CHEMOTHERAPY

SPECIFIC OBJECTIVES

At the end of the class the students will be able to:

- Enlist the drugs used in chemotherapy
- Enumerate the preparation of various drugs
- Explain the actions of drugs
- Explain the use of various drugs.
- Describe the adverse effects of drugs.

Drugs used in Chemotherapy

- 1.Antibacterial drugs.
- 2.Antituberculous & Antileprotic drugs.
- 3.Antiprotozoal drugs (antiamoebic & antimalarial).
- 4.Antifungal drugs.
- 5.Antiviral drugs.
- 6.Antihelmenthic drugs.
- 7.Cytotoxic drugs.

Classification of antibacterial drugs

- 1.Inhibitors of bacterial cell wall formation as B-lactam antibiotics (penicillins,cephalosporins,carbapenems and monobactams),vancomycin & bacitracin.
- 2.Inhibitors of protein synthesis as tetracyclin,aminoglycosides,macrolides,clindamycin and chloramphenicol.
- 3.Inhibitors of nucleic acid synthesis as quinolones and rifampicin.
- 4.Inhibitors of metabolic pathways (folate antagonist) as sulphonamides,trimethoprim and co-trimoxazole.
- 5.Drugs affecting cell membrane permeability as polymyxin.

B-lactam antibiotics
I.Penicillins

- **Mechanism of action:** Bactericidal by inhibiting transpeptidation (last step in bacterial cell wall synthesis) through binding to penicillin binding proteins (PBP).
  ●B-lactamase is an enzyme secreted by some bacteria e.g staphylococci leading to inactivation of B-lactam antibiotics (resistance developed).

- **Preparations of penicillins:-** Members of this family of antibiotics differ from each other due to different groups attached to B-lactam ring. These differences include spectrum,stability to gastric acidity and susceptibility to bacterial B-lactamase enzyme.
- 1.Natural penicillins [penicillin G (benzyl penicillin) and penicillin V.
  2.Anti-staph penicillins e.g oxacillin,cloxacillin and flucloxacillin.
  3.Extended-spectrum penicillins e.g ampicillin and amoxicillin.
  4.Antipseudomonal penicillins e.g ticarcillin and carbenicillin

- **Therapeutic uses of penicillins:**
  (1)Streptococcal infections as acute tonsillitis,wound sepsis, puerperal sepsis and subacute bacterial endocarditis.
  (2)Staphylococcal infections.
  (3)Pneumococcal infections.
  (4)Meningococcal meningitis:Penicillin G or ampicillin IV+chloramph-enicol
  (5)Syphilis and gonorrhea.
  (6)Typhoid fever:amoxicillin & ampicillin.
  (7)Diphtheria,tetanus and gas gangrene + specific antitoxins.
  (8)Prophylaxis to (a)Prevent recurrence of rhumatic fever e.g benzathine penicillin 1.2 million units given monthly IMI.
  (b)Prevent subacute bacterial endocarditis with aminoglycosides.
  Adverse effects:
  1.Hypersensitivity (most important) as rashes,angioedema and anaphylactic shock.
  2.Diarrhea specially with ampicillin.
  3.Neurotoxicity as seizures specially if intrathecally injected.
  4.Platelet dysfunction.
  5.Cation disturbances e.g carbenicillin is given as Na or K salts.

II.Cephalosporins

- B-lactam antibiotics similar to penicillins in their mode of action but are more resistant to B-lactamase.There is cross allergy & cross resistance with penicillins→better avoided in patients allergic to penicillins or infections resistant to penicillins.
- **Classification of cephalosporins**:
  ●1st generation active on gm+ve cocci (strept-staph) and gm-ve organisms (E coli-Klebsiella).members include cephalexin (oral) & cefazolin (parenteral) which is used in orthopedic surgery (due to good penetration into bone & resistance to B-lactamase producing staph.).
  ●2nd generation less active on gm+ve organisms than 1st generation with extended spectrum on gm-ve organisms e.g cefuroxime & cefoxitin which is used in H.influenza and B.fragillis.

