CHAPTER 12

CHEMOTHERAPEUTIC DRUGS

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INTRODUCTION

Chemotherapy is the employment of chemical agents (synthetic or natural) to kill infective agents (bacteria, fungi, and viruses, protozoa, and helminths) and stop malignant or cancerous cells from growing. Chemotherapeutic agents are chemicals that are designed to be poisonous to parasitic cells but not to the host. This selective toxicity is based on the existence of a biochemical difference that can be exploited between the parasite and the host cell.

Antimicrobials are manufactured or natural chemical compounds that are used to treat bacterial, fungal, and viral infections. Antibiotics are chemicals produced by bacteria, fungus, and actinomycetes that inhibit the growth of other bacteria, fungi, and actinomycetes. Antimicrobial medication toxicity is selective. In other words, the medicine is toxic to the parasite but not to the host.

Bactericidal vs. bacteriostatic activity: Bactericidal action occurs when antimicrobial agents kill the susceptible microorganism (e.g. bacteria), whereas bacteriostatic action occurs when antimicrobial drugs just impede the growth and spread of the microbial population. Anticancer medications: Medications or chemicals used to treat cancer.

Malaria, amoebiasis, gardiasis, trichomoniasis, toxoplasmosis, pneumocystis carinii pneumonia, trypanosomiasis, and leshmaniasis are all treated with antiprotozoals. Antihelminthics are medications that are used to treat intestinal and tissue worms.

Antimicrobias, antiprotozoals, and antihelimenthics are discussed in terms of classification, pharmacokinetics, pharmacodynamics, clinical applications, and bad effects. A brief introduction to cancer treatment is provided.

ANTIMICROBIAL DRUGS

Mechanisms of antimicrobial drug action:

1. Inhibition of cell wall synthesis
2. Cell membrane function inhibitors
3. Inhibition of protein synthesis
4. Inhibition of nucleic acid synthesis
5. Antimetabolites

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Mechanisms of Antibiotic Resistance

1. Production of inactivating enzymes (for example, b-lactamase, which inactivates beta lactam antibiotics; acetyl transferases, which inactivate chloramphenicol; kinases and other enzymes, which inactivate aminoglycosides).
2. Drug-binding site alteration: this happens with penicillins, aminoglycosides, and erythromycin.
3. Tetracyclines, for example, reduce bacterial drug absorption.
4. Enzyme changes, such as dihydrofolate reductase becoming insensitive to trimethoprim.

ANIBACTERIAL AGENTS

Cell wall synthesis inhibitors

Members the group: Beta-lactam antibiotics, vancomycin, bacitracine, and cycloserine

Penicillins, cephalosporins, carbapenems, and monobactams are all members of the beta-lactam antibiotic family. Because all members of the family have a beta-lactam ring and a carboxyl group, their pharmacokinetics and mechanisms of action are similar. They are water-soluble, and the organic anion transport system is used for main renal elimination.

Penicillins: Penicillins are related in structure, pharmacology, and toxicology. Penicillin G is the first penicillin and is naturally generated from the penicillium genus of moulds.

Classification: Penicillins can be classified into three groups: Natural Penicillins, Antistaphylococcal penicillins, and Extended-spectrum penicillins. Penicillins suppress bacterial growth by interfering with a key stage in the creation of bacterial cell walls (block the transpeptidation reaction). Betalactamase enzymes render sensitive pencillins inactive.

Penicillin G is unstable in acid environments and is hence destroyed by gastric juice. Acid-stable antibiotics including ampicillin, amoxicillin, and dicloxacillin are reasonably easily absorbed following oral administration. To avoid food protein binding and acid inactivation, oral penicillins should be taken 1-2 hours before or after meals (except ampicilin). After IM treatment, most penicillin is absorbed completely and quickly. Penicillin is quickly excreted via the kidneys. Tubular secretion and glomerular filtration account for 10% of renal excretion (90 percent). Oral use of probenecid, which inhibits tubular production of weak acids, can boost blood levels of all penicillins.

CLINICAL USES

Natural Penicillins: Natural penicillins include penicillin G and penicillin V. Streptococci, meningococci, enterococci, penicillin-susceptible pneumococci, non-beta-lactamase-producing staphylococci, Treponema pallidum and many other spirochetes, Bacillus anthracis, Clostridium species, Actinomyces, and other gram-positive rods and non-beta-lactamase-producing gram-negative ana Although penicillin V is acid stable, it is not as effective as penicillin G.

[Methicillin, Nafcillin, and isoxazolyl penicillins (Oxacillin, Cloxacillin, and Dicloxacillin)] are antistaphylococcal penicillins. Infections generated by beta-lactamase-producing staphylococci are the only cause. For serious systemic staphylococcal infections, intermittent intravenous infusions of oxacillin or nafcillin are used.

Aminopenicillins (ampicillin, amoxicillin), Carboxypenicillins (Carbenicillin, ticarcillin, effective at lower doses), and Ureidopenicillins (piperacillin, mezlocillin, and azlocillin) are all extended-spectrum penicillins. Penicillin G has a similar spectrum of activity, but it is more effective against gram-negative bacteria due to its increased ability to permeate the gram-negative outer membrane.

The range and activity of the aminopenicillins are similar, but amoxicillin is better absorbed from the gut. Urinary tract infections, sinusitis, otitis, and lower respiratory tract infections are all treated with these medications. Ampicillin IV is used to treat serious infections caused by penicillin-resistant organisms such as anaerobes, enterococci, Listeria monocytogenes, and susceptible gram-negative cocci and bacilli such E coli, H influenzae, and Salmonella species. Pseudomonas aeruginosa and Enterobacter species are included in the carboxypenicillin spectrum of action.

Adverse Effects: Three categories: Allergy: Beta-lactams have a lot of cross sensitivity and cross reactivity. Skin rashes, fever, bronchospasm, oral lesions, interstitial nephritis (autoimmune reaction to penicillin-protein complex), eosinophilia, hemolytic anaemia, vasculitis, and anaphylactic shock are some of the reactions that can occur. Antibiotic-associated enterocolitis (ampicillin) is a biological condition. Diarrhea (ampicillin), nephritis (particularly methicillin), and platelet dysfunction are all toxic (antipseudomonal penicillins).

Cephalosporins Cephalosporins are categorised into four generations based on their antibacterial activity range. The first-generation chemicals are more effective against gram-positive bacteria, while the subsequent compounds are more effective against gram-negative aerobic bacteria.

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FIRST-GENERATION CEPHALOSPORINS

Cefadroxil, cefazolin, cephalexin, and cephalothin are among the members. These antibiotics are extremely effective against gram-positive bacteria (pneumococci, streptococci, and staphylococci). Pseudomonas aeruginosa, indole-positive Proteus, Enterobacter, Serratia marcescens, Citrobacter, and Acinetobacter are typically susceptible, but activity against Pseudomonas aeruginosa, indole-positive Proteus, Enterobacter, Serratia marcescens, Citrobacter, and Acinetobacter is weak. Peptococcus, Peptostreptococcus, and other anaerobic cocci are usually sensitive, while B fragilis is not.

Cephalexin and cefadroxil are absorbed to varying degrees from the intestines. Urine concentrations are typically relatively high, while most tissues have lower amounts than serum. Cefazolin is injected intramuscularly or intravenously (the only first generation administered parentrally). Probenecid is excreted through the kidneys, and it can significantly raise serum levels.

Oral medicines can be used to treat urinary tract infections, small staphylococcal lesions, and minor polymicrobial infections such cellulitis or soft tissue abscess.

Second-generation cephalosporins

Cefaclor, cefamandole, and cefuroxime are all members. Individual variances in activity, pharmacokinetics, and toxicity are evident in the group. Second-generation cephalosporins are all less effective against gram-positive bacteria than first-generation cephalosporins, but they cover a wider range of gram-negative bacteria. Most Klebsiella and H influenzae strains are susceptible. Orally or through parenteral administration

Sinusitis, otitis, or lower respiratory tract infections, mixed anaerobic infections, and community-acquired pneumonia are all examples of clinical uses.

Third-generation cephalosporins:-Members: cefotaxime, ceftazidime, ceftriaxone, and proxetil. Antimicrobial activity: The capacity of some of these medications to pass the blood-brain barrier and their increased gram-negative coverage are two of their most notable qualities (active against Citrobacter, Serratia marcescens, Providencia, and beta-lactamase-producing strains of Haemophilus and Neisseria). Infections caused by pseudomonas are treated with ceftazidime.

They can be given orally, intramuscularly, or intravenously. They have good penetration of bodily fluids and tissues. Most bacteria, including gram-negative rods, are inhibited by cefotaxime, ceftazidim, and ceftriaxone because they pass the blood-brain barrier.

Clinical uses: Meningitis (pneumococci, meningococci, H influenzae, and susceptible enteric gram-negative rods), penicillin-resistant pneumococci (ceftriaxone, cefotaxime), and sepsis (ceftriaxone, cefotaxime).

Fourth-generation cephalosporins (e.g.cefepime):- It's similar to third-generation agents, but it's more resistant to beta-lactamase hydrolysis. It's effective against P. aeruginosa.

Adverse Effects: Cephalosporins are sensitising and can cause hypersensitivity reactions similar to those caused by penicillins. Superinfection can be caused by the overgrowth of resistant bacteria and fungi.

A monocyclic beta-lactam ring is seen in monobactams (e.g. aztreonam). They are beta-lactamase resistant and effective against gram-negative rods. In terms of activity, it's similar to aminoglycosides.

Ipenem and meropenem are two carbapenems with a broad spectrum of activity (against most Gram-positive and negative bacteria). Because a kidney proteolytic enzyme inactivates imipenem, it must be taken with cilastatin, which inhibits the enzyme.

Beta-lactamase inhibitors: (clavulanic acid, sulbactam, and tazobactam).

They have no antibacterial action and, when used in combination with beta lactamase labile antibiotics, inhibit beta-lactamases irreversibly. Ticarcillin and clavulanate (Timentin), ampicillin and sulbactam (Unasyn), and amoxicillin and clavulanate (Augmentin) are some examples of antibiotics. Vancomycin:- Vancomycin is active only against gram-positive bacteria, particularly staphylococci. It inhibits cell wall synthesis.

Vancomycin is poorly absorbed from the intestine and is used only to treat Clostridium difficile-related antibiotic-associated enterocolitis. Intravenous administration of parenteral dosages is required. The medication is broadly disseminated throughout the body. 90% of the medication is eliminated by glomerular filtration. Clinical Uses:- Sepsis or endocarditis caused by methicillin-resistant staphylococci are treated with parenteral vancomycin. It causes a red man or red neck syndrome by irritating the tissues surrounding the injection site.

Bacitracin:- Bacitracin is an antibiotic that works against gram-positive bacteria. It prevents the development of cell walls. Because it is nephrotoxic when taken systemically, it is only used topically. Bacitracin has a low absorption rate.

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Cycloserine:- Cycloserine inhibits a wide range of gram-positive and gram-negative bacteria however it is virtually solely used to treat tuberculosis caused by M tuberculosis strains that are resistant to first-line drugs. It's found in a lot of tissues. The majority of the medication is eliminated in urine in active form. Cycloserine produces severe central nervous system toxicity, including headaches, tremors, acute psychosis, and convulsions, when taken in high doses.

CELL MEMBRANE FUNCTION INHIBITORS

Antimirobials, such as polymyxins, disrupt the functional integrity of the cytoplasmic membrane, allowing macromolecules and ions to exit the cell, resulting in cell damage and death. Poymyxin B and colistin are the two most well-known agents. Gram-negative bacteria, notably pseudomonas species, are susceptible to polymyxins. Nephrotoxicity, disorientation, altered feeling, and neuromuscular paralysis are the most serious side effects.

PROTIEN SYNTHESIS INHIBITORS

The 30S and 50S ribosomal subunits are found in bacteria. The 30S subunit binds mRNA and retains the expanding peptide chain during initiation. Charged tRNAs are accepted and translocated by the 50S subunit. Bacteriostatic and bactericidal inhibitors of protein synthesis are the two types. Bacteriostatic antibiotics include chloramphenicol, macrolides, clindamycin (Lincosamides), and tetracyclines, while bactericidal antibiotics include aminoglycosides.

