifabutin has adverse effects similar to those of rifampin but can also cause uveitis, skin hyperpigmentation, and neutropenia.

Rifapentine: has a longer half-life than that of rifampin. In combination with isoniazid, rifapentine may be used once weekly in patients with LTBI and in select HIV-negative patients with minimal pulmonary TB.

Pyrazinamide:

Pyrazinamide is a synthetic, orally effective short-course agent used in combination with isoniazid, rifampin, and ethambutol. It is bactericidal by an unknown mechanism. Pyrazinamide is a prodrug that must be hydrolyzed to the active form. Pyrazinamide may contribute to liver toxicity. Uric acid retention is common, but rarely precipitates a gouty attack. Most of the clinical benefit from pyrazinamide occurs early in treatment. Therefore, this drug is usually discontinued after 2 months of a 6-month regimen.

Ethambutol: inhibits mycolic acid synthesis but is only bacteriostatic and specific for mycobacteria.

The most important adverse effect is optic neuritis, which results in diminished visual acuity and loss of ability to discriminate between red and green. The risk of optic neuritis increases with higher doses and in patients with renal impairment. Visual acuity and color discrimination should be tested prior to initiating

therapy and periodically thereafter. Uric acid excretion is decreased by ethambutol, and caution should be exercised in patients with gout.

Alternate second-line drugs

Streptomycin, para-aminosalicylic acid, capreomycin, cycloserine, ethionamide, bedaquiline, fluoroquinolones, and macrolides are second-line TB drugs.
In general, these agents are less effective and more toxic than the first-line agents.

Anifungal drugs:

Overview
Infectious diseases caused by fungi are called mycoses, and they are often chronic in nature. Mycotic infections may involve only the skin (cutaneous mycoses extending into the epidermis), or may cause subcutaneous or systemic infections.
Unlike bacteria, fungi are eukaryotic, with rigid cell walls composed largely of chitin rather than peptidoglycan (a characteristic component of most bacterial cell walls). In addition, the fungal cell membrane contains ergosterol rather than the cholesterol found in mammalian membranes. These structural characteristics are useful targets for chemotherapeutic agents against mycoses.
Fungi are generally resistant to antibiotics; conversely, bacteria are resistant to antifungal agents.
The incidence of mycoses such as candidemia has been on the rise for the last few decades. This is attributed to an increased number of patients with chronic immune suppression due to organ transplantation, cancer chemotherapy, or human immunodeficiency virus (HIV) infection.

Examples on antifungal drugs:
Amphotericin B: is the drug of choice for the treatment of several life-threatening mycoses.

Nystatin:

It is used for the treatment of cutaneous and oral Candida infections. The drug is negligibly absorbed from the gastrointestinal tract, and it is not used parenterally due to systemic toxicity (acute infusion-related adverse effects and nephrotoxicity).
It is administered as an oral agent (“swish and swallow” or “swish and spit”) for the treatment of oropharyngeal candidiasis (thrush), intravaginally for vulvovaginal candidiasis, or topically for cutaneous candidiasis.
To treat oral candidiasis, 2 to 3 mL of a suspension containing 100,000 U/mL of nystatin is placed in the mouth, swished, and held for at least 5 minutes before swallowing. This regimen is repeated every 6 hours for at least 10 days or for 48 hours after remission of symptoms. Alternatively, 1 to 2 lozenges (200,000 U per each) may be used four to five times per day.
For denture stomatitis, nystatin ointment (100,000 U/g) can be applied topically every 6 hours to the tissue surface of the denture.
Nystatin is well tolerated. Only mild and transient gastrointestinal disturbances, such as nausea, vomiting, and diarrhea, have occurred after oral ingestion. The major complaint associated with nystatin is its bitter, foul taste

Clotrimazole: is available as a troche (lozenge). Clotrimazole is frequently used for the treatment of oropharyngeal candidiasis. It can be used as gel, lotion or troche (troche 10 mg to be allowed to dissolve in the mouth QID for 14 days) Patient compliance is believed to be enhanced by the more pleasant taste of clotrimazole compared with nystatin. Clotrimazole also seems to be useful for the topical treatment of oral candidiasis in patients with AIDS..

Miconazole: is available as a buccal tablet for the treatment of thrush.

Fluconazole: is effective in oral, oropharyngeal, oesophageal, cutaneous and invasive candidiasis.

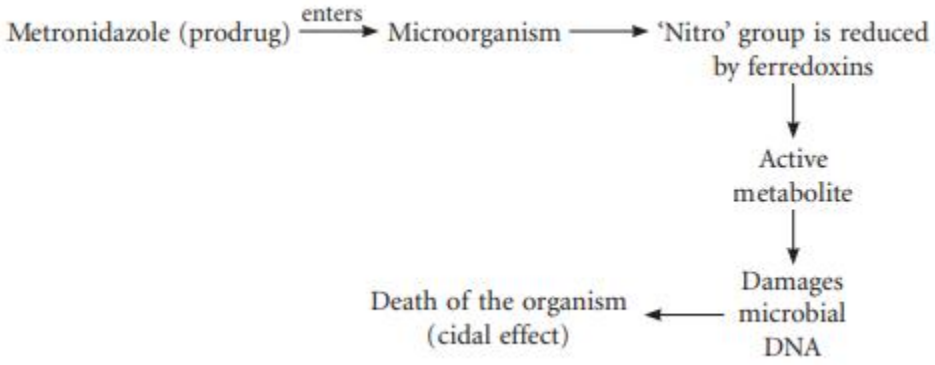
Itraconazole is an effective antifungal agent but rarely used in dental practice. It is effective for oesophageal, oropharyngeal and vaginal candidiasis, but not superior to fluconazole.

