UNIT 12 CHEMOTHERAPY-I

Structure

12.1 INTRODUCTION

Chemotherapy is the use of chemical compounds for the treatment of infectious diseases by killing or inhibiting the growth of causative organisms without damaging the host tissues or cells. The term Chemotherapy can be broadly classified into the following groups depending on the nature of the organism against which it is used.

Objectives

After studying this unit, you should be able to know about:

- broad classification of chemotherapeutic agents;
- various types of penicillinase and sulphonamides;
- various type of cephalosporins and other antibiotics; and
- antiprotozoal and anthelmintic agents.

Classification

i) **Antibacterial drugs:** These drugs are used in the treatment of bacterial infections like Streptococcal infections, Staphylococcal infections, etc.

ii) **Antiprotozoal drugs:** These drugs are used in the treatment of infections caused by protozoa like *E. histolytica, Giardia lamblia*, *P. falciparum*, etc.

iii) **Antifungal drugs:** These drugs are used in the treatment of fungal infections caused by Candida, Aspergillus, etc.

iv) **Anthelmintic drugs:** These drugs are used in the treatment of worm (Ascaris, Ankylostoma, etc.) infestations.

v) **Anticancer drugs:** These are drugs used in the treatment of neoplastic diseases like lymphomas, leukaemias, etc.

Paul Ehrlich demonstrated the effective use of methylene blue in the treatment of malaria. He also synthesized arsenical compounds effective in the treatment of syphilis. The synthesis of newer and powerful antibacterial substances gave the recognition to Paul Ehrlich as 'the father of modern chemotherapy' and awarded the Nobel Prize of medicine in 1909.

In 1928, Sir Alexander Fleming found that a diffusible substance was elaborated by *Penicillium notatum* (a fungus) which prevented the growth of surrounding bacterial colonies in culture plate. He named this as 'penicillin' but this discovery remained a scientific curiosity for more than a decade. This work was followed up by Chain, Falk and Florey who established the efficacy of penicillin in 1941 and in 1945, Fleming, Chain and Florey were awarded the Nobel Prize.

The antimicrobial agents are either bactericidal or bacteriostatic in nature.

a) **Primarily bactericidal:** Penicillin, cephalosporins, aminoglycosides, vancomycin, poly-peptides, INH, cotrimoxazole, rifampicin, fluoroquinolones, nalidixic acid.

b) **Primarily bacteriostatic:** Ethambutol, erythromycin, chloramphenicol, tetracyclines, sulfonamides.

Beta lactam antibiotics having a beta-lactam ring, which includes penicillin, in which a thiazolidine ring is attached to a beta-lactam ring that carries a secondary amino group. Other similar compounds are cephalosporins, monobactams and carbapenems.

12.2 PENICILLINS (BETA LACTAM ANTIBIOTICS)

Penicillin was originally extracted from the mould *Penicillium notatum* but now it is extracted from its related mould *Penicillium chrysogenum* due to its high yield. Penicillin consists of a beta lactam ring which is essential for its antibacterial activity. The bacterial cell wall is a rigid outer layer that

completely surrounds the cytoplasmic membrane. Penicillin and other beta-lactam antibiotics inhibit bacterial growth by interfering with a specific step in bacterial cell wall synthesis. The pharmacology of penicillin are discussed below:

12.2.1 Penicillinase Sensitive Penicillins

Benzyl Pencillin

It is the most potent β-lactam antibiotic and inhibits the growth of susceptible microorganism *in vitro* in lowest concentration and is available in water soluble sodium and potassium salts. Penicillin is effective against gram positive and negative cocci and some gram positive bacilli. Among the cocci, streptococci are highly sensitive. Gonococci, pneumococci and meningococci are sensitive to penicillin. The main therapeutic uses of Penicillins are as follows:

- Streptococcal infections: Pharyngitis, rheumatic fever, otitis media and even for subacute bacterial endocarditis.
- Staphylococcal infections: Penicillinase resistant penicillin can be used.
- Meningococcal infections: Meningitis & other infections caused by meningococci.
- Pneumococcal infections: Pneumonia and meningitis.
- Gonococcal infection: Procaine penicillin along with probenecid can be used.
- Syphilis: Penicillin is a drug of choice in the treatment of syphilis.
- In the treatment of actinomycosis and anthrax.
- In the treatment of diphtheria, tetanus and gas gangrene.
- Penicillins are also used in the prophylaxis of rheumatic fever, sexually transmitted diseases e.g. gonorrhoea and syphilis and bacterial endocarditis.