Mechanisms of action

Chloramphenicol prevents the 50S site from binding properly, halting protein synthesis. Because these ribosomes are 70S, the same as those found in bacteria, it inhibits mitochondrial ribosomal protein production. It does not bind to mammalian ribosomes of the 80S subunit. The dose-related anaemia caused by chloramphenicol could be due to this.

Clindamycin and other macrolides inhibit the developing polypeptide chain from passing through the 50S site, preventing a new charged tRNA from binding to the ribosome and therefore stopping protein synthesis.

Tetracyclines bind to the 30S ribosomal subunit at a location that prevents charged tRNA from attaching to the ribosome's 50S site. Tetracyclines have the ability to suppress mammalian protein synthesis, however because they are "pumped" out of

most mammalian cells, they seldom reach the amounts required to severely limit mammalian protein synthesis.

Aminoglycosides: Aminoglycosides inhibit protein synthesis in at least three ways: (1) they interfere with the "initiation complex" of peptide formation; (2) they cause mRNA misreading, resulting in incorrect amino acid incorporation into the peptide, resulting in a nonfunctional or toxic protein; and (3) they break up polysomes into nonfunctional monosomes. These events happen almost simultaneously, and the total result is permanent and fatal to the cell.

CHLORAMPHENICOL

Chloramphenicol is a bacteriostatic broad-spectrum antibiotic that kills gram-positive and gram-negative bacteria in both aerobic and anaerobic environments. It's also effective against rickettsiae. Chloramphenicol may be bactericidal against Haemophilus influenzae, Neisseria meningitidis, and some Bacteroides strains that are particularly sensitive. The synthesis of chloramphenicol acetyltransferase, an enzyme that inactivates the medicine, may be the cause of clinically significant resistance.

Pharmacokinetics:- Chloramphenicol is promptly and completely absorbed after oral treatment. It can be found in practically all tissues and bodily fluids. The medication easily penetrates cell membranes. The urine is where active chloramphenicol and inactive breakdown products are excreted. The active medication is excreted in minute amounts in the bile or faeces. Chloramphenicol clearance is insufficient in newborns less than a week old and preterm neonates.

Clinical Uses:-Chloramphenicol should only be used to treat major rickettsial infections, bacterial meningitis caused by a highly penicillin-resistant strain of pneumococcus or meningococcus, and thyphoid fever because to potential toxicity, bacterial resistance, and the availability of more effective medications.

ADVERSE REACTIONS

Adults can experience nausea, vomiting, and diarrhoea on occasion. Alterations in normal microbial flora can lead to oral or vaginal candidiasis.

Chloramphenicol frequently induces a dose-related reversible reduction of red cell formation after 1-2 weeks at dosages more than 50 mg/kg/d. Aplastic anaemia is a rare side effect of chloramphenicol treatment, regardless of route. It's a one-of-a-kind reaction that's unrelated to dosage, albeit it happens more commonly with long-term use. It is usually irreversible and sometimes lethal.

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Toxicity in newborn infants: For the breakdown and detoxification of chloramphenicol, newborn infants lack an adequate glucuronic acid conjugation pathway. As a result, when infants are given doses greater than 50 mg/kg/d, the medication may accumulate, causing the grey baby syndrome, which includes vomiting, flaccidity, and other symptoms.

Interaction with other drugs: Chloramphenicol inhibits hepatic microsomal enzymes involved in drug metabolism. Chloramphenicol, like other bacteriostatic inhibitors of microbial protein synthesis, can work against bactericidal medications like penicillins and aminoglycosides.

TETRACYCLINES

Tetracyclines are a vast class of medicines that share a basic structure and function. Based on serum half-lives, tetracyclines are classed as short (chlortetracycline, tetracycline, oxytetracycline), intermediate (demeclocycline and methacycline), or long (doxycycline and minocycline).

Tetracyclines are antibiotics with a broad spectrum of activity. They are effective against a wide range of gram-positive and gram-negative bacteria, including anaerobes, rickettsiae, chlamydiae, mycoplasmas, and protozoa. Reduced intracellular accumulation due to either impaired influx or enhanced efflux by an active transport protein pump is one of the key mechanisms of tetracycline resistance.

Pharmacokinetics: Tetracyclines differ primarily in their absorption and excretion following oral treatment. Doxycycline is better absorbed than tetracycline following oral treatment. Tetracycline is eliminated in the faeces after a portion of an orally delivered dose lingers in the gut lumen and changes intestinal flora. Food (excluding doxycycline and minocycline) inhibits absorption, as do divalent cations (Ca^{2+}, Mg^{2+}, Fe^{2+}) or Al^{3+}; dairy products and antacids, which include multivalent cations; and alkaline pH. Except for cerebral fluid, they are broadly distributed in tissues and body fluids. Minocycline reaches extremely high quantities in tears and saliva, making it effective in the treatment of meningococcal carriers. Tetracyclines are excreted in milk and pass the placenta to reach the foetus. Unlike other tetracyclines, doxycycline is removed by nonrenal processes.

Clinical applications: Infections with Mycoplasma pneumoniae, chlamydiae, rickettsiae, and certain spirochetes are treated with tetracyclines. They're utilised in combination regimens to treat Helicobacter pylori-caused gastric and duodenal ulcers. They can be used to treat gram-positive and gram-negative bacterial infections, as well as Vibrio infections. For plague, tularemia, and brucellosis, a tetracycline in conjunction

with an aminoglycoside is recommended. Tetracyclines are sometimes used to treat E. histolytica and P. falciparum infections.

ADVERSE REACTIONS

Nausea, vomiting, and diarrhoea are the most prevalent gastrointestinal side effects, which are caused by direct local irritation of the digestive system. Tetracyclines induce Pseudomonas, Proteus, staphylococci, resistant coliforms, clostridia, and Candida overgrowth by suppressing susceptible coliform organisms. Intestinal dysfunction, anal pruritus, vaginal or oral candidiasis, or enterocolitis (associated with Clostridium difficile) with shock and death are all possible outcomes. Metronidazole should be used to treat pseudomembranous enterocolitis.

Tetracyclines bind easily to calcium deposited in freshly formed bone or teeth in young infants. It causes discolouration and enamel dysplasia, and it can also deposit in bone, causing deformity or growth inhibition. Similar alterations can occur if the medicine is administered to youngsters under the age of eight for an extended period of time. They are hepato- and nephrotoxic drugs that cause photosensitivity (demeclocycine) as well as vestibular responses (doxycycline, and minocycline). Macrolides: include erythromycin, clarithromycin and azithromycin.

ERYTHROMYCIN

Erythromycin is water insoluble but rapidly dissolves in chemical solvents. Erythromycins are commonly administered as esters and salts.

Erythromycin has antimicrobial activity against gram-positive bacteria, such as pneumococci, streptococci, staphylococci, and corynebacteria. Also vulnerable are Mycoplasma, Legionella, Chlamydia trachomatis, Helicobacter, Listeria, Mycobacterium kansasii, and Mycobacterium scrofulaceum. Gram-negative bacteria including Neisseria gonorrhoeae, Bordetella pertussis, Treponema pallidum, and Campylobacter species are vulnerable.

Pharmacokinetics: Because stomach acid destroys erythromycin base, it must be given with enteric coating. Absorption is hampered by food. Stearates and esters are acid-resistant and absorbable in some ways. A large portion of a dose is eliminated in the bile and lost in the stool. Except for the brain and CSF fluid, the medication is broadly dispersed after absorption.

Clinical Applications: Because its spectrum of activity includes the pneumococcus, Mycoplasma, and Legionella, erythromycin is the drug of choice in

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corynebacterial infections (diphtheria, corynebacterial sepsis, erythrasma); respiratory, neonatal, ocular, or genital chlamydial infections; and community-acquired pneumonia treatment. In penicillin-allergic people with infections caused by staphylococci, streptococci, or pneumococci, erythromycin can be administered as a penicillin alternative.

ADVERSE REACTIONS

Anorexia, nausea, vomiting, and diarrhoea are among gastrointestinal side effects. Erythromycins, notably the estolate, can cause acute cholestatic hepatitis in the liver (reversibile).

Erythromycin metabolites block cytochrome P450 enzymes, causing theophylline, oral anticoagulants, and terfenadine serum concentrations to rise. It enhances the bioavailability of oral digoxin, which raises serum concentrations.

Clarithromycin

Erythromycin is the source of clarithromycin. It is more readily absorbed than erythromycin. Clarithromycin and erythromycin have nearly comparable antibacterial action, with the exception that clarithromycin is more effective against H. influenzae, M. leprae, and T. gondii. Clarithromycin penetrates most tissues at quantities that are equivalent to or greater than those seen in the blood. It is broken down in the liver. In the urine, a fraction of the active medication and main metabolite is excreted. Drug interactions are comparable to those seen with erythromycin. Clarithromycin has a lower prevalence of gastrointestinal intolerance and requires less frequent dose than erythromycin.

Azithromycin

The range of activity and therapeutic applications of azithromycin and clarithromycin are identical. Orally, it is quickly absorbed and well tolerated. Unlike erythromycin, azithromycin does not inactivate cytochrome P450 enzymes.

Clindamycin

Clindamycin is effective against gram-positive and gram-negative streptococci, staphylococci, bacteroides species, and other anaerobes. In terms of action and resistance mechanisms, it is similar to erythromycin. Clindamycin is well absorbed and 90% protein-bound when taken orally. The liver, bile, and urine are the primary routes of elimination. It penetrates most tissues well.

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Clindamycin is a drug that is used to treat severe anaerobic infections caused by Bacteroides. It is used to prevent endocarditis in people with valvular heart disease who are having dental operations done. Clindamycin with primaquine is an effective treatment for Pneumocystis carinii pneumonia that is moderate to moderately severe. It's also used to treat AIDS-related brain toxoplasmosis when combined with pyrimethamine.

Diarrhea, nausea, and skin rashes are common side effects, as are liver dysfunction. Toxic C difficile causes severe diarrhoea and enterocolitis (infrequently part of the normal faecal flora but is selected out during administration of oral antibiotics).

Aminoglycosides:

Members: Streptomycin, neomycin, kanamycin, amikacin, gentamicin, netilmicin. Aminoglycosides are poorly absorbed from the intact gastrointestinal system, according to pharmacokinetics. Aminoglycosides are well absorbed after intramuscular administration. They are polar chemicals that do not readily penetrate cells. Aminoglycosides are excreted by the kidney, and their excretion is proportional to creatinine clearance.

Negative consequences: Aminoglycosides cause renal and VIII nerve injury. Ototoxicity can show as auditory damage, which causes tinnitus and high-frequency hearing loss, or vestibular injury, which causes vertigo, ataxia, and loss of balance. Increased serum creatinine levels or decreased creatinine clearance are signs of nephrotoxicity. The most ototoxic antibiotics are neomycin, kanamycin, and amikacin. The most vestibulotoxic antibiotics include streptomycin and gentamicin.

Streptomycin

Streptomycin is primarily used to treat tuberculosis as a first-line medication. Adverse Effects: Vestibular dysfunction (vertigo, loss of balance) is very prevalent. The frequency and severity of this disturbance are proportional to the patient's age, drug blood levels, and medication administration time. Vestibular dysfunction can occur after a few weeks of abnormally high blood levels or months of extremely low blood levels. Vestibular poisoning is usually permanent. Streptomycin can cause deafness in newborns if taken during pregnancy.

Gentamicin

Many strains of staphylococci, coliforms, and other gram-negative bacteria are inhibited by gentamicin. It fights Pseudomonas, Proteus, Enterobacter, Klebsiella,

Serratia, Stenotrophomonas, and other gram-negative rods that are resistant to numerous antibiotics.

Gentamicin is also used in conjunction with penicillin G to treat endocarditis caused by viridans streptococci. Gentamicin sulphate creams, ointments, and solutions are used to treat infected burns, wounds, and skin lesions.