  ●3th generation with increased spectrum against gm-ve organisms e.g pseudomonas.Most agents cross the BBB so useful in serious infections of meningitis.Examples include cefoperazone,cefotaxime and ceftriaxone.

- Ceftriaxone has the longest half life with good bone penetration, crosses the BBB so used in meningitis,40% excreted in the bile so can be used in biliary tract infections & in patients with renal dysfun- ction.It is used in a single dose in treatment of gonorrhea and used in treatment of resistant cases of typhoid fever.
  ●4thgeneration cefepime which is resistant to all subtypes of B-lactamase enzyme & used in treatment of penicillin resistant streptococci. It is broad spectrum against resistant gm –ve bacilli.
- **Adverse effects of cephalosporines:**
  1.Hypersensitivity reactions.
  2.Nephrotoxicity especially if given with aminoglycosides.
  3.Local irritation→severe pain after IMI and thrombophlebitis after IVI.
  4.Platelet dysfunction & hypoprothrombinemia with cefoperazone→ bleeding (avoided by vitamin K).
  5.Intolerance to alcohol (cefoperazone)→disulfiram like reaction.

Other B-lactam antibiotics

- **III.Carbapenems e.g Imipenem**.
  ●The broasest spectrum B-lactam.It is effective against gm+ve, gm-ve organisms and anaerobes.
  ●It is resistant to B-lactamase.
  ●It is given IV,metabolized in the renal tubules to inactive nephrotoxic metabolite and **Cilastatin** is combined with imipenem to inhibit renal metabolism.
  ●It has extensive cross allergy with penicillin.
- **IV.Monobactams e.g Aztreonam**
  ●Has a narrow spectrum against aerobic gram-ve organisms.
  ●It is resistant to B-lactamase.
  ●It is given IM and IV and relatively non-toxic.
  ●No cross allergy with other B-lactam antibiotics.

Other agents inhibiting cell wall synthesis (Vancomycin & Bacitracin

- Vancomycin is a bactericidal acting by inhibition of cell wall synthesis at an earlier stage than B-lactam antibiotics.It is effective against gm+ve organisms.
- **Pharmacokinetics of vancomycin:**
  -Given by IV infusion but given orally in antibiotic-induced pseudo-membraneous colitis due to clostridium deficile.
  -Excreted renally so we adjust the dose in renal dysfunction.
- **Therapeutic uses of vancomycin:**
  1.Oxacillin-resistant staph aureus (ORSA) drug of choice.
  2.Serious allergy to penicillins.
  3.Pseudomembraneous colitis following antibiotic use.
- **Adverse effects of vancomycin:**
  1.Fever,rigors and phlebitis.
  2.Shock with rapid infusion→red man syndrome due to histamine release.
  3.Hearing affection or loss.
  4.Renal dysfunction.
- **Bacitracin:** Effective against gm+ve organisms.Restricted to topical application because it is potentially nephrotoxic.

Tetracyclins

(Tetracyclin-Doxycyclin-Minocyclin-Demeclocyclin)

- Mechanism of action by binding to 30s ribosomal bacterial subunit leading to inhibition of binding of tRNA and inhibition of protein synthesis.
- **Therapeutic uses:**
  Chlamydial infections – Cholera – Amoebiasis - Acne vulgaris - Mycoplasma pneumonia - Meningococcal carriers - Brucellosis - Demeclocyclin is used in treatment of syndrome of inappropriate ADH secretion as it antagonizes the effect of ADH on renal tubules.
- **Adverse effects & contraindications:**
  1.Epigastric pain due to gastric irritation (non-compliance).
  2.Teeth discoloration & bone hypoplasia as it chelate calcium (contraindicated in pregnancy,lactation and children less than 8 y).
  3.Hepatotoxicity.
  4.Phototoxicity.
  5.Suprainfection with candida,clostredium deficile or resistant staph in the intestine.
  6.Fanconi-like syndrome: renal tubular dysfunction with outdated tetracyclin.

Aminoglycosides (streptomycin-gentamycin-tobramycin-amikacin-netilmicin-neomycin)

- **Mechanism of action** by irreversible binding with 30s ribosomal bacterial subunits leading to inhibition of protein synthesis.