Semisynthetic Penicillins

Semisynthetic penicillins are produced by combining the specific side chains in place of benzyl side chain. They have been produced to overcome the shortcomings of benzyl penicillin like poor bioavailability, susceptibility to penicillinase and narrow spectrum of activity. **Phenoxymethyl penicillin** has an antibacterial spectrum similar to benzyl penicillin but is less active. It is used in tonsillitis, otitis media, erysipelas, prophylaxis of rheumatic fever and pneumococcal infections.

12.2.2 Penicillinase Resistant Penicillin

It is resistant to degradation by penicillinase. Mainly it exhibits activity against gram positive microorganisms and is useful against penicillinase producing *Staph. aureus*. **Cloxacillin** has weaker antibacterial activity than benzyl

penicillin. It is devoid of any serious side effect but can cause hypersensitivity reaction in some patients. Other analogs of cloxacillin are dicloxacillin and flucloxacillin.

12.2.3 Broad Spectrum Penicillins

They have broad antibacterial spectrum and are effective against both gram positive and gram negative organisms. They are hydrolysed by penicillinase. **Ampicillin** is a broad spectrum penicillin. It is more effective than benzyl penicillin against a variety of gram negative microorganisms. It is used in infection caused by susceptible gram positive and gram negative organisms (respiratory tract, soft tissue, gonococcal, GI and genitourinary infections), septicaemia, meningitis, chronic bronchitis, otitis media, sinusitis, invasive salmonellosis and cholecystitis.

Amoxycillin is a semisynthetic penicillin, a close congener of ampicillin and active against gram positive and negative organisms. It is used in respiratory, genitourinary, skin and soft tissue, ENT infections caused by pneumococci, streptococci, staphylococci, *H. influenzae, E. coli* and other susceptible organisms. Amoxycillin is also used in combination with clavulanate potassium, bromhexine and carbocisteine .cloxacillin and probenecid is used in bacterial septicaemia, skin and soft tissue infection, acute and chronic respiratory tract infections.

12.2.4 β-Lactamase Inhibitors

Clavulanic acid is a 'progressive' inhibitor of a wide variety of β-lactamases produced by gram positive and negative organisms. It is obtained from *Streptomyces clavuligerus*. It has no antibacterial activity of its own. It is used along with amoxycillin in various infections as discussed above. **Sulbactam** is another semisynthetic β-lactamase inhibitor used along with ampicillin. It is related to clavulanic acid both chemically and in activity. It is indicated in gynaecological, intra-abdominal, skin and soft tissue infections.

12.2.5 Antipseudomonal Penicillins

These are indicated mainly to treat gram negative bacilli infection by pseudomonas, proteus and enterobacter. **Carbenicillin** is principally indicated for serious infection caused by *Pseudomonas aeruginosa*. It is effective against certain other gram negative bacilli including *Proteus* species and *Bacteroides fragilis*. It is indicated in bacteriaemia, septicaemia, genitourinary and respiratory tract infections, endocarditis and postoperative infections caused by pseudomonas or proteus. **Piperacillin** has broad spectrum of antibacterial activity and excellent antipseudomonal activity. It is indicated in systemic and local infections, gynaecological infections, UTI, RTI, neo-natal and life-threatening paediatric infections, burns and septicaemia caused by susceptible organisms.

Ticarcillin has broad spectrum of activity against both gram positive and negative organisms. It is more potent than carbenicillin against *Pseudomonas.*

It is indicated in bacterial septicaemia, skin and soft tissue infections, acute and chronic respiratory infections.

SAQ 1

a) Penicillin is commercially isolated from _____.

b) Penicillinase resistant penicillins are specially useful against penicillinase producing _____.

c) _____ and _____ are the most commonly used β-lactamase inhibitors.

d) Penicillins primarily act on the bacterial _____.

12.3 SULFONAMIDES AND TRIMETHOPRIM

12.3.1 Sulphonamides

Chemically, all sulfonamides may be considered to be derivatives of sulfanilamide (p-amino-benzene sulfonamide). Sulfonamides were the first antimicrobial agents effective against pyogenic bacterial infections. The sulfonamides can be classified according to their therapeutic utility and pharmacokinetic parameters. However, because of bacterial resistance and discovery of many safer and more effective antibiotics, the utility of sulfonamides is limited to few infections which are of clinical interest.