Amikacin

Amikacin is a semisynthetic kanamycin derivative that is less toxic than the original. It can be used against germs that are resistant to gentamicin and tobramycin since it is resistant to several enzymes that inactivate them. Amikacin is frequently vulnerable to multidrug-resistant Mycobacterium TB strains, including streptomycin-resistant strains.

Neomycin, Paromomycin, Kanamycin

This group also includes medications that are closely related. All of them have comparable characteristics. Neomycin and kanamycin are presently only used topically and orally since they are too toxic for parenteral administration. Neomycin is an antibiotic that is taken orally in preparation for intestinal surgery. In hepatic coma, the coliform flora can be inhibited for longer lengths of time by providing 1 g every 6-8 hours together with a lower protein intake, resulting in less ammonia poisoning. Intestinal amebiasis can be treated with paromomycin.

Spectinomycin

Spectinomycin is an aminocyclitol antibiotic related to aminoglycosides in structure. Spectinomycin is virtually exclusively used as a gonorrhoea treatment in patients who are allergic to penicillin or whose gonococci are drug-resistant. After intramuscular injection, it is immediately absorbed. A single 2 g (40 mg/kg) dosage is given. There is pain at the injection site, as well as fever and nausea on occasion.

Inhibitors of Nucleic Acid Synthesis Acid nalidixic

The first antibacterial quinolone is nalidixic acid. It is not fluorinated and eliminated too quickly to have antibacterial effects in the system. They prevent normal bacterial DNA transcription and replication. These medicines were only effective in the treatment of urinary tract infections and shigellosis due to their low antibacterial activity.

Fluoroquinolones

Quinolones are fluorinated synthetic analogues of nalidixic acid, which is used in nucleic acid synthesis. Gram-negative cocci and bacilli, such as Enterobacteriaceae, Pseudomonas, Neisseria, Haemophilus, and Campylobacter, are inhibited by ofloxacin and ciprofloxacin. Many staphylococci are also responsive to these antibiotics. Fluoroquinolones suppress intracellular organisms such as Legionella, Chlamydia, Mycobacterium TB, and Mycobacterium avium complex.

Pharmacokinetics: Fluoroquinolones are readily absorbed and broadly dispersed in bodily fluids and tissues after oral administration. Divalent cations, such as those found in antacids, impede oral absorption. Fluoroquinolones are mostly eliminated through tubular secretion and glomerular filtration. In renal failure, all fluoroquinolones build up.

Clinical Uses Fluoroquinolones are useful in treating urinary tract infections caused by multidrug-resistant bacteria, such as Pseudomonas aeruginosa. Norfloxacin 400 mg, ciprofloxacin 500 mg, and ofloxacin 400 mg are all effective when taken orally twice daily. Shigella, Salmonella, toxigenic E coli, and Campylobacter cause bacterial diarrhoea, and these agents can help. Fluoroquinolones (except norfloxacin, which does not achieve adequate systemic concentrations) have been used to treat infections of the soft tissues, bones, and joints, as well as infections of the intra-abdominal and respiratory tract, including infections caused by multidrug-resistant bacteria like Pseudomonas and Enterobacter. Ciprofloxacin and ofloxacin are both effective against gonococcal infections, including disseminated illness, and ofloxacin is also effective against chlamydial urethritis and cervicitis.

Adverse Effects: Nausea, vomiting, and diarrhoea are the most prevalent side effects. When theophylline and quinolones are taken together, theophylline levels can rise, posing a risk of toxic consequences, particularly seizures. Fluoroquinolones can cause arthropathy by damaging developing cartilage. As a result, they are not generally advised for individuals under the age of 18. Fluoroquinolones are not recommended for nursing women since they are excreted in breast milk.

Rifampin

Rifampin suppresses RNA production by binding tightly to the bacterial DNA-dependent RNA polymerase. It is well absorbed after oral dosing and primarily eliminated into bile via the liver. Rifampin is found in large amounts in human fluids and tissues. Because it is relatively protein-bound, appropriate cerebrospinal fluid

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concentrations are only attained when meningeal inflammation is present. Rifampin is a drug that is used to treat mycobacterial infections.

Rifampin causes urine, perspiration, and tears to turn a harmless orange colour. Rashes, thrombocytopenia, nephritis, cholestatic jaundice, and hepatitis are all possible side effects. Rifampin promotes the clearance of anticoagulants, anticonvulsants, and contraceptives by inducing microsomal enzymes (cytochrome P450). When rifampin is used with ketoconazole or chloramphenicol, the blood levels of these medicines are considerably reduced.

Antimetabolites

Sulfonamides

There are three types of sulfonamides: (1) oral, absorbable; (2) oral, nonabsorbable; and (3) topical. On the basis of their half-lives, oral, absorbable sulfonamides can be classed as short, medium, or long acting.

Action mechanisms: Extracellular para-aminobenzoic acid (PABA) is required by microorganisms to produce dihydrofolic acid, which is required for the formation of purines and the synthesis of nucleic acids. Sulfonamides are PABA structural analogues that inhibit dihydropteroate synthase competitively. They stop growth by blocking folic acid synthesis in a reversible way.

Gram-positive and gram-negative bacteria, Nocardia, Chlamydia trachomatis, and certain protozoa are all inhibited by sulfonamides. E. coli, Klebsiella, Salmonella, Shigella, and Enterobacter are among the microorganisms that are inhibited.

Pharmacokinetics: They are absorbed through the stomach and small intestine and transported throughout the body, including tissues, bodily fluids, the placenta, and the foetus. Sulfonamides are absorbed and become attached to serum proteins in different degrees, ranging from 20% to over 90%. In the liver, a portion of the medication is acetylated or glucuronidated. Sulfonamides and inactivated metabolites are then eliminated primarily by glomerular filtration into the urine.

Clinical Applications

Absorbable Oral Agents: Short- and medium-acting antibiotics, sulfisoxazole and sulfamethoxazole, are used to treat urinary tract infections, respiratory tract infections, sinusitis, bronchitis, pneumonia, otitis media, and dysentery. The combination of sulfadiazine and pyrimethamine is the first-line treatment for acute

toxoplasmosis. Long-acting sulfonamide sulfadoxine, in combination with pyrimethamine, is used as a second-line treatment for malaria.

Sulfasalazine, an oral nonabsorbable agent, is commonly used to treat ulcerative colitis, enteritis, and other inflammatory bowel diseases. Intestinal microflora splits sulfasalazine into sulfapyridine and 5-aminosalicylate. A high concentration of salicylate produced in the colon has an anti-inflammatory impact. Due to substantial gastrointestinal damage, oral ingestion of typical salicylate formulations cannot produce such high salicylate concentrations in the colon.

Topical Sodium sulfacetamide ophthalmic solution or ointment is an excellent treatment for bacterial conjunctivitis and as a trachoma adjunct. Silver sulfadiazine is a less toxic topical sulfonamide that is favoured over mafenide for burn wound infection prevention.

Fever, skin rashes, exfoliative dermatitis, photosensitivity, urticaria, nausea, vomiting, and diarrhoea are the most prevalent side effects. Crystalluria, hematuria, hemolytic or aplastic anaemia, granulocytopenia, and thrombocytopenia are less common. Sulfonamides are linked to an increased risk of kernicterus in babies when taken near the end of pregnancy.

Trimethoprim

Trimethoprim inhibits the dihydrofolic acid reductase enzyme in bacteria. Dihydrofolic acid reductases convert dihydrofolic acid to tetrahydrofolic acid, a precursor to purine synthesis and, eventually, DNA synthesis.

Trimethoprim is typically taken by mouth. It is well absorbed from the intestines and broadly disseminated throughout the body, including the cerebrospinal fluid. Trimethoprim concentrations in the more acidic prostatic and vaginal fluids than plasma. As a result, it has greater antibacterial action in prostatic and vaginal secretions than many other antibiotics.

Because most community-acquired organisms are tolerant to high quantities of trimethoprim, it can be used alone to treat acute urinary tract infections. Trimethoprim has the expected antifolate medication side effects, such as megaloblastic anaemia, leukopenia, and granulocytopenia. This can be avoided by taking folinic acid at a dose of 6-8 mg per day.

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Trimethoprim-Sulfamethoxazole (Cotrimoxazole)

Trimethoprim and sulfamethoxazole have comparable half-lives. When trimethoprim is combined with sulfamethoxazole, this metabolic pathway is sequentially blocked, resulting in a significant increase in the activity of both medicines. When compared to the bacteriostatic activity of a sulfonamide alone, the combination is frequently antibacterial.

Clinical applications: Pneumocystis carinii pneumonia, shigellosis, systemic Salmonella infections, urinary tract infections, and prostatitis can all be treated with trimethoprim-sulfamethoxazole. Pneumococcus, Haemophilus species, Moraxella catarrhalis, and Klebsiella pneumoniae are among the pathogens that it can kill.

ANTIMYCOBACTERIAL DRUGS

Mycobacterial infections are the most hardest to treat of all the bacteria. Mycobacteria are slow-growing organisms (which can also be latent), and as a result, they are fully resistant to many medications, or are only killed very slowly by the few active ones.

Many chemicals cannot penetrate the lipid-rich mycobacterial cell wall. A large percentage of mycobacterial organisms are intracellular, dwelling within macrophages, and are therefore inaccessible to medications that have a poor penetration rate.

Finally, mycobacteria are infamous for developing resistance to virtually every drug. To overcome these barriers and prevent the establishment of resistance during treatment, medication combinations are required. Mycobacterial infections respond slowly to chemotherapy, and treatment can last anywhere from months to years, depending on the medications employed.

Antimycobacterial medications are divided into three categories: those used to treat tuberculosis, those used to treat atypical mycobacterial infections, and those used to treat leprosy.

Drugs Used In Tuberculosis

First-Line Antimycobacterial Drugs

Members: Isoniazid (INH), rifampin, pyrazinamide, ethambutol, and streptomycin are the five first-line agents for treatment of tuberculosis. INH and rifampin are the two most active drugs.

Isoniazid (INH)

INH is the most effective medication for tuberculosis caused by susceptible strains. It has a similar structure to pyridoxine. It kills tubercle bacilli that are actively proliferating. INH may enter phagocytic cells, making it effective against both external and intracellular microbes.

INH blocks the production of mycolic acids, which are important components of mycobacterial cell walls.

INH is easily absorbed from the gastrointestinal system and diffuses quickly throughout the body. INH metabolism is genetically determined, particularly acetylation by liver N-acetyltransferase. The urine primarily excretes INH metabolites and a minor amount of unmodified medication. In cases of severe hepatic insufficiency, the dose must be adjusted.

Clinical Applications: Tuberculosis treatment and prevention.

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Rifampin

Rifampin is used in combination with INH, ethambutol, or another antituberculous medicine to prevent drug-resistant mycobacteria from forming. Rifampin is an alternative to INH for prophylaxis in patients who cannot take INH or who have had close contact with an INH-resistant, rifampin-susceptible strain of tuberculosis.

Ethambuto

Ethambutol suppresses mycobacterial cell wall production. Ethambutol is easily absorbed through the gastrointestinal tract. Renal failure causes it to build up. Only when the meninges are inflamed does ethambutol permeate the blood-brain barrier.

For the treatment of tuberculosis, ethambutol hydrochloride is administered as a single daily dose in combination with INH or rifampin. The greater dose is indicated for tuberculous meningitis therapy.

Retrobulbar neuritis, which causes loss of vision, is the most prevalent significant adverse event, and red-green colour blindness is a dose-related side effect. Ethambutol is contraindicated in children who are too young to have their visual acuity and red-green colour discrimination assessed.