- **Spectrum & activity:** effective against aerobic organisms but ineffective against anerobes as it requires oxygen for transport into cells.Act mainly against gm-ve organisms e.g E.coli,pseudomonas and cholera.Gentamycin is also effective against staph.

- **Therapeutic uses:**
  1.Peritonitis,septicemia & pneumonia.
  2.Subacute bacterial endocarditis.
  3.Complicated urinary tract infections.
  4.Streptomycin is used in tuberculosis.
  5.Amikacin & Netilmicin are reserved for resistant cases.
  6.Neomycin is used only orally in hepatic coma (not absorbed) & topically in infected wounds.It is too toxic for systemic use.

- **Pharmacokinetics:**
  1.They are not absorbed orally and have to be given parenterally.
  2.They don`t cross the BBB even when the meninges are inflammed.
  3.They are concentrated in the renal cortex,perilymph and endolymph of the inner ear→nephrotoxicity & ototoxicity.
  4.They are excreted unchanged through the kidneys so caution should be taken in patients with renal dysfunction.
- **Adverse effects of aminoglycosides:**
  1.Nephrotoxicity as acute tubular necrosis which may be irrevesible.Risk ↑by dehydration,old age,↑dose,↑duration of treatment and concurrent use of nephrotoxic drugs.
  2.Ototoxicity which may be irreversible.
  3.Neuromuscular paralysis especially after intraperitoneal infusion of large doses (inhibits acetyl choline release).
  4.Allergy as contact dermatitis with topically applied neomycin.
- **Spectinomycin:**
  Is structurally related to aminoglycosides and inhibits protein synthesis at 30s ribosomal subunit.Its use is limited to gonorrhea in patients allergic to penicillins or patients with penicillin-resistant gonococcal infection (single deep IMI) .

Macrolides (Erythromycin,Clarithromycin, Azithromycin and Roxithromycin)

- **Mechanism of action** is inhibition of protein synthesis by binding with 50s bacterial ribosomal subunits.
- Spectrum and uses of erythromycin:
  1.Drug of choice in patients having spirochetes or gm+ve coccal infections with allergy to B-lactam antibiotics.
  2.Drug of choice in urogenital chlamydial infection in pregnancy and mycoplasma pneumonia in children (tetracyclines contraindicated).
- **Adverse effects of erythromycin**:
  1.Epigastric pain & intestinal colic.
  2.Cholestatic jaundice (contraindicated in liver disease).
  3.Ototoxicity & transient deafness.
  4.Thrombophlebitis if injected IV.
- **Azithromycin:** 1.Less effective on gm+ve & more effective on gm-ve organisms than erythromycin.
  2.Potent against chlamydia.
  3.Long half life allowing once daily dose.
  4.Excreted through the bile.

Clindamycin & Chloramphenicol

- It acts by binding to 50s ribosomal subunit inhibiting protein synthesis.
- It is used specifically against anerobic infections and it is also effective against gm+ve organisms as staph and strept.infections.
- It is used in bone infection as it has good penetration into bones.
- **Adverse effects**: 1.Pseudomembraneous colitis. 2.Skin rash.
- 3.Diarrhea. 4.Liver dysfunction.
- **Chloramphenicol:** Acts by binding to 50s ribosomal subunits inhibiting protein synthesis.
- **Therapeutic uses of chloramphenicol:**
  1.Typhoid fever but replaced by fluorinated quinolones.
  2.Bacterial meningitis (H.influenza) + penicillin.
  3.Topically in eye infections e.g conjunctivitis.
  4.Anerobic infections e.g anerobic brain abscess.
- **Adverse effects of chloramphenicol:**
  1.GIT upset & superinfection.
  2.Bone marrow depression (dose independent or idiosyncrasy).
  3.Grey baby syndrome in neonates. 4.Optic neuritis.
  5.Inhibition of hepatic microsomal enzymes →drug interaction.