The most important pharmacological action of sulfonamides is its antibacterial activity against variety of gram positive and gram negative organisms (mainly bacteriostatic) and certain species of chlamydia infections such as:

- Streptococci, staphylococci, pneumococci, gonococci, meningococci, *Haemophilus influenzae, Vibrio comma*, *Vibrio cholerae*, *E. coli*, *Pasteurella pestis*, *Shigella*.
- *Actinomyces*, *Nocardia* and *Toxoplasma*.
- *Chlamydia* causing lymphogranuloma venereum, psittacosis, trachoma and inclusion conjunctivitis.

The important therapeutic uses of sulphonamides are:

i) Urinary tract infection: Used in chronic suppressive therapy in various UTI conditions e.g. acute cystitis.

ii) Acute bacillary dysentery.

iii) Ulcerative colitis, mainly sulfasalazine (a chemical combination of sulfapyridine and 5-amino salicylic acid) is used in the treatment of ulcerative colitis.

iv) Streptococcal pharyngitis, prophylaxis of rheumatic fever and tonsillitis.

v) Trachoma and inclusion conjunctivitis: Sulphacetamide (10-30%) local eye drops.

vi) Chancroid: Sulfadimidine may be used.

vii) In the treatment of meningococcal meningitis.

viii) Sulfonamides in combination with pyrimethamine are used in the treatment of chloroquine resistant malaria.

ix) Toxoplasmosis: Sulfadiazine and pyrimethamine combination is used.

x) Burns: Topical silver sulfadiazine or mafenide is used.

12.3.2 Trimethoprim

Trimethoprim is related to antimalarial drug pyrimethamine, which selectively inhibits bacterial dihydrofolate reductase, necessary for the conversion of dihydrofolate to tetrahydrofolic acid.

Sulfonamides act by inhibiting the incorporation of PABA into dihydrofolate by bacteria. A combination of trimethoprim and sulfamethoxazole (cotrimoxazole) act sequentially in the same metabolic pathway in the synthesis of nucleotides. The important therapeutic uses of this combination are:

i) Urinary tract infection: Acute cystitis.

ii) Bacterial diarrhoea and dysentery.

iii) Respiratory tract infection such as chronic bronchitis and otitis media etc.

iv) In the treatment of typhoid.

v) Chancroid.

vi) Sexually transmitted diseases.

vii) Prophylaxis and treatment of certain HIV associated infections.

viii) For the prophylaxis of certain concurrent bacterial infections e.g. organ transplantation patients receiving immunosuppressants.

ix) Nosocomial infections.

Despite development of resistance to this combination in certain microorganisms, it has been used widely for several clinical indications. The combination is cheaper than newer antibiotics.

SAQ 2

a) Chemically, all _____may be considered to be derivatives of sulfanilamide.

b) Cotrimoxazole is a combination of _____ and _____.

c) Trimethoprim acts by inhibiting the enzyme _____.

12.4 CEPHALOSPORINS

Cephalosporins are important bactericidal broad spectrum β-lactam antibiotics used for the treatment of septicaemia, pneumonia, meningitis, urinary tract infections, peritonitis and biliary tract infections. They are obtained from fungus *Cephalosporium acremonium* and are chemically related to penicillin. It consists of β-lactam ring which is responsible for its antibacterial activity. All cephalosporins act by inhibiting bacterial cell wall synthesis and are bactericidal.

Cephalosporins are classified on the basis of the chronology of their development.

12.4.1 First Generation Cephalosporins

These agents are highly active against gram positive but weaker against gram negative bacteria. **Cephalexin** is orally active first generation cephalosporin and less active against penicillinase producing staphylococci. It is indicated in respiratory, genitourinary, skin and soft tissue infections, bone and joint infections, dental and ENT infections. **Cefazolin** is a semisynthetic potent cephalosporin for parenteral administration. It is used in infections of genitourinary tract, bone, joint and soft tissue infections, septicaemia, endocarditis, gonorrhoea, postoperative chest infections, biliary tract infection and surgical prophylaxis. **Cefadroxil** has good tissue penetration. Excreted unchanged in urine. Used in soft tissue and skin infection caused by staphylococci or streptococci, pharyngitis, tonsillitis, ENT infections and urinary tract infections.

12.4.2 Second Generation Cephalosporins

Cefuroxime and **cefaclor** areeffective against a wide range of gram positive and negative organisms. It is indicated in lower respiratory tract infections, ENT infections, Genitourinary tract infections, skin and soft tissue infections, etc. **Ceftazidime** is a broad spectrum cephalosporin having anti-pseudomonal activity. Used in serious infections of respiratory tract, ENT and soft tissue infection, septicaemia, meningitis, GI and biliary tract infections. **Cefoxitin** is produced by an *Actinomyces*. Used in the treatment of anaerobic and mixed surgical infections and lung abscess.