Pyrazinamid

Pyrazinamide (PZA) is a stable, water-insoluble cousin of nicotinamide. Macrophages absorb the drug, which destroys the bacilli that live in this acidic environment. PZA is easily absorbed from the gastrointestinal tract and is widely disseminated throughout the body, especially in inflamed meninges. Resistance to pyrazinamide develops quickly in tubercle bacilli. Hepatotoxicity, nausea, vomiting, drug fever, and hyperuricemia are all serious side effects of pyrazinamide. Acute gouty arthritis can be triggered by hyperuricemia

Streptomycin

Streptomycin inhibits the majority of tubercle bacilli. Streptomycin is only effective against extracellular tubercle bacilli since it enters cells poorly. With inflamed meninges, streptomycin passes the blood-brain barrier and reaches therapeutic quantities. It's mostly used to treat people with severe, potentially fatal tuberculosis (meningitis and disseminated disease), as well as infections that are resistant to other medications.

Combination Tuberculosis Chemotherapy

The length of tuberculosis treatment is determined by the severity of the disease, the organ involved, and the combination of drugs used. The therapy for tuberculosis is divided into two phases; the intensive phase, which lasts eight weeks, renders patients noninfectious. The continuation phase should continue at least 6 months and include at least two medicines. Ethiopia presently uses four different

medication regimens: Short-term Directly Observed Treatment (DOTS), re-treatment regimens, and short-term and long-term chemotherapy (LCC)

Treatment Categories and Drug Regimens

Directly Observed Treatment Short Course (DOTS) TB in children aged 6 years; new pulmonary TB smear positive patients; new pulmonary TB smear negative and Extrapulmonary TB patients who are very unwell. During the intense phase, patients are given 8 weeks of Streptomycin, Rifampicin, Isoniazid, and Pyrazinamide, followed by 6 months of Ethambutol and Isoniazid or 4 months of Rifampin and Isoniazid (RH). (2S (RHZ)/6 (EH). In the continuation phase, children aged 6 get 4 months of Rifampicin and INH (RH). During the intense phase of DOTS, drugs must be collected daily and taken under the supervision of a health worker. Drugs must be collected and self-administered by the patient every month throughout the continuation phase.

Re- treatment Regimen

Patients who have been treated with short course chemotherapy (SCC) or long course chemotherapy (LCC) for more than one month and are still smear positive. These individuals are pulmonary tuberculosis positive relapses, treatment failures, and returns after default. Streptomycin, INH, Ethambutol, Rifampicin, and other antibiotics are used for two months.

In the intensive phase, Pyrazinamide is followed by 1 month of INH, Ethambutol, Rifampicin, and Pyrazinamide, followed by 5 months of Ethambutol, Rifampicin, and Pyrazinamide. [2SE (RH) Z/1E (RH) Z/5E3 (RH) 3], [2SE (RH) Z/1E (RH) Z/5E (For pregnant women, streptomycin should not be included in the retreatment regimen.) Throughout Retreatment, including the continuation phase, the medications should be taken under the direct supervision of a health worker.

Short course Chemotherapy

Is prescribed for new patients with smear-negative pulmonary tuberculosis, extrapulmonary tuberculosis, and TB in children aged 6 and up. During the intense phase, patients are treated with Rifampicin, Isoniazid, and Pyrazinamide for 8 weeks, followed by 6 months of Ethambutol and Isoniazid. [2(RHZ)/6(EH)].

Chemotherapy for a long time (LCC)

Is to be prescribed in all cases of tuberculosis in areas where the DOTS programme has not yet begun. The intense phase consisted of 2 months of Streptomycin, Ethambutol, and INH, followed by 10 months of Ethambutol and INH.

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Ethionamide, para-aminosalicylic acid, capreomycin, cycloserine, amikacin, and ciprofloxacin are examples of second-line antitubercular medicines. When first-line medications fail to work, these agents are evaluated under the supervision of their side effects.

Antibiotics that are effective against atypical mycobacteria Atypical mycobacteria cause disease that is often less severe than tuberculosis and is not spread from person to person. In the late stages of AIDS, the Mavium complex is a significant and prevalent cause of widespread illness.

Treatment of disseminated illness with azithromycin or clarithromycin plus ethambutol is a successful and well-tolerated therapy. Some authorities advise using ciprofloxacin or rifabutin as a third agent. Rifabutin has been proven to lower the incidence of M avium complex bacteremia in AIDS patients when given in a single daily dose of 300 mg. Clarithromycin also protects against MAC bacteremia.

Drugs used in Leprosy Leprosy is caused by mycobacterium leprae. I t can be treated dapsone, rifampin, clofazimine, ethionamide, etc.

Because of increasing reports of dapsone resistance, treatment of leprosy with combinations of the drugs is recommended.

Dapsone

Dapsone (diaminodiphenylsulfone) is the most commonly prescribed medicine for the treatment of leprosy. It works by inhibiting folate production. In huge populations of M leprae, resistance can develop. As a result, dapsone, rifampin, and clofazimine are indicated as a first treatment. Sulfones are easily absorbed through the intestines and broadly dispersed in body fluids and tissues. The amount of medication discharged in urine varies, and the majority of it is acetylated.Dapsone is commonly accepted. The symptoms include gastrointestinal intolerance, fever, pruritus, and rashes. In lepromatous leprosy, erythema nodosum is common during dapsone therapy. Corticosteroids may be used to treat Erythema nodosum leprosum. Hemolysis and methemoglobinemia are possible side effects.

Rifampin

This medication is beneficial in the treatment of lepromatous leprosy. Because of the potential for rifampin-resistant M leprae to arise, the medicine is only given in small doses.

Clofazimine

Clofazimine absorption from the gut is varied, and the majority of the medicine is eliminated in faeces. Clofazimine is abundantly stored in reticuloendothelial and epidermal tissues. Clofazimine is used to treat sulfone-resistant leprosy or people who are sulfone intolerant. Orally, a usual dose is 100 mg/d. Skin darkening ranging from red-brown to practically black is the most noticeable side effect.

AGENTS ANTIFUNGAL

The use of broad-spectrum antimicrobials and the HIV epidemic have both increased the prevalence and severity of fungal infections in recent years. Antifungal antibiotics and synthetic antifungals are the two types of antifungal medications.

Antifungal medications

Amphotericin B

The gastrointestinal system absorbs amphotericin B weakly. As a result, oral amphotericin B is only effective against fungus in the gastrointestinal tract lumen. Although the medicine is widely disseminated in tissues, CSF only reaches 2-3 percent of the blood level, necessitating intrathecal therapy for some kinds of fungal meningitis.

Amphotericin B binds to ergosterol (a sterol found in cell membranes) and affects cell permeability by creating amphotericin B-associated holes in the cell membrane. The pore permits intracellular ions and macromolecules to flow out, eventually killing the cell.

Fever, chills, muscle spasms, vomiting, headache, hypotension (due to infusion), renal damage associated with impaired renal function are all possible side effects of amphotericin B.

Amphotericin B is an antifungal drug with a broad spectrum of activity. It kills Candida albicans and Cryptococcus neoformans yeasts, as well as moulds like Aspergillus fumigatus.

Amphotericin B is still the first-line treatment for nearly all life-threatening mycotic infections. For serious fungal infections, this is the initial induction treatment (immunosuppressed patients, severe fungal pneumonia, and cryptococcal meningitis with altered mental status).

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Nystatin

Nystatin has a similar structure to amphotericin B and acts in the same way, creating pores. It's too poisonous to be administered systemically, thus it's only used topically. Skin, mucous membranes, and the gastrointestinal tract do not absorb it. Nystatin inhibits the growth of most Candida species and is often used to treat local candidal infections. Nystatin is a drug that is used to treat diabetes.

Griseofulvin

Griseofulvin is a fungistatic antibiotic that is used to treat dermatophytosis. When administered with fatty foods, absorption is boosted. Griseofulvin is deposited in freshly formed skin, where it binds to keratin and protects it against infection. For skin and hair infections, it must be given for 2-6 weeks to allow infected keratin to be replaced by resistant structures. Nail infections may require months of treatment to allow for the regeneration of the new, protected nail, and relapse is common. Hepatitis, an allergic condition similar to serum sickness, and medication interactions with warfarin and phenobarbital are among the side effects. Newer antifungal drugs such as itraconazole and terbinafine have mostly replaced griseofulvin.

Synthetic Antifungal Agents Flucytosine

Flucytosine is a fluorouracil derivative (5-FU). It has a substantially restricted range of action than amphotericin B. Orally, it is well absorbed. It has a low protein binding capacity and permeates all bodily fluid compartments, including the CSF. Glomerular filtration eliminates it. Toxicity is more common in AIDS patients especially when renal impairment is present.

Flucytosine is metabolised to 5-FU, 5-fluorodeoxyuridine monophosphate (F-dUMP), and fluorouridine triphosphate (FUTP) intracellularly, which impede DNA and RNA production, respectively.

Clinical Use: Effective against Cryptococcus neoformans, Candida species, and chromoblastomycosis-causing dematiaceous moulds. At the moment, itraconazole is only used in combination with amphotericin B for cryptococcal meningitis or itraconazole for chromoblastomycosis.

Flucytosine's negative effects are caused by its metabolism (intestinal flora) into the poisonous antineoplastic chemical flucytosine. The most prevalent side effects are bone marrow toxicity, which includes anaemia, leukopenia, and thrombocytopenia, with liver enzyme abnormalities occurring less commonly.

Azoles

Azoles are synthetic substances that are divided into two categories: imidazoles and triazoles. Ketoconazole, miconazole, and clotrimazole are the imidazoles. Itraconazole and fluconazole are two triazoles.

The antifungal action of azole medicines stems from the suppression of fungal cytochrome P450 enzymes, which reduces ergosterol synthesis. Azole medicines' specificity comes from their higher affinity for fungal cytochrome P450 enzymes than for human cytochrome P450 enzymes. Imidazoles have a lower degree of selectivity than triazoles, which explains why they have a higher rate of medication interactions and side effects.

Many Candida species, Cryptococcus neoformans, endemic mycoses (blastomycosis, coccidioidomycosis), dermatophytes, and Aspergillus infections are all susceptible to azoles (itraconazole). Negative Effects: The azoles are not particularly poisonous. Minor stomach upset is the most prevalent side effect. The majority of azoles induce abnormal liver enzymes and, in rare cases, clinical hepatitis.

Imidazoles Ketoconazole

Fluconazole and itraconazole are more selective for fungal P450 than ketoconazole (inhibit mammalian cytochrome P450 enzymes).

Because of medication interactions, endocrine adverse effects, and its narrow therapeutic range, it has limited clinical usage. At a low stomach pH, oral formulation absorbs well. Mucocutaneous candidiasis and nonmeningeal coccidioidomycosis are treated with ketoconazole. It's also used to treat pityriasis versicolor and seborrheic dermatitis (Topical/ shampoo).

The suppression of human cytochrome P450 enzymes by ketoconazole interferes with the manufacture of adrenal and gonadal steroid hormones, resulting in substantial endocrine consequences such as gynecomastia, infertility, and monthly abnormalities. Second, interactions with P450 enzymes might change the metabolism of other medicines, thereby increasing their toxicity (eg. increased levels and enhanced arrhythmogenic effects of the nonsedating antihistamines, and terfenadine).

Miconazole with clotrimazole

Clotrimazole and miconazole are over-the-counter medications that are commonly used to treat vulvovaginal candidiasis. Oral clotrimazole troches are a pleasant-tasting alternative to nystatin for the treatment of oral thrush. Both medicines,

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in cream form, are effective against dermatophytic infections such as tinea corporis, tinea pedis, and tinea cruris. Absorption is minimal, and side effects are uncommon.

Triazoles:-Itraconazole

Itraconazole is available in an oral formulation, and meals and a low gastric pH improve absorption. Hepatic metabolism is quite extensive. Itraconazole is the azole of choice for treating dermatophytoses and onychomycosis, and it's the only one that works against Aspergillus species.