Antiprotozoal Drugs:

Protozoa are unicellular eukaryotes. The protozoal cells have metabolic processes closer to those of the human host than to prokaryotic bacterial pathogens. Therefore, protozoal diseases are less easily treated than bacterial infections, and many of the antiprotozoal drugs cause serious toxic effects in the host, particularly on cells showing high metabolic activity. Most antiprotozoal agents have not proven to be safe for pregnant patients.

Example on antiprotozoal drugs

Metronidazole: It is highly effective against most anaerobic bacteria and several protozoa.



In the presence of oxygen (aerobes), metronidazole cannot be reduced to its active metabolite; hence it is ineffective against aerobes.

Metronidazole is available for oral, i.v. and topical administration. It is usually well absorbed after

oral administration and poorly bound to plasma proteins. It diffuses well into the tissues including brain; therapeutic levels are achieved in various body fluids—saliva, semen, vaginal secretion, bile, breast milk and CSF. Metronidazole is metabolized in the liver and the metabolites are excreted mainly in urine.

Adverse effects are rarely severe to necessitate the discontinuation of the drug.

1. Gastrointestinal: Anorexia, nausea, metallic taste, dry mouth, epigastric distress, abdominal cramps and occasionally vomiting.
2. Allergic reactions: These include skin rashes, urticaria, itching and flushing.
3. CNS: Dizziness, vertigo, confusion, irritability, headache, rarely convulsions and ataxia may occur. Polyneuropathy may occur on prolonged therapy.
4. Disulfiram-like reaction may occur if taken with alcohol; hence, patient should be warned to avoid alcohol during treatment with metronidazole.

(Disulfiram inhibits aldehyde dehydrogenase and causes accumulation of acetaldehyde in blood and tissues (acetaldehyde syndrome). The signs and symptoms include nausea, vomiting, flushing, headache, sweating, tachycardia, palpitation, breathlessness, chest pain, hypotension, hypoglycaemia, confusion, shock and even death. This reaction is unpleasant; hence the person on disulfiram develops aversion to alcohol.

Teratogenic effect is seen in experimental animals; hence metronidazole should be avoided in pregnant women.

Drug interactions

1. Metronidazole potentiates the anticoagulant effect of warfarin and other oral coumarins by inhibiting their metabolism. There is prolongation of prothrombin time; hence, reduction of warfarin dose may be needed.
2. Metronidazole may potentiate lithium toxicity by decreasing the renal clearance of lithium.

Uses

1. Anaerobic infections: Metronidazole is highly effective in most of the anaerobic infections caused by Bacteroides spp., Borrelia vincenti, Fusobacterium, Peptostreptococcus, Clostridium and other anaerobic organisms.

a. Vincent's angina (acute ulcerative gingivitis): It is an anaerobic infection associated with Borrellia vincenti and Fusobacterium. Metronidazole (200-400 mg three times daily for 7 days) is highly effective in Vincent's angina as it is secreted in the saliva. It is often used with penicillins (amoxicillin 500 mg TDS for 7 days).

b. Metronidazole is used in the treatment of alveolar abscess, pericoronitis, periodontitis, etc. It is often used in combination with penicillins (penicillin V or amoxicillin).

c. In antibiotic-associated pseudomembranous colitis, metronidazole is effective. It is cheaper and less toxic than vancomycin.

d. In anaerobic brain abscess, metronidazole is often used in combination with a third-generation cephalosporin.

e. In the treatment of H. pylori infection, metronidazole is useful in combination with clarithromycin or amoxicillin and a proton pump inhibitor.

2. Amoebiasis: Metronidazole (400–800 mg TDS for 7–10 days) is the drug of choice for the treatment of all forms of amoebiasis. Thus, it is useful in the treatment of both intestinal and extraintestinal amoebiasis.
3. Other uses are trichomonas vaginitis, giardiasis, etc.

Tinidazole

Most of the features are similar to metronidazole. Tinidazole has a longer duration of action and better tolerability than metronidazole. It is more expensive than metronidazole.

Uses

1. Orodental infections: Tinidazole 600 mg twice a day for 5 days or 2 g once daily orally for 3 days is used for anaerobic infections of oral cavity.
2. Amoebiasis: 2 g once daily orally for 3 days or 600 mg twice daily for a week.

Hydroxychloroquine: is an antimalarial (prophylaxis & treatment), is given orally.

It is also used for SLE to reduce skin problems and in early, mild rheumatoid arthritis in which may be combined with methotrexate. Its mechanism of action in autoimmune disorders is unknown.

It may cause ocular toxicity, including irreversible retinal damage and corneal deposits, CNS disturbances, GI upset, and skin discoloration and eruptions.

It is not recommended for coronavirus infections (COVID-19) outside of the hospital setting or a clinical trial due to the risk of serious heart rhythm problems.