12.4.3 Third Generation Cephalosporins

Cefotaxime is used in respiratory, genitourinary infections including gonorrhoea, septicemia, meningitis, endocarditis; surgical, abdominal, bone and joint infections; preoperative prophylaxis in those at increased risk of infection and CNS infections. **Ceftriaxone** is a broad spectrum cephalosporin having a long half life and administered once daily and indicated in meningitis, septicaemia, typhoid, urinary tract infections, prophylaxis in surgical infections, pneumonia, STD, bacteremia and pelvic inflammatory disease.

Cefixime is indicated in respiratory tract infections, gonorrhoea, otitis media, urinary tract infection and typhoid fever.

12.4.4 Fourth Generation Cephalosporins

Cefepime and **Cefpiirome** are fourth generation cephalosporins used mainly in serious infections including septicaemia and respiratory tract infections and infections acquired from hospitals. These drugs are only administered by the parenteral route.

SAQ 3

a) On the basis of the chronology of development, cephalosporins are divided into _____.

b) Fourth generation cephalosporins are administered only by the _____ route.

c) Ceftriaxone is a _____ generation cephalosporin.

d) Cephalosporins produce bacteriocidal action by inhibiting _____.

12.5 QUINOLONES

Quinolones, are synthetic antimicrobial agents effective against gram negative bacteria. Although newer compounds (second generation quinolones – the fluoroquinolones) are also effective against gram positive bacteria. Quinolones block bacterial DNA synthesis by inhibiting bacterial topoisomerase II (DNA gyrase) and topoisomerase IV. The important quinolones are described below.

Nalidixic acid was the first member of this group of synthetic antibacterials. It is effective against gram negative bacteria mainly *E. coli* and *Shigella*. It is mainly used as urinary antiseptic and in diarrhoea caused by *E. coli*, *Shigella* and *Salmonella*. Later by addition of fluoride ions to the nucleus, Fluoroquinolones were synthesized. The newer compounds have relatively broader spectrum of action and are effective against gram positive and gram negative organisms. The main therapeutic use of these fluoroquinolones are:

- Urinary tract infections,
- Bacterial gastroenteritis,
- Typhoid fever,
- In septicemia,
- In otitis media,
- Respiratory infections e.g. acute pneumonia etc.,
- Ocular infections, and
- Other infections caused by *E. coli*, *K. pneumoniae*, *Enterobacter*, *Salmonella typhi*, *N. gonorrhoeae*, *N. meningitidis*, *H. influenzae*, *H. ducreyi*, *Shilgella*, *Vibrio cholerae*, *Pseudomonas aeruginosa*, *Staph. aureus* etc.

Ciprofloxacin is the most potent first generation fluoroquinolone, effective against a broad range of microorganisms. It has been used widely as a drug of first choice for typhoid fever; however, resistance has also been reported. It is also useful in respiratory infections due to *Mycoplasma*, *Legionella,* multidrug resistant tuberculosis and as topical agent in conjunctivitis. The drug is used alone as well as in combination. **Norfloxacin** is less potent than ciprofloxacin and is primarily used in genitourinary tract infections. It is relatively more potent than ciprofloxacin in above condition. It is not useful in respiratory and systemic infections due to gram positive cocci. **Pefloxacin** is a derivative of norfloxacin preferred for meningeal infections. It is used in the treatment of gonorrhoea and typhoid. **Sparfloxacin** is difluorinated quinolone effective against gram positive bacteria, anaerobes and mycobacteria. It is used in the treatment of pneumonia, chronic bronchitis, sinusitis etc. **Ofloxacin** is more potent than ciprofloxacin for gram positive organisms. It is also used in the treatment of chronic bronchitis and other ENT infections. Also used in gonorrhoea, gonococcal urethritis and urinary tract infections due to *E. coli*, *K. pneumoniae, P. mirabilis*, *Citrobacter diversus* or *paeruginosa. Mycoplasma pneumoniae, U. urealyticum* are also susceptible.

SAQ 4

a) Quinolones block bacterial DNA synthesis by inhibiting bacterial _____ and_____.

b) _____ is mainly used as urinary antiseptic and in diarrhoea.

c) _____ is a derivative of norfloxacin.

d) _____ is the most potent first generation fluoroquinolone.