Fluconazole

Fluconazole penetrates the cerebrospinal fluid well. It can be administered intravenously or orally. Hepatic microsomal enzymes are least affected by fluconazole. As a result, it has a large therapeutic window. In the treatment and secondary prophylaxis of cryptococcal meningitis, fluconazole is the drug of choice. It also works to treat mucocutaneous candidiasis**.**

ANTIVIRAL AGENTS

Viruses are obligatory intracellular parasites that rely on the host cell's synthetic processes for replication. There are multiple steps in viral replication: (1) adsorption to and penetration into susceptible host cells; (2) viral nucleic acid uncoating; (3) synthesis of early regulatory proteins, such as nucleic acid polymerases; (4) synthesis of RNA/DNA; (5) synthesis of late structural proteins; (6) assembly (maturation) of viral particles; and (7) release from the cell

Antiviral drugs may be used to target any of these processes. The majority of currently known antiviral drugs target purine and pyrimidine synthesis (step 4); reverse transcriptase inhibitors hinder HIV RNA genome transcription into DNA, blocking viral mRNA and protein synthesis. Protease inhibitors stop late proteins from being made.

Antiherpes Agents

Acyclovir

Acyclovir triphosphate inhibits viral DNA synthesis by two mechanisms: competitive inhibition of the viral DNA polymerase and irreversible binding to the DNA template.Oral, injectable, and topical forms of acyclovir are available. Acyclovir diffuses into most tissues and bodily fluids, resulting in serum concentrations of 50-100 percent. Cerebrospinal fluid concentrations are 50% of serum concentrations.Treatment of original infection and recurrences of genital and labial herpes with oral acyclovir is effective. For herpes simplex encephalitis, neonatal HSV infection, severe primary,

recurrent HSV genital and labial infections, and individuals who cannot take oral pills, intravenous acyclovir is the therapy of choice.Acyclovir is generally well tolerated by patients. Nausea, diarrhoea, and headaches have been reported on occasion.

Ganciclovir

The active chemical inhibits viral DNA polymerase competitively, resulting in an unstable complex but no chain termination. Ganciclovir has activity against CMV, HSV, VZV, and EBV, with CMV activity up to 100 times stronger than acyclovir.Intravenous ganciclovir is used to treat CMV retinitis in patients with AIDS. When given before an organ transplant, the medication also lowers the risk of symptomatic CMV infection. In immunocompromised patients with CMV pneumonitis, intravenous ganciclovir is generally useful, especially when combined with intravenous cytomegalovirus immunoglobulin.

CMV colitis and esophagitis have also been treated with intravenous ganciclovir.Myelosuppression, particularly neutropenia, is the most prevalent adverse reaction to ganciclovir treatment. It's possible that myelosuppression is additive.

Foscarnet

Foscarnet is a pyrophosphate inorganic chemical that directly inhibits viral DNA polymerase, RNA polymerase, and HIV reverse transcriptase. It is active against HSV, VZV, CMV, EBV, HHV-6, HBV, and HIV in vitro.Only an intravenous formulation of the medication is available. Concentrations in the cerebrospinal fluid are roughly two-thirds of those in steady-state serum. The kidney is responsible for the majority of foscarnet clearance.

In patients with normal renal function, the initial elimination half-life is 4-8 hours, followed by a prolonged terminal elimination half-life of 3-4 days.Foscarnet is used to treat CMV retinitis and acyclovir-resistant HSV infection in patients. Foscarnet has also been used to treat acyclovir-resistant VZV infection and CMV colitis and esophagitis.Renal insufficiency, hypocalcemia, and hypercalcemia are some of the potential side effects.High amounts of ionised medication in the urine may be the cause of genital ulcers linked with foscarnet therapy. Hallucinations and convulsions are examples of central nervous system toxicity.

Idoxuridine: Idoxuridine (IDU, IUDR) is a substituted pyrimidine analogue that was approved as the first antiviral agent. It is used topically to treat herpes keratitis (0.1 percent solution), but it is too toxic for systemic administration due to its lack of selectivity.

Vidarabine

HSV-related acute keratoconjunctivitis, superficial keratitis, and recurring epithelial keratitis can all be treated with vidarabine as a 3% ointment. In immunocompromised patients, intravenous vidarabine (10-15 mg/kg daily) is useful in treating HSV encephalitis, newborn herpes, and VZV infection. The medication is predominantly removed as the hypoxanthine metabolite through renal processes. GI discomfort, neurologic symptoms (confusion, myoclonus, seizures), and myelosuppression are all possible side effects.

Antiretroviral Agents

Antiretroviral medications are synthetic antiviral drugs that are used in the treatment of HIV infection. Antiretroviral drugs are currently available in four main classes on the market: Fusion inhibitors, nonnucleoside reverse transcriptase inhibitors (NNRTI), and nucleoside reverse transcriptase inhibitors (NRTI).

Inhibitors of reverse transcriptase

Zidovudine

Zidovudine (AZT) is a deoxythymidine analogue that is activated to the 5'-triphosphate form through anabolic phosphorylation. Zidovudine is phosphorylated by three cellular kinases after entering the cell via passive diffusion; the triphosphate is a competitive inhibitor of deoxythymidine triphosphate for reverse transcriptase. In the creation of proviral DNA, it also works as a chain terminator. In vitro, zidovudine is effective against HIV-1, HIV-2, and human T-cell lymphotropic viruses.

Resistance to zidovudine is caused by changes in the reverse transcriptase gene, and it is more common in people who have severe HIV infection. Withdrawing zidovudine exposure may allow HIV-1 isolates to revert to the susceptible (wild-type) phenotype.

Zidovudine is offered in intravenous and oral forms with different pharmacokinetics. It is well absorbed from the gut and transported to most body tissues and fluids, including the cerebrospinal fluid, where medication levels are roughly 60% of serum levels. A systemic bioavailability of roughly 65 percent derives from significant first-pass metabolism to an inactive glucuronidated metabolite.

Zidovudine reduces HIV-1 replication in infected individuals, which has been found to slow the progression of clinical illness and prolong survival. Zidovudine is effective in the treatment of HIV-related infections. Zidovudine has efficacy in the

treatment of HIV-associated encephalopathy and thrombocytopenia, and in the prevention of vertical (mother to newborn) transmission of HIV. Clinical efficacy is limited by the relatively rapid development of resistance, particularly when used as monotherapy.

Adverse Reactions: The most common adverse effect is myelosuppression gastrointestinal intolerance, headaches, and insomnia may occur but tend to resolve if ingestion is continued. Less frequent unwanted effects include thrombocytopenia, acute cholestatic hepatitis, and myopathy.

Didanosine

Didanosine (ddI) is a deoxyadenosine analogue that is synthesised. It is degraded by a number of cellular enzymes within the cell, and its active component, 2,3-dideoxyadenosine-5-triphosphate, suppresses viral replication by inhibiting HIV reverse transcriptase and causing chain termination.Food reduces absorption, according to pharmacokinetics. The drug's concentrations in the cerebrospinal fluid are about 20% of those in the blood. The active compound's intracellular half-life is around 12 hours, whereas its elimination half-life is 0.6-1.5 hours.

The medication is removed through tubular secretion and glomerular filtration.Didanosine, either used alone or in combination with zidovudine, is beneficial in delaying the clinical course of HIV infection. For people who are underweight, the dosage should be lowered.The most common clinical toxicity related with didanosine treatment is

Lamivudine: Lamivudine (3TC) is a nucleoside analog with in vitro activity against HIV-1, including zidovudine resistant strains, and HBV. Lamivudine inhibits the reverse transcriptase of HIV-1 and is synergistic with zidovudine against HIV-1. As with zidovudine, lamivudine requires intracellular triphosphorylation for activation. Lamivudine, administered in combination with zidovudine or another nucleoside analog to retard the emergence of resistance, is indicated for treatment of advanced HIV disease. Potential side effects are headache, insomnia, fatigue, and gastrointestinal discomfort, though these are typically mild.

Zalcitabine

Zalcitabine (ddC) is a pyrimidine nucleoside that inhibits the replication of HIV-1. Like zidovudine, intracellular activation by triphosphorylation is catalyzed by cellular enzymes; competitive inhibition of the reverse transcriptase and chain termination result. The drug is effective as treatment for patients with HIV infection. It

is available in oral formulation only and is typically prescribed in combination with zidovudine. Zalcitabine therapy is associated with a dose-dependent peripheral neuropathy that appears to occur more frequently in patients with low serum cobalamin levels and in those with a history of excessive ethanol consumption. Other reported toxicities include pancreatitis, esophageal ulceration and stomatitis, and arthralgias. Coadministration of drugs that cause either peripheral neuropathy or pancreatitis may increase the frequency of these adverse effects.

Stavudine

Stavudine (d4T) is a thymidine analog that requires intracellular triphosphorylation for activation, acting as a competitive inhibitor of HIV-1 reverse transcriptase and as a chain terminator. The major dose-limiting toxicity is peripheral sensory neuropathy. Less common adverse effects include pancreatitis, arthralgias, and elevation in serum transaminases.

Protease Inhibitors

Indinavir

Indinavir is a specific inhibitor of the HIV-1 protease, an enzyme essential for the production of mature, infectious virions. It is currently used for the treatment of individuals with HIV-1 infection and is recommended for use in combination with a reverse transcriptase inhibitor to delay emergence of resistance. The drug must be consumed on an empty stomach for maximal absorption. Oral bioavailability is excellent.

Resistance: Resistance to indinavir is mediated by the expression of multiple and variable protease amino acid substitutions. At least two-thirds of indinavir-resistant strains are cross- resistant to saquinavir and ritonavir; however, saquinavir-resistant isolates tend to retain susceptibility to indinavir.

Adverse Effects: The most common adverse effects reported thus far are indirect hyperbilirubinemia and nephrolithiasis. Thrombocytopenia, nausea, diarrhea, and irritability have also been reported in some patients. Indinavir and ritonavir are inhibitors of as well as substrates for cytochrome P450 CPY3A4.

Serum levels of indinavir will increase in the presence of antifungal azoles (themselves CYP3A4 inhibitors) and decrease in the presence of rifabutin and rifampin (CYP3A4 inducers). Increased levels of rifabutin (also a CYP3A4 substrate) that result from use of indinavir require a reduction in the rifabutin dosage by 50%. Increased

levels of antihistamines, cisapride, and benzodiazepines may also occur with potential toxicity from these drugs. More precise delineation of drug interactions is underway.

Ritonavir

Ritonavir is an HIV-1 protease inhibitor with a high bioavailability (60-80 percent). GI problems, circumoral paresthesia, raised hepatic aminotransferase levels, altered taste, and hypertriglyceridemia are the most common side effects of ritonavir. When delivering the medicine to people who have poor hepatic function, use caution. This medication should be stored in the refrigerator. Indinavir-resistant HIV-1 isolates are also resistant to ritonavir.

Saquinavir

Saquinavir is a synthetic peptide-like substrate analogue that inhibits HIV-1 protease activity and prevents viral polyprotein cleavage. Saquinavir's anti-HIV-1 action in vitro is additive to or synergistic with reverse transcriptase inhibitors. Combination therapy with nucleoside drugs, as with other medications in this family, is likely to be the most effective clinically. There has been little indication of cross-resistance between saquinavir and other protease inhibitors or saquinavir and nucleoside analogues to yet.

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTI)

Nonnucleoside reverse transcriptase inhibitors (NNRTIs)- are a class of antiretroviral drugs with a common mechanism of action. Nonnucleoside reverse transcriptase inhibitors attach directly to reverse transcriptase in a noncompetitive manner, interfering with its action. NNRTIs do not require intracellular conversion to an active metabolite to work. There are two commercially available nonnucleoside reverse transcriptase inhibitors.

Delavirdine (DLV)

Delavirdine is a nonnucleoside reverse transcriptase inhibitor and a synthetic antiretroviral drug. Delavirdine is structurally different from nevirapine, a nonnucleoside reverse transcriptase inhibitor derived from dipyridodiazepinone. The medication prevents HIV-1 replication by interfering with reverse transcriptase's RNA- and DNA-directed polymerase activities.

DLV derivatives appear to have a mode of action similar to other nonnucleoside reverse transcriptase inhibitors (e.g., nevirapine, loviride, efavirenz). In their manner of retroviral inhibition, all nonnucleoside reverse transcriptase inhibitors appear to bind to a common area of reverse transcriptase and have similar kinetic characteristics.