Inhibitors of nucleic acid synthesis (I.Fluoroquinolones:ciprofloxacin-ofloxacin-norfloxacin & pefloxacin)

- **Mechanism of action** by inhibiting DNA gyrase enzyme which is responsible for unwinding of double stranded DNA leading to inhibition of DNA replication.
- **Therapeutic uses**:
  1.Typhoid fever.
  2.Urinary tract infections (gm-ve bacilli) & prostatitis.
  3.Gonorrhea (ofloxacin single dose).
  4.Respiratory tract infections not responding to B-lactam antibiotics.
  5.Bone and soft tissue infections.
- **Adverse effects & contraindications**:
  1.CNS symptoms as headache,dizziness & phototoxicity.
  2.Nephrotoxicity.
  3.Arthropathy in children less than 18 years.
  4.Inhibit liver microsomal enzymes → dangerous drug interactiona as ↑ level of theophylline & warfarin.
  ●Quinolones are contraindicated in pregnancy,lactation & patients less than 18 years as it may lead to arthropathy.

Inhibitors of nucleic acid synthesis (II.Rifampicin)

- **Mechanism of action** by inhibiting the enzyme DNA-dependent RNA polymerase in mycobacteria (but not in human cells)→ inhibition of RNA synthesis.
- **Therapeutic uses**:
  1.Potent bactericidal drug against mycobacteria tuberculosis at all sites (600mg/d with other antituberculous drugs for 6-18 months).
  2.Treatment of leprosy.
  3.Prophylaxis of meningitis.
  4.Oxacellin-resistant staph aureus.
- **Adverse effects**:
  1.Skin rash,fever and GIT upset.
  2.Liver damage & jaundice.
  3.Enzyme induction→serious drug interaction.
  4.An influenzae-like syndrome (malaise,headache and fever).
  5.Red discoloration of the urine,tears and sputum.
  6.Resistance rapid due to modification of DNA-dependent RNA polymerase by chromosomal mutation.

Folate-Antagonists (Sulfonamides,Trimethoprim & Co-Trimethoprim)

- **Sulfonamides:** sulfadiazine,sulfadoxine, sulfacetamide,sulfasalazine and sulfamethoxazole.
- **Mechanism of action:** sulfonamides are structural analogues of PABA.They compete with it for the enzyme dihydropteroate synthetase leading to inhibition of folic acid synthesis with consequent inhibition of DNA & RNA synthesis (human cells utilize already formed folic acid).
- **Therapeutic uses**:
  1. Eye infection (topical sulfacetamide).
  2. Burns (topical silver sulfadiazine).
  3. Ulcerative colitis (sulfasalazine).
  4. Malaria (sulfadoxine combined with pyrimethamine).

- **Adverse effects:**
  1.Hypersensitivity reactions.
  2.Crystalluria & nephrotoxicity due to insoluble metabolite precipitation and can be avoided by ↑ fluid intake & alkalinization of urine.
  3.Hemopoietic disturbances as granulocytopenia ,thrombocytopenia and hemolytic anemia in patients with G6PD deficiency.
  4.Kernicterus as sulfonamides displaces bilirubin from plasm protein → cross BBB in premature infants→CNS depression.
  5.Drug interaction as it ↑ plasma level of oral hypoglycemic & anticoagulants due to plasma protein displacement.
- **Trimethoprim:**
  It inhibits dihydrofolate reductase which converts folic acid into folinic acid (tetrahydrofolic acid) which is essential for DNA synthesis
  It is combined with sulfamethoxazole to form co-trimoxazole.
- **Adverse effects**:
  1.Megaloplastic anemia due to folate deficiency & avoided by folinic acid administration.
  2.Granulocytopenia & leucopenia.

- **Co-Trimoxazole:**
  It is a combination of sulfamethoxazole(400mg)+trimethoprim(80mg)

- **Mechanism of action:** as sufonamides and trimethoprim.

- **Advantages of Co-trimoxazole**:
  1.Synergestic combination.
  2.More potent.
  3.Less and delayed bacterial resistance.
  4.Bactericidal & wider spectrum including proteus,salmonella,shigella,Hemophilus influenza & gonococci.

- **Theraapeutic uses**:
  1.Urinary tract infections,gonococcal urethritis and prostatitis.
  2.Salmonella & shigella infections.
  3.Respiratory tract infections due to H.influenza & pneumococci.