12.6 MACROLIDE AND POLYPEPTIDE ANTIBIOTICS

12.6.1 Macrolide Antibiotics

Macrolides, as their name indicates are characterized by a large or macrocyclic lactone ring with attached sugar residue(s). They are discussed as under:

Erythromycin was the first macrocyclic antibiotic which was isolated from *Streptomyces erythreus*. The exert bacteriostatic action by binding to the 50S subunit of bacterial ribosome and inhibiting bacterial protein synthesis It is used as a substitute to penicillin in allergic patients for upper respiratory tract infections, e.g. tonsillitis, pharyngitis and mastoiditis, pneumococcal infection and prophylaxis of rheumatic fever. It is drug of choice in treatment of atypical pneumonia due to *Mycoplasma pneumoniae,* Legionnaire's pneumonia and whooping cough. It is also useful in wound and burn infections and severe impetigo not responding to topical antibiotics. **Roxithromycin** is a semi-synthetic macrolide antibiotic. It is longer acting than erythromycin and has better penetration into infected tissue. **Clarithromycin** is also similar to other macrolides and is more active against H. pylori than other compounds of the

same class. **Azithromycin** is the longest acting member of this group and is employed in the treatment of respiratory tract infections. Clarithromycin and azhithromycin have significant activity against mycobacterium species and are employed in alternative regimens for the treatment of tuberculosis and leprosy.

12.6.2 Polypeptide Antibiotics

They have bactericidal activity against gram negative bacteria only and are low molecular cationic polypeptide antibiotics.

Polymyxin B

It is used systemically in enteric infections caused by gram negative organisms and topically for pseudomonal infections of conjunctiva and cornea, burns and skin.

Bacitracin

It is obtained from *Bacillus subtilis.* It is effective against gram positive (cocci and bacilli), *Neisseria* and *H. influenzae*. It is used only topically as antibacterial powder, and skin and eye ointment.

Tyrothricin

It is obtained from *Bacillus bravis* and effective against gram positive and some gram negative organisms. It acts on bacterial cell membrane causing leakage and uncoupling of oxidative phosphorylation. Used topically as skin cream and solution.

12.6.3 Miscellaneous Antibiotics

Clindamycin

It inhibits most of the gram positive cocci e.g. streptococci, staphylococci and pneumococci, *C. diphtheriae, Actinomyces, Nocardia* and *Toxoplasma*. It is used in the treatment of severe anaerobic infections caused by bacteroides and other anaerobes. It is also used in combination with aminoglycoside in the treatment of abdomen and GIT wounds, infections of female genital tract, pelvic abscesses, aspiration pneumonia and septic abortion. It is also used for prophylaxis of endocarditis. Clindamycin is used along with primaquin in *Pneumocystis* pneumonia in AIDS patients**.**

Lincomycin

It is indicated in upper and lower respiratory tract infections, skin infections, septicaemia, bone and joint infection including acute haematogenous osteomyelitis.

Vancomycin

It is indicated in serious life threatening staphylococcal infections resistant to other antibiotics, in severe staphylococcal infections in patients who are allergic to penicillin and cephalosporin.

a) Macrolides, as their name indicates are composed of a large _____ with _____.

b) Macrolides inhibit protein synthesis by binding with _____of bacteria.

c) Clindamycin is used along with _____in *Pneumocystis carinii* pneumonia in AIDS patients.

12.7 ANTIPROTOZOAL AND ANTHELMINTIC AGENTS

12.7.1 Antiprotozoal Agents

Antiamoebic Agents

Amoebiasis is an infectious disease caused by *Entamoeba histolytica*. It can cause asymptomatic intestinal infection, colitis (mild to moderate), dysentery (severe intestinal infection), ameboma, liver abscess etc. The drugs used in chemotherapy of amoebiasis are discussed below.

Imidazoles

Metronidazole is the drug of choice for all forms of amoebic infections used in trichomonas vaginitis, anaerobic postoperative infections, giardiasis, acute ulcerative gingivitis, *H. pylori* infection, pseudomembranous enterocolitis and anaerobic vaginosis. **Tinidazole** and **secnidazole** are similar to metronidazole, but they have longer duration of action.

Quinolone Derivatives

Diiodohydroxyquinoline and **iodochlorohydroxyquin** are effective against *E. histolytica, Trichomonas* and *Giardia.* They are indicated in giardiasis, trichomonas vaginitis, intestinal amoebiasis and amoebic colitis. **Chloroquine** kills the trophozoites of *E. histolytica* and because of its selective concentration in liver, it is used in the treatment of hepatic amoebiasis concurrently or immediately after metronidazole for complete cure. It is not effective in amoebic dysentery and in cyst passers.