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Spectrum: Delavirdine is a highly selective antiretroviral drug with a narrow therapeutic window. The medication displays virustatic activity against HIV-1 in vitro, but not against HIV-2.

Resistance: In vitro, HIV-1 strains with reduced susceptibility to delavirdine (a 10- to 100-fold decrease in susceptibility from baseline) have been created by serial passage of the retrovirus in the presence of increasing delavirdine concentrations. The exact mechanism of delavirdine resistance or reduced susceptibility has yet to be discovered, however HIV reverse transcriptase mutation appears to be involved.

Clinical Uses: Adults with human immunodeficiency virus type 1 (HIV-1) infection are treated with oral delavirdine in combination with other antiretroviral drugs.

Adverse reactions: The most common side effect of delavirdine medication is rash. Rarely, severe or life-threatening rashes (e.g., erythema multiforme, Stevens-Johnson syndrome) have been described, and they have all gone away once the medicine was stopped. Rash appears within 1-3 weeks (median: 11 days) of starting delavirdine therapy and is typically diffuse, maculopapular, erythematous, and pruritic; rash appears primarily on the upper body and proximal arms, with less intensity of lesions on the neck and face and less on the rest of the trunk and limbs.

Nevirapine

Nevirapine is an inhibitor of nonnucleoside reverse transcriptase. The medicine prevents the human immunodeficiency virus type 1 (HIV-1) from replicating by interfering with reverse transcriptase's RNA- and DNA-directed polymerase activities. By functioning as a selective, noncompetitive HIV-1 reverse transcriptase inhibitor, nevirapine binds directly to HIV-1 reverse transcriptase and has a virustatic impact. Nevirapine is a highly selective antiretroviral drug with a narrow therapeutic range.

Pharmacokinetics: Nevirapine is taken by mouth. The medication can be taken with or without food. Concomitant administration of nevirapine with a substantial meal, an antacid, or didanosine compounded with an alkaline buffering agent had no effect on its systemic availability. Because nevirapine is highly metabolised by the liver and nevirapine metabolites are widely excreted by the kidneys, individuals with renal or hepatic impairment should use the medicine with caution. According to the manufacturer, there is currently insufficient data to propose a nevirapine dosage for individuals with hepatic dysfunction, renal insufficiency, or who are on hemodialysis.

Oral nevirapine is approved for use in individuals with HIV-1 infections in conjunction with dideoxynucleoside reverse transcriptase inhibitors.

Resistance: In vitro, HIV-1 strains with decreased nevirapine susceptibility were created. Some nonnucleoside reverse transcriptase inhibitors may be cross-resistance to HIV-1 strains resistant to nevirapine.

Adverse effects: When used in conjunction with zidovudine, the medicine looks to be well tolerated (with or without didanosine). The most common side effect related with nevirapine is rash, which can be severe or life-threatening. Severe rash or rash that is accompanied with constitutional symptoms.

Fusion Inhibitors

Enfuvirtide (T-20): Enfuvirtide was the first fusion inhibitor to receive FDA approval. For experienced HIV patients whose viral load remains detectable despite continued medication, it can be administered in combination with other antiretroviral drugs. Enfuvirtide susceptibility was found in HIV-1 isolates resistant to NRTIs, NNRTIs, and PIs. Enfuvirtide has a good safety record.

Other Antiviral Agents

Amantadine, Rimantadine

Amantadine and rimantadine prevent the viral RNA of influenza A from being uncoated within infected host cells, halting its multiplication. In high-risk people, both medicines are helpful in preventing influenza virus infection. Both medications can also be used to treat influenza A, effectively lowering the length of symptoms when given within 48 hours of the commencement of symptoms. GI intolerance and central nervous system symptoms are the most typical side effects (eg, nervousness, difficulty in concentrating, lightheadedness).

Antineoplastic agents

A malignant neoplasm or development of abnormal cells is referred to as cancer. Uncontrolled proliferation, loss of function due to a loss of differentiation capacity, invasiveness, and the tendency to spread are all characteristics of cancer cells. Cancer is caused by genetic alterations in the cell, the most common of which are tumor suppressor gene inactivation and oncogene activation.

There are three approaches to cancer management: Radiotherapy, Surgery and Chemotherapy. Most anticancer drugs are antiproliferative, and hence affect rapidly growing dividing normal cells. Anticancer drugs are broadly categorized into two: cytotoxic drugs and hormones.

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Cytotoxic drugs are further divided into:

- Alkylating agents and related compounds: These drugs act by forming covalent bonds with DNA and thus inhibit DNA replication. Examples are cyclophosphamide, lomustine, thiotepa, cisplatin.
- Antimetabolites: These drugs block or destabilize pathways in DNA synthesis. Examples are methotrexate, mercaptopurine, and fluorouracil.
- Cytotoxic antibiotics: These drugs inhibit DNA or RNA synthesis or cause fragmentation to DNA chains or interfere with RNA polymerase and thus inhibit transcription. Examples are Doxorubicin, bleomycin, dactinomycin.
- Plant derivatives: These inhibit mitosis. Examples are vincristine, vinblastine.

Hormones and their antagonists are mainly used in hormone sensitive tumors such as glucocorticoids are employed in lymphomas, estrogens for prostatic cancer, tamoxifen for breast tumors, etc.

In general, anticancer drugs produce toxic effects like bone marrow toxicity, impaired wound healing, sterility, loss of hairs and damage to gastrointestinal epithelium.

Treatment of Protozoal Infections

TREATMENT OF MALARIA

Human malaria is caused by four Plasmodium species i.e., P. vivax, P. malariae, P. ovale, and P. falciparum. Although any of these parasites can cause significant sickness, P. falciparum is the one that causes most serious complications and deaths. Antimalarial drug effectiveness varies by parasite species and life cycle stage.

Parasite Life Cycle: The mosquito is infected by sucking human blood, which contains parasites in their sexual phase. At the mosquito's next feeding, the developed sporozoites are inoculated into humans. The sporozoites replicate in the liver to create tissue schizonts during the exoerythrocytic stage.

The parasites then exit the liver as merozoites and enter the circulation. Merozoites enter red blood cells, multiply to produce blood schizonts, and then burst the cells, unleashing a new crop of merozoites. This process can be repeated several times. The gametocytes (sexual stage) developed and are discharged into the bloodstream, where they may be consumed by another mosquito. P. falciparum and P. malariae only have one cycle of liver cell invasion and multiplication, and liver infection stopped in less than four weeks.

Multiplication is thereafter restricted to red blood cells. Thus, treatment that removes these species from red blood cells four weeks or more after sporozoite inoculation can cure these infections. In P. vivax and P. ovale infections, sporozoites also induce the dormant stage (hypnozoite) in hepatic cells, which leads to infection recurrences (relapses). To cure these illnesses, medication that eliminates parasites from both the red cells and the liver is essential.

The antimalarial drugs are classified by their selective actions on the parasite's life cycle.

- Tissue schizonticides: drugs that eliminate tissue schizonts or hypnozoites in the liver, e.g., primaquine.
- Blood schizonticides: drugs that act on blood schizonts, e.g., chloroquine, amodiaquine, proguanil, pyrimethamine, mefloquine, quinine.
- Gametocides: drugs that prevent infection in mosquitoes by destroying gametocytes in the blood, e.g., primaquine for P. falciparum and chloroquine for P. vivax, P. malariae, and P. ovale.
- Sporonticidal agent: drugs that render gametocytes noninfective in the mosquito, e.g., pyrimethamine, proguanil.

None of these drugs prevent infection except for pyrimethamine and proguanil which prevent maturation of P. falciparum hepatic schizonts. Blood schizonticides do destroy circulating plasmodia. Primaquine destroys the persisting liver hypnozoites of P. vivax and P. ovale.

Antimalarial drugs

a) Chloroquine: Chloroquine is a synthetic 4-aminoquinoline. It is a highly effective blood schizonticide that is mostly used for chemoprophylaxis and treatment of attacks of P. vivax, P. ovale, P. malariae or sensitive P. falciparum infections. It is effective against P. vivax, P. ovale, and P. malariae gametocytes, but not against P. falciparum gametocytes. Chloroquine has no effect on preerythrocytic plasmodium and has no radical curative effect. The precise mechanism of action is unknown. A chloroquine-concentrating process in parasitized cells is responsible for malarial parasites' selective toxicity. Normal erythrocytes have a chloroquine concentration of 10-20 times that of plasma, while parasitized erythrocytes have a concentration of roughly 25 times that of normal erythrocytes.

- **Pharmacokinetics:** It is rapidly and almost completely absorbed from the gastrointestinal tract and is rapidly distributed to the tissues. From these sites

it is slowly released and metabolized. The drug readily crosses the placenta. Renal excretion is increased by acidification of the urine.

- **Clinical uses:** Acute Malaria attacks (it clears the parasitemia of acute attacks of P. vivax, P. ovale, and P. malariae and of malaria due to nonresistant strains of P. falciparum), and chemoprophylaxis (It is the preferred drug for prophylaxis against all forms of malaria except in regions where P. falciparum is resistant to 4-aminoquinolines).
- **Adverse Effects:** Gastrointestinal symptoms, mild headache, pruritus, anorexia, malaise, blurring of vision, and urticaria are uncommon.
- **Contraindications:** Contraindicated in patients having a history of liver damage, alcoholism, or neurologic or hematologic disorders, psoriasis or porphyria, in whom it may precipitate acute attacks of these diseases.

a. Primaquine: Primaquine phosphate is an 8-aminoquinoline derivative made synthetically. The drug is normally well absorbed, thoroughly metabolized, and eliminated in the urine after oral treatment. Primaquine kills the late hepatic stages of P. vivax and P. ovale (hypnozoites and schizonts) and thereby cures the infections completely. Primaquine is also effective against P. falciparum primary exoerythrocytic stages. It protects against P. vivax and P. ovale when used with chloroquine for prophylaxis. Primaquine is highly gametocidal against all four types of malaria.

- **Clinical Uses:** Terminal prophylaxis and radical cure of P. vivax and P. ovale malaria, gametocidal action, and pneumocystis carinii pneumonia (PCP).
- **Adverse Effects:** Primaquine is generally well tolerated. It infrequently causes nausea, epigastric pain, abdominal cramps, and headache. Serious adverse effects like leukopenia and agranulocytosis are rare.

b. Quinine: Quinine is a blood schizonticide that works rapidly and effectively against all four malaria parasites. The drug is effective against P. vivax and P. ovale gametocytes, but not so much against P. falciparum gametocytes. The molecular mechanism of the medication is unknown.

- **Pharmacokinetics:** Quinine is rapidly absorbed, reaches peak plasma levels in 1-3 hours, and is widely distributed in body tissues. The elimination $t_{1/2}$ of quinine is 7-12 hours in normal persons but 8-21 hours in malaria-infected persons in proportion to the severity of the disease. Bulk of the drug is metabolized in the liver and excreted in the urine. Excretion is accelerated in acidic urine.

- **Clinical Uses:** Parenteral treatment of severe P. falciparum malaria, oral treatment of P. falciparum malaria resistant to chloroquine, prophylaxis, and sometimes quinine sulfate used for leg cramps.
- **Adverse Effects:** Quinine often causes nausea, vomiting, hypoglycemia. Cinchonism; a less common effect and manifested by headache, nausea, slight visual disturbances, dizziness, and mild tinnitus and may subside as treatment continues. Severe toxicity like fever, skin eruptions, gastrointestinal symptoms, deafness, visual abnormalities, central nervous system effects (syncope, confusion), and quinidine-like effects occurs rarely.

c. Proguanil and Pyrimethamine: These are dihydrofolate reductase inhibitors. They are slowly but adequately absorbed from the gastrointestinal tract. These are slow acting blood schizonticides against susceptible strains of all four malarial species. Proguanil (but not pyrimethamine) has a marked effect on the primary tissue stages of susceptible P. falciparum and therefore may have causal prophylactic action. Resistance to pyrimethamine and proguanil is found worldwide for P. falciparum and somewhat less ubiquitously for P. vivax.