- **Adverse effects**:
  As sulfonamides and trimethoprim.

Anti-Tuberculous Drugs

- **First-line drugs:** Isoniazid-Rifampicin-Pyrazinamide-Ethambutol.
- **Second-line drugs:** Streptomycin-Capreomycin-Clarithromycin-Ciprofloxacin and cycloserine.They are used only in patients with infection resistant to the first line drugs or patients can`t tolerate the first line drugs.
  ●To prevent drug resistance we use combination of drugs.
  ●To prevent relapse after treatment continue treatment for 18-24 months with two drugs isoniazid & rifampicin are the best.

- **Effective course regimens**:
  1.Initial phase for 2 months give 3 drugs together isoniazid,rifampicin & pyrazinamide (+ethambutol if the organism is suspected to be resistant).
- 2.Continuation phase with two drugs isoniazid & rifampicin for 4-6 months or long term treatment for 18-24 months for patients with TB meningitis,bone & joint affection or drug-resistant cases.

Isoniazid (Isonicotinic acid hydrazide;INH)

- **Mechanism of action**:
  1.Inhibition of cell wall synthesis by inhibiting enzymes essential for mycolic acid synthesis (an important constituent of mycobacterial cell wall).
  2.Disorganization of cell metabolism.
- **Therapeutic uses**:
  1.Treatment of active cases of TB (5mg/kg/d) with other anti-TB drugs & pyridoxine 10mg/100 mg INH to avoid neurotoxicity.
  2.Chemoprophylaxis as the sole drug (300mg/d for 9-12 months) in Close contacts to active TB case.
  Adverse effects of INH:
  1.Allergic skin eruption (commonest).
  2.Hepatotoxicity occuring more in elderly.
  3.Neurotoxicity with slow acetylators (due to B_6 deficiency) →peripheral neuritis, insomnia, memory impairment,optic neuritis and convulsions.
  4.Hemolytic anemia in G6PD deficiency.
  5.Systemic lupus erythematosis (SLE)-like syndrome (vasculitis & arthritis).
  6.Enzyme inhibition in the liver →↑serum phenytoin & carbamazepine levels.

- **Ethambutol** (single daily dose 15mg/kg) It is a selective anti-TB drug,taken up by the actively growing mycobacteria,to inhibit RNA synthesis & growth.It is less active than INH & rifampicin.
- **Adverse Effects:** Optic neuritis (dose related & reversible) starts by red/green color blindness followed by a decrease in visual acuity.
  Pyrazinamide: It is a tuberculostatic and inhibits intracellular mycobacteria present inside macrophages (mechanism of action is unknown).
- **Adverse effects:**
  1.Hyperuricemia & arthralgia (monitor serum uric acid level & give NSAIDs).
  2.Hepatotoxicity in high doses (assess liver function before treatment).
  3.GIT disturbances,malaise and fever.

Treatment of Amebiasis

- Amebiasis is an infection with Entameba histolytica produced by ingestion of cysts of this parasite.In the intestine the cysts develop into trophozoites (active invasive form) which adhere to colonic epithelial cells.Trophozoites lyse host cells & invade the submucosa resulting in:
  (A)Bowel lumen amebiasis:A symptomatic but cysts pass in the stool transmit infection to others.Treatment is directed at eradicating cysts with luminal amebicidal drugs:
  Diloxanide-Iodoquinol-Paromomycin-Tetracyclin.

- (B)Tissue invating amebiasis may give rise to dysentery,amebic granuloma in the intestinal wall,hepatitis or liver abscess and extra-intestinal diseases.We use tissue amebicidal drugs:
  Nitroimidazole (metronidazole or tinidazole)-Dehydroemetine-Chloroquine.

Metronidazole

- **Mechanism of action**: Within an aerobis bacteria & sensitive protozoa the nitro group of the drug is reduced into toxic O_2 product which bind to DNA causing its damage,disrupting transcription & replication.
- **Therapeutic uses**:
  1.Antiprotozoal as it is the drug of first choice in treatment of
  (a)Amebiasis: trophoziticidal but ineffective