Emetine Derivatives

Emetine and dehydroemetine are effective against tissue trophozoites of *E. histolytica*

Diloxanide Furoate

It is a dichloroacetamide derivative, very effective luminal amoebicide. Used alone for cyst passers or usually with metronidazole for other forms of amoebic infections. It is also used in combination with tinidazole and metronidazole in

the treatment of intestinal amoebiasis, hepatic amoebiasis and other systemic diseases due to *E. histolytica*.

Furazolidone

It is indicated in bacterial enteritis, diarrhoea, giardiasis and bacillary dysentery.

Leishmaniasis

Visceral leishmaniasis (kala-azar) is caused by *Leishmania donovani* and transmitted by *Phlebo-tomus* sandfly. In human being, it is found intracellularly within macrophages in the nonflagellate form. The important drugs used in leishmaniasis are pentamidine, sodium stibogluconate, antifungal antibiotics (amphotericin B and ketoconazole) and antigout agent (allopurinol).

Pentamidine

Pentamidine is an aromatic diamidine formulated as an isoethionate salt used parenterally. It is used in the treatment of pneumocystosis (pulmonary and extrapulmonary disease caused by *P. carinii*), African trypanosomiasis (disease caused by *Trypanosoma brucei*) and leishmaniasis.

Sodium Stibogluconate

It is the drug of choice in leishmaniasis. It is pentavalent antimonial It is rapidly absorbed after IM injection and excreted unchanged in urine. Used in cutaneous and visceral leishmaniasis.

Trypanosomiasis

It is caused by genus *Trypanosoma* which is characterized by skin eruptions, sustained fever, lethargy and lymphadenitis, progressive brain dysfunction. Apart from imidazole derivative like metronidazole, other agents like hydroxyquinolines, iodine preparation (povidone-iodine) and antifungal antibiotics like clotrimazole (used mainly as vaginal pessaries), are also used for treatment of trypanosomiasis. Newer compounds have also been developed for treatment of trypanosomiasis. **Suramin** is a sulfated napthylamine and used as first line therapy for early hemolymphatic African trypanosomiasis (caused by *T. brucei gambiense*). It is also used for chemoprophylaxis against African trypanosomiasis. **Melarsoprol** is a arsenic containing compound used for advanced CNS African trypanosomiasis It is highly toxic and used only in advanced trypanosomiasis when no alternative is there.

Trichomoniasis

It is caused by *Trichomonas vaginalis* and is mainly associated with vulvovaginitis which is characterized by greenish yellow and cheesy vaginal discharge. The various agents used in trichomoniasis are metronidazole, tinidazole and secnidazole which are already described earlier. They produce 100% cure.

12.7.2 Anthelmintic Agents

Anthelmintic agents are used to eradicate (either kill or expel) the infesting helminths. The important anthelmintic agents along with their specific uses and dosage are described below:

Mebendazole

It has a wide spectrum of anthelmintic activity. After administration it is poorly absorbed and approximately 90 percent of the drug is passed in faeces. Complete clearance of the parasites from the GIT may take up to three days. Albendazole is similar to mebendazole, but has a longer duration of action.

Levamisole

It is a synthetic derivative, highly effective in eradicating ascariasis and ancylostomiasis.

Niclosamide

It acts by inhibiting anaerobic phosphorylation of ADP by the mitochondria of the parasite. It is used in taeniasis.

Piperazine Citrate

It is an alternative drug for treatment of ascariasis and pinworms.

Pyrantel Pamoate

It is a broad spectrum anthelmintic effective in pinworm, ascariasis and hook worm infestation.

Diethylcarbamazine

It is indicated in filariasis and tropical eosinophilia.

Ivermectin

It is the only orally active drug against ectoparasites. It is mainly indicated in scabies, ascariasis trichuriasis, strongyloidiasis, enterobiasis, filariasis, onchocerciasis (River blindness) and elephantiasis. It is drug of choice for onchocerciasis producing long lasting reduction in microfilaria without affecting adult worm.

Praziquantel

Effective against schistosomes, other trematodes, cestodes and their larval forms but not against nematodes.