- **Clinical Uses:** Chemoprophylaxis, treatment of chloroquine-resistant P. falciparum malaria, and toxoplasmosis treatment
- **Adverse Effects:** In malaria treatment, pyrimethamine and proguanil are well tolerated. In the high doses pyrimethamine causes megaloblastic anemia, agranulocytosis, and thrombocytopenia (leucovorin calcium is given concurrently).

d. Sulfones and Sulfonamides: Sulfonamides and sulfones have blood schizonticidal action against P. falciparum by inhibition of dihydrofolic acid synthesis. But the drugs have weak effects against the blood schizonts of P. vivax, and they are not active against the gametocytes or liver stages of P. falciparum or P. vivax. When a sulfonamide or sulfone is combined with an antifol, synergistic blockade of folic acid synthesis occurs in susceptible plasmodia. Sulfadoxine with pyrimethamine (Fansidar) and dapsone with pyrimethamine (Maloprim) are the most used combination.

e. Pyrimethamine-Sulfadoxine (Fansidar): Pyrimethamine-Sulfadoxine (Fansidar) is well absorbed. Its components display peak plasma levels within 2-8 hours and are excreted mainly by the kidneys. Average half-lives are about 170 hours for sulfadoxine and 80-110 hours for pyrimethamine. Pyrimethamine-Sulfadoxine is effective against certain strains of P. falciparum malaria. But quinine must be

given concurrently in treatment of seriously ill patients, because Fansidar is slowly active. It is not effective in the treatment of P. vivax malaria.

- **Clinical uses:** Treatment and Presumptive Treatment of Chloroquine-Resistant P. falciparum
- **Adverse Effects:** Rare adverse effects to single-dose Fansidar are those associated with sulfonamide allergy, including the hematologic, gastrointestinal, central nervous system, dermatologic, and renal systems. Fansidar is no longer used in prophylaxis because of severe reactions. However, it is used for prevention of malaria in pregnant women after the first trimester.
- **Contraindications:** Contraindicated in patients who had adverse reactions to sulfonamides, in pregnancy, in nursing women, or in children less than 2 months of age. Fansidar should be used with caution in those with severe allergic disorders, and bronchial asthma.

f. Mefloquine: Mefloquine hydrochloride is chemically related to quinine. Mefloquine has blood schizonticidal activity against P. falciparum and P. vivax. Sporadic and low levels of resistance to mefloquine have been reported from Southeast Asia and Africa. Resistance to the drug can emerge rapidly, and resistant strains have been found in areas where the drug has never been used.

- **Pharmacokinetics:** It can only be given orally because intense local irritation occurs with parenteral use. It is well absorbed. The drug is highly bound to plasma proteins, concentrated in red blood cells, and extensively distributed to the tissues, including the central nervous system. Mefloquine is cleared in the liver. Its acid metabolites are slowly excreted, mainly in the feces. Its elimination half-life, which varies from 13 days to 33 days, tends to be shortened in patients with acute malaria.
- **Clinical uses:** Mefloquine is used in prophylaxis and treatment of chloroquine-resistant and multidrug-resistant P. falciparum malaria. It is also effective in prophylaxis against P. vivax, P. ovale, P. malariae, and P. falciparum.
- **Adverse Reactions:** The frequency and intensity of reactions are dose related. In prophylactic doses, it causes gastrointestinal disturbances, headache, dizziness, syncope, and extra systoles and transient neuropsychiatric events (convulsions, depression, and psychoses). In treatment doses, the incidence of neuropsychiatric symptoms (dizziness,

headache, visual disturbances, tinnitus, insomnia, restlessness, anxiety, depression, confusion, acute psychosis, or seizures) may increase.

- **Contraindications:** History of epilepsy, psychiatric disorders, arrhythmia, sensitivity to quinine and the first trimester of pregnancy.

g. Doxycycline: Doxycycline is generally effective against multidrug-resistant P. falciparum. The drug is also active against the blood stages of the other Plasmodium species but not against the liver stages. In the treatment of acute malaria, it is used in conjunction with quinine.

h. Halofantrine: Halofantrine hydrochloride is an oral schizonticide for all four malarial species. A fatty food increases absorption up to six-times. Thus, the drug should not be given from 1 hour before to 3 hours after a meal. Excretion is mainly done through the feces.

i. Qinghaosu (Artemisinin): These drugs are especially useful in treatment of cerebral P. falciparum malaria. The drugs produce abdominal pain, diarrhea.

AMEBIASIS TREATMENT

Entamoeba histolytica, a protozoan parasite, causes amebiasis. A severe intestinal infection (dysentery), a mild to moderate symptomatic intestinal infection, an asymptomatic intestinal infection, ameboma, liver abscess, or any sort of extraintestinal infection can all be symptoms of E. histolytica infection. The drug of choice is determined by the clinical picture and the target site of action, such as the intestinal lumen or the tissues. Antiamebic drugs all work against Entamoeba histolytica trophozoites, but most don't work on the cyst stage.

Antiamebic drugs are classified as tissue amebicides and luminal amebicides.

- **Tissue Amebicides** eliminate organisms primarily in the bowel wall, liver, and other extraintestinal tissues and are not effective against organisms in the bowel lumen.
  - Metronidazole, and tinidazole are highly effective against amebas in the bowel wall and other tissues.
  - Emetine and dehydroemetine act on organisms in the bowel wall and other tissues but not on amebas in the bowel lumen.
  - Chloroquine is active against amebas in the liver.
- **Luminal Amebicides** act primarily in the bowel lumen.

- Diloxanide furoate
- Iodo-quinol
- Tetracyclines, paromomycin and erythromycin

Treatment of Amebiasis:

- **Asymptomatic Intestinal Infection:** The drugs of choice, diloxanide furoate and iodoquinol. Alternatives are metronidazole plus iodoquinol or diloxanide.
- **Intestinal Infection:** The drugs of choice, metronidazole and a luminal amebicide.
- **Hepatic Abscess:** The treatment of choice is metronidazole. Diloxanide furoate or iodoquinol should also be given to eradicate intestinal infection whether organisms are found in the stools. An advantage of metronidazole is its effectiveness against anaerobic bacteria, which are a major cause of bacterial liver abscess. Dehydroemetine and emetine are potentially toxic alternative drugs.
- **Ameboma or Extraintestinal Forms of Amebiasis:** Metronidazole is the drug of choice. Dehydroemetine is an alternative drug; chloroquine cannot be used because it does not reach high enough tissue concentrations to be effective (except in the liver). A simultaneous course of a luminal amebicide should also be given.

Antiamebic drugs:

(a) Metronidazole: The nitro group of metronidazole is chemically reduced by ferredoxin within sensitive organisms. The reduction products appear to be responsible for killing the organisms by reacting with various intracellular macromolecules.

- **Pharmacokinetics:** Oral metronidazole is readily absorbed and permeates all tissues including cerebrospinal fluid, breast milk, alveolar bone, liver abscesses, vaginal secretions, and seminal fluid. Intracellular concentrations rapidly approach extracellular levels whether administered orally or intravenously. Protein binding is low. The drug and its metabolites are excreted mainly in the urine.
- **Clinical Uses:** Metronidazole is active against amebiasis, urogenital trichomoniasis, giardiasis, anaerobic infections, acute ulcerative gingivitis, cancrum Oris, decubitus ulcers, and bacterial vaginitis and Helicobacter pylori infection.
- **Adverse effects:** Nausea, headache, dry mouth, or metallic tastes occur commonly. Rare adverse effects include vomiting, diarrhea, insomnia,

weakness, dizziness, stomatitis, rash, urethral burning, vertigo, and paresthesias. It has a disulfiram-like effect.

(b) Other Nitroimidazoles: Other nitroimidazole derivatives include tinidazole, and ornidazole. They have similar adverse effects. Because of its short half-life, metronidazole must be administered every 8 hours; the other drugs can be administered at longer intervals. However, apart from tinidazole, the other nitroimidazoles have produced poorer results than metronidazole in the treatment of amebiasis.

(c) Chloroquine: Chloroquine reaches high liver concentrations and is highly effective when given with emetine in the treatment and prevention of amebic liver abscess. Chloroquine is not active against luminal organisms.

(d) Dehydroemetine Emetine: Emetine and dehydroemetine are administered parenterally. They are stored primarily in the liver, lungs, spleen, and kidneys. They are eliminated slowly via the kidneys. These drugs act only against trophozoites, which they directly eliminate.

- **Clinical Uses:** Severe Intestinal Disease (Amebic Dysentery)
- **Adverse Effects:** Sterile abscesses, pain, tenderness, and muscle weakness around the injection are frequent. Emetine and dehydroemetine should not be used in patients with cardiac or renal disease, in patients with a history of polyneuritis, or in young children or liver abscess. They should not be used during pregnancy.

(e) Diloxanide Furoate: Diloxanide furoate is direct-acting amebicidal, but its mechanism of action is not known. In the gut, diloxanide furoate is split into diloxanide and furoic acid; about 90% of the diloxanide is rapidly absorbed and then conjugated to form the glucuronide, which is rapidly excreted in the urine. The unabsorbed diloxanide is the active antiamebic substance. Diloxanide furoate is the drug of choice for asymptomatic infections. For mild intestinal disease, and other forms of amebiasis it is used with another drug.

(f) Iodoquinol: Iodoquinol is effective against organisms in the bowel lumen but not against trophozoites in the intestinal wall or extraintestinal tissues. The mechanism of action of iodoquinol against trophozoites is unknown. Iodoquinol is an alternative drug for the treatment of asymptomatic or mild to moderate intestinal amebiasis. Adverse Effects are reversible severe neurotoxicity (optic atrophy, visual loss, and peripheral neuropathy). Mild and infrequent adverse effects that can occur at the standard dosage include diarrhea, which usually stops after several days,

anorexia, nausea and vomiting, gastritis, abdominal discomfort, slight enlargement of the thyroid gland, headache, skin rashes, and perianal itching.

(g) Paromomycin Sulfate: Paromomycin is an alternative drug for the treatment of asymptomatic amebiasis. In mild to moderate intestinal disease, it is an alternative luminal drug used concurrently with metronidazole. Paromomycin is both directly and indirectly amebicidal; the indirect effect is caused by its inhibition of bowel bacteria. It can be used only as a luminal amebicide and has no effect in extraintestinal amebic infections.

(h) Other Antibiotics: The tetracyclines (oxytetracycline) have very weak direct amebicidal action, and useful with a luminal amebicide in the eradication of mild to severe intestinal disease. Erythromycin although less effective can be used in the treatment of luminal amebiasis.

DRUGS USED IN GIARDIASIS AND TRICHOMONIASIS

Metronidazole is a drug of choice for giardiasis and trichomoniasis, and the alternate drug is tinidazole.

TREATMENT OF LEISHMANIASIS

Kala-azar, cutaneous, and mucocutaneous leishmaniasis are caused by the genus Leishmania. Treatment of leishmaniasis is difficult because of drug toxicity, the long courses of treatment, treatment failures, and the frequent need for hospitalization.

a) The drug of choice is **sodium antimony gluconate** (sodium stibogluconate). Alternative drugs are amphotericin B and pentamidine.

b) Amphotericin B: Amphotericin B is injected slowly intravenously. Patients must be closely monitored in hospital because adverse effects may be severe.

TREATMENT OF PNEUMOCYSTIS CARINII PNEUMONIA, TRYPANOSOMIASIS

(a) Pentamidine: Pentamidine is administered parenterally because it is not well absorbed from the gastrointestinal tract. The drug leaves the circulation rapidly and is bound avidly by the tissues, especially the liver, spleen, and kidneys. The drug is excreted slowly and unchanged in the urine. Pentamidine does not cross the blood-brain barrier. The mechanisms of pentamidine's antiparasitic action are not well known. The drug may interfere with the synthesis of DNA, RNA, phospholipids, and proteins.