SAQ 6

a) _____ is drug of choice for all forms of amoebic infections.

b) _____ is the drug of choice in leishmaniasis.

c) _____ is used alone in cyst passers since it is a very effective luminal amoebicide.

d) _____ acts by stimulating ganglia of the worm which results in tonic paralysis.

e) _____ is the anthelmintic that can be safely used during pregnancy.

f) _____is the drug of choice for filariasis.

12.8 SUMMARY

- Beta lactam antibiotics having a β-lactam ring, which includes penicillin, cephalosporins, monobactams and carbapenems.
- Penicillins are primarily bacteriocidal and kill bacteria by interfering with cell wall formation.
- Sulfonamides, exert bacteriostatic action by inhibiting bacterial folate synthetase, so that folic acid is not formed which is needed for a number of metabolic reactions.
- Trimethoprim selectively inhibits bacterial dihydrofolate reductase, necessary for the conversion of dihydrofolate to tetrahydrofolic acid.
- Cephalosporins are also classified under β-lactam antibiotics as they have a β-lactam ring in their structure which is responsible for the antibacterial activity.
- Cephalosporins have been classified into four generations depending on their developmental chronology.
- Cephalosporins are bacteriocidal agents and produce this effect by inhibition of the bacterial cell wall synthesis.
- Quinolones are synthetic antimicrobial agents primarily effective against gram negative bacteria.
- Fluoroquinolones are quinolone antimicrobial agents having one or more fluorine substitutions, relatively broad spectrum of action and effective against gram positive and gram negative organisms.
- Quinolones block bacterial DNA synthesis by inhibiting bacterial topoisomerase II (DNA gyrase) and topoisomerase IV leads to bacterial cell death.
- Erythromycin is a narrow spectrum antibiotic, bacteriostatic at low concentration and bactericidal at high concentrations.
- Macrolides inhibit bacterial protein syntheisis by binding to the 50S ribosomal subunit.

- *Entamoeba histolytica* can cause asymptomatic intestinal infection, colitis (mild to moderate), dysentery (severe intestinal infection), ameboma, liver abscess etc.
- Drug of choice for treatment of amoebiasis, trypanosomiasis, trichomoniasis and giardiasis are nitro-imidazole derivatives like metronidazole, tinidazole and secnidazole.
- Anthelmintics are those agents that are used in the treatment of worm infestations.
- Mebendazole and albendazole are broad spectrum antihelmintics.
- Ivermectin is the only orally active ectoparasiticide.

12.9 TERMINAL QUESTIONS

1. What are beta lactam antibiotics? Classify them.
2. What is the mechanism of action of beta-lactam antibiotics?
3. Write a note on beta-lactamase inhibitors.
4. Classify sulphonamides. What is the mechanism of action of sulphonamides?
5. What is cotrimoxazole?
6. What are quinolones?
7. What are macrolides? Classify them.
8. What are their clinical uses of macrolides?
9. Write a note about treatment of amoebiasis.
10. What are the drugs used for treatment of worm infestations in humans?

12.10 ANSWERS

Self Assessment Questions

1. a) *Penicillium chrysogenum*
   b) *Staph. aureus*
   c) Clavulanic acid, sulbactam
   d) Cell wall

2. a) Sulfonamides
   b) Trimethoprim and sulfamethoxazole
   c) Dihydrofolate reductase

3. a) Four generation

b) Parenteral
c) Third
d) Cell wall formation

4. a) DNA gyrase and topoisomerase IV
b) Nalidixic acid
c) Pefloxacin
d) Ciprofloxacin

5. a) Macrocyclic lactone ring, attached sugars
b) Primaquine
c) Inhibiting cell wall synthesis

6. a) Metronidazole
b) Sodium stibogluconate
c) Diloxanide furoate
d) Levamisole
e) Piperazine citrate
f) Diethyl carbamazine

Terminal Questions

1. Beta-lactam antibiotics are those antibiotics which have a four membered beta lactam ring in their structure. The antibacterial activity is dependent on the integrity of this beta-lactam ring. The drugs which are included in this category are:

   Penicillins, Cephalosporins, Carbapenems, and Monopenams

2. The beta-lactam antibiotics are primarily active against gram positive organisms as they possess the cell wall, which is the site of action of beta-lactam antibiotics. The bacterial cell wall is a rigid outer layer that completely surrounds the cytoplasmic membrane. Penicillin and other beta-lactam antibiotics inhibit bacterial growth by interfering with a specific step in bacterial cell wall synthesis.

3. Beta-lactamase inhibitors are agents that are administered along with beta lactam antibiotics in infections caused by beta-lactamase elaborating microorganisms. These agents protect the beta lactam group of the antibiotic from the enzyme and return senstivity to the antibiotic. Clavulanic acid is a 'progressive' inhibitor of a wide variety of β-lactamases produced by gram positive and negative organisms and is obtained from Streptomyces clavuligerus. It has no antibacterial activity of its own. It is used along with amoxycillin in various infections as discussed above. Sulbactam is another semisynthetic β-lactamase inhibitor used along with ampicillin. It is related to clavulanic acid both chemically and in activity. It is indicated in gynaecological, intra-abdominal, skin and soft tissue infections.

4. Sulphonamides are bacteriostatic drugs which primarily exert their action by the inhibition of folic acid synthesis within the bacterial cell. As a result,

synthesis of nucleic acids does not take place in the bacteria and the bacteria cannot multiply. Sulphonamides can be classified as follows:

I. Highly absorbed sulfonamides

   a) Short acting: Sulfadiazine, Sulfadimidine, Sulfafurazole, Sulfamethizol

   b) Intermediate acting: Sulfamethoxazole

   c) Long acting: Sulfadimethoxine, Sulfamethoxine, Sulfamethoxypyridazine

II. Poorly absorbed sulfonamides (for GIT local action): Phthalyl sulfathiazole, Succinyl sulfathiazole, Sulfaguanidine

III. Special purpose sulfonamides: Sulfacetamide, Sulfacetamide, Sulfasalazine, Silver sulfadiazine, Mafenide propionate

5. Cotrimoxazole is a fixed dose combination of trimethoprim and sulphamethoxazole. Sulphamethoxazole is a sulphonamide and it inhibits the enzyme folate synthase. Trimethoprim is an inhibitor of the enzyme dihydro-folate-reductase. The combination produces sequential blockade of folic acid synthesis pathway. Sulphamethoxazole and trimethoprim are combined in a ratio of 5:1, as follows: Sulfamethoxazole 400 mg + Trimethoprim 80 mg.
6. Quinolones, are synthetic antimicrobial agents effective against gram negative bacteria. Although newer compounds (second generation quinolones – the Fluoroquinolones, which contain one or more fluoride atoms in the molecule) are also effective against gram positive bacteria. Quinolones block bacterial DNA synthesis by inhibiting bacterial topoisomerase II (DNA gyrase) and topoisomerase IV. Some quinolones are Ciprofloxacin, gatifloxacin, sparfloxacin, nalidixic acid, norfloxacin.
7. Macrolides antibiotics are characterized by a large or macrocyclic lactone ring with attached sugar residue(s) in their structure. They primarily inhibit protein synthesis in the bacteria by binding to the 50S ribosomal unit. As they inhibit protein synthesis, they are primarily bacteriostatic. The individual agents in this group are: erythromycin, roxithromycin, azithromycin and clarithromycin.
8. As a group, macrolides are used as an alternative to penicillin in allergic patients for upper respiratory tract infections, e.g. tonsillitis, pharyngitis and mastoiditis, pneumococcal infection and prophylaxis of rheumatic fever. Erythromycin is drug of choice in treatment of atypical pneumonia due to Mycoplasma pneumoniae, Legionnaire's pneumonia and whooping cough. It is also useful in wound and burn infections and severe impetigo not responding to topical antibiotics. Clarithromycin is used in the treatment of H. pylori infections and both clarithromycin and azithromycin are used in the treatment of tuberculosis.

9. Amoebiasis is an infectious disease caused by Entamoeba histolytica. It can cause asymptomatic intestinal infection, colitis (mild to moderate), dysentery (severe intestinal infection), ameboma, liver abscess etc. The drugs used in chemotherapy of amoebiasis are as follows:

   I) Imidazole derivatives: Metronidazole, Tinidazole, Secnidazole, Ornidazole

   II) Quinoline derivative: Iodochlorohydroxyquin, Diiodohydroxyquin, Chloroquine

   III) Emetine derivatives: Dehydroemetine, Emetine

   IV) Miscellaneous: Diloxanide furoate, Furazolidone, Paromomycin, Tetracycline

10. Anthelmintic agents are those chemical substances that are used in the treatment of worm infestations in humans. The commonly used drugs are their indications are as follows:

    Mebendazole/albendazole/thiabendazole:

    - Levamisole
    - Niclosamide
    - Piperazine (as citrate)
    - Pyrantel pamoate
    - Diethyl carbamazine
    - Ivermectin
    - Praziquantel