- **Clinical Uses:** Leishmaniasis; Trypanosomiasis; and in Pneumocystosis
- **Adverse Effects:** Pain at the injection site is common; infrequently, a sterile abscess develops and ulcerates. Occasional reactions include rash, gastrointestinal symptoms, neutropenia, abnormal liver function tests, serum folate depression, hyperkalemia, and hypocalcemia. Severe hypotension, hypoglycemia, hyperglycemia, hyponatremia, and delayed nephrotoxicity.

TREATMENT OF HELMINTHIC INFECTIONS

Anthelmintic drugs are used to eradicate or reduce the numbers of helminthic parasites in the intestinal tract or tissues of the body. Most anthelmintics are active against specific parasites; thus, parasites must be identified before treatment is started.

(a) Albendazole: Albendazole, a broad-spectrum oral anthelmintic, is used for pinworm infection, ascariasis, trichuriasis, strongyloidiasis, and infections with both hookworm species. Albendazole is also the drug of choice in hydatid disease and cysticercosis. It blocks glucose uptake by larval and adult stages of susceptible parasites, depleting their glycogen stores and decreasing formation of ATP. As a result, the parasite is immobilized and dies. The drug has larvicidal effects in necatoriasis and ovicidal effects in ascariasis, ancylostomiasis, and trichuriasis. The drug is teratogenic and embryotoxic in some animal species and contraindicated in the first trimester.

- **Clinical Uses:**
  - Ascariasis, Trichuriasis, and Hookworm and Pinworm Infections: For pinworm infections, ancylostomiasis, and light ascariasis, necatoriasis, or trichuriasis, a single dose of 400 mg is given orally for adults and in children over two years of age. In pinworm infection, the dose should be repeated in 2 weeks.
  - Strongyloidiasis: 400 mg twice daily for three days (with meals).
  - Hydatid Disease: 800 mg/kg/d in divided doses for three months
  - Neurocysticercosis: 15 mg/kg /d for 8 days
  - Other Infections: At a dosage of 200-400 mg twice daily, albendazole is the drug of choice in treatment of cutaneous larval migrans (give daily for 3-5 days) and in intestinal capillariasis (10-day course).

- **Adverse Reactions:** Mild and transient epigastric distress, diarrhea, headache, nausea, dizziness. In 3-month treatment courses cause jaundice, nausea, vomiting, abdominal pain, alopecia, rash, or pruritus occurs.

(b) Diethylcarbamazine Citrate: Diethylcarbamazine is a drug of choice in the treatment of filariasis, loiasis, and tropical eosinophilia. It immobilizes microfilariae and alters their surface structure, making them more susceptible to destruction by host defense mechanisms. The mode of action of diethylcarbamazine against adult worms is unknown.

- **Clinical Uses:** Diethycarbamazine is the drug of choice for treatment of infections with Wuchereria bancrofti, Loa loa parasites, given its high order of therapeutic efficacy and lack of serious toxicity. Diethylcarbamazine temporarily kills microfilariae but are poorly effective against adult worms. If diethylcarbamazine is used in onchocerciasis treatment, suramin (a toxic drug) must be added to the regimen to kill the adult worms.
- **Adverse Reactions:** Mild and transient reactions include headache, malaise, anorexia, and weakness are frequent. Reactions may be induced by dying parasites. Reactions in onchocerciasis affect the skin and eyes in most patients. Reactions in W bancrofti, and L loa infections are usually mild in W bancrofti, and occasionally severe in L loa infections which include fever, malaise, papular rash, headache, gastrointestinal symptoms, cough, chest pains, and muscle or joint pains.

(c) Ivermectin: Ivermectin is the drug of choice in individual and mass treatment of onchocerciasis and for strongyloidiasis. The drug is rapidly absorbed. The drug has a wide tissue distribution. It apparently enters the eye slowly and to a limited extent. Excretion of the drug and its metabolites is almost exclusively in the feces. It paralyzes nematodes and arthropods by intensifying GABA- mediated transmission of signals in peripheral nerves. In onchocerciasis, ivermectin is microfilaricidal and affects embryogenesis. The mode of action of ivermectin on microfilariae is uncertain.

- **Clinical Uses:** Onchocerciasis, Bancroftian Filariasis, Strongyloidiasis, scabies and cutaneous larva migrans
- **Adverse Reactions:** The adverse effects of ivermectin are the Mazotti reaction, which starts on the first day after a single oral dose and peaks on the second day. The reaction is due to killing of microfilariae and its intensity correlates with skin microfilaria loads. The Mazotti reaction includes fever,

headache, dizziness, somnolence, weakness, rash, increased pruritus, diarrhea, joint and muscle pains, hypotension, tachycardia, lymphadenitis, lymphangitis, and peripheral edema. The Mazotti reaction diminishes with repeated dosing. Steroids may be necessary for several days.

(d) Levamisole: Levamisole hydrochloride is highly effective in eradicating Ascaris and moderately effective against both species of hookworm.

(e) Mebendazole: Mebendazole has a broad spectrum of anthelmintic activity and a low incidence of adverse effects. Poorly absorbed after oral administration. It rapidly metabolized and excreted mostly in the urine, either unchanged or as decarboxylated derivatives. It inhibits microtubule synthesis in nematodes, thus irreversibly impairing glucose uptake. As a result, intestinal parasites are immobilized or die slowly.

- **Clinical Uses:** The drug can be taken before or after meals; the tablets should be chewed before swallowing. Used in pinworm Infection, Ascaris lumbricoides, Trichuris trichiura, and Hookworm, Hydatid Disease, Taeniasis, and Strongyloidiasis.
- **Adverse Reactions:** Mild nausea, vomiting, diarrhea, and abdominal pain have been reported infrequently, more often in children heavily parasitized by Ascaris.

(f) Metrifonate: Metrifonate is a safe, alternative drug for the treatment of Schistosoma haematobium infections. Metrifonate, an organophosphate compound, is rapidly absorbed after oral administration. Clearance appears to be through nonenzymatic transformation to its active metabolite (dichlorvos). Metrifonate and the active metabolite are well distributed to the tissues and are eliminated in 24-48 hours. Adverse reactions are mild and transient cholinergic symptoms, including nausea and vomiting, diarrhea, abdominal pain, bronchospasm, headache, sweating, fatigue, weakness, dizziness, and vertigo.

(g) Niclosamide: Niclosamide is a drug of choice for the treatment of most tapeworm infections. It appears to be minimally absorbed from the gastrointestinal tract: neither the drug nor its metabolites have been recovered from the blood or urine.

- **Clinical Uses:** Niclosamide should be given in the morning on an empty stomach. The tablets must be chewed thoroughly and are then swallowed with water. In T. saginata, T. solium, and Diphyllobothrium latum; Hymenolepis nana and H. niclosamide; and Intestinal Fluke Infections.

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- **Adverse Reactions:** Adverse effects, mild, and transitory. It causes nausea, vomiting, diarrhea, and abdominal discomfort.

(h) Oxamniquine: Oxamniquine is used for the treatment of S. mansoni infections. It is active against both mature and immature stages of S. mansoni. It has also been used extensively for mass treatment. Oxamniquine is readily absorbed orally.

- **Clinical Uses:** Oxamniquine is safe and effective in all stages of S. mansoni disease, including advanced hepatosplenomegaly. It is better tolerated if given with food, although food delays absorption. In mixed infections with S. mansoni and S. haematobium, oxamniquine has been successfully used in combination with metrifonate.
- **Adverse Reactions:** Central nervous system symptoms are most common; nausea and vomiting, diarrhea, colic, pruritus, and urticaria also occur.

(i) Piperazine: The piperazine salts are alternative drugs in the treatment of ascariasis. Piperazine is readily absorbed from the gastrointestinal tract, and maximum plasma levels are reached in 2-4 hours. Most of the drug is excreted unchanged in the urine in 2-6 hours. It causes paralysis of Ascaris by blocking acetylcholine at the myoneural junction. The paralyzed roundworms are unable to maintain their position in the host and are expelled live by normal peristalsis.

- **Clinical Uses:** Ascariasis
- **Adverse Reactions:** Piperazine cause nausea, vomiting, diarrhea, abdominal pain, dizziness, and headache.

(j) Praziquantel: It is effective in the treatment of schistosome infections of all species and most other trematode and cestode infections, including cysticercosis. The drug's safety and effectiveness as a single oral dose have also made it useful in mass treatment of several of the infections. It is rapidly absorbed after oral administration. Most of the drug is rapidly metabolized to inactive products after a first pass in the liver. Excretion is mainly via the kidneys and bile. The drug increases cell membrane permeability to calcium, resulting in marked contraction, followed by paralysis of worm musculature. Vacuolization and disintegration of the tegumen occur, and parasite death follows.

- **Clinical Uses:** Schistosomiasis, Taeniasis and Diphyllobothriasis, Neurocysticercosis, H. nana infections
- **Adverse Reactions:** Most frequent are headache, dizziness, drowsiness, and lassitude; others include nausea, vomiting, abdominal pain, loose stools,

pruritus, urticaria, arthralgia, myalgia, and low-grade fever. Praziquantel appears to be better tolerated in children than in adults. Adverse effects may be more frequent in heavily infected patients, especially in S. mansoni infections.

(k) Pyrantel Pamoate: It is a broad-spectrum anthelmintic highly effective for the treatment of Ascaris and pinworm. As it is weakly absorbed from the gastrointestinal tract, it is active mostly against luminal organisms. Pyrantel is effective against mature and immature forms of susceptible helminths within the intestinal tract but not against migratory stages in the tissues or against ova. The drug is a depolarizing neuromuscular blocking agent that causes release of acetylcholine and inhibition of cholinesterase; this results in stimulation of ganglionic receptors and worm paralysis, which is followed by expulsion from the host's intestinal tract. Pyrantel is effective in Enterobius vermicularis, lumbricoides, and hookworm infections.

(l) Suramin: It is an alternative drug for the eradication of adult parasites of Onchocerca volvulus and a drug of choice in the treatment of the hemolymphatic stage of African trypanosomiasis due to Trypanosoma brucei gambiense and Trypanosoma brucei rhodesiense. It is a non-specific inhibitor of many enzymes. Toxic reactions are frequent and sometimes severe, comprising nausea, vomiting, urticaria, fever, nephrotoxicity, peripheral neuritis, anemia, jaundice, and exfoliative dermatitis. The drug should be given only under expert guidance.

(m) Thiabendazole: It is the drug of choice for the treatment of strongyloidiasis and an alternative drug for cutaneous larva migrans. It may also be tried in trichinosis and visceral larva migrans, given in the absence of other effective drugs. It is no longer recommended for the treatment of pinworm, ascarid, trichurid, or hookworm infection unless the safer drugs of choice are not available. It is quickly absorbed after ingestion. The drug is almost completely metabolized in the liver. 90% of the drug is excreted in the urine. It has anti-inflammatory properties, which may be an important factor in its ability to relieve symptoms in some parasitic diseases. It also has immunomodulating effects on T-cell function appears to be an immune-restorative agent. It also has antipyretic and mild antifungal and scabicidal actions. Thiabendazole's vermicidal action may be a result of interference with microtubule aggregation acting through inhibition of the enzyme fumarate reductase. The drug has ovicidal effects for some parasites.

- **Clinical Uses:** Effective in Strongyloides stercoralis (The standard dose is given twice daily for 2 days). In patients with hyperinfection syndrome, the

standard dose is continued twice daily for 5-7 days. Thiabendazole is highly effective in the treatment of cutaneous larva migrans. Cutaneous Larva Migrans (Creeping Eruption) The standard dose is given twice daily for 2 days.

- **Adverse Reactions:** Adverse effects are generally mild and transient but can be severe; the most common are dizziness, anorexia, nausea, and vomiting.

Questions:

i. Explain the mechanisms of action of antimicrobials.

ii. Differentiate between bacteriostatic and bactericidal drug action?

iii. List down the potential adverse effects of aminoglycosides?

iv. How can chloroquine - resistant P. falciparum malaria be treated?

v. Discuss the antiretroviral drugs with regard to their efficacy and safety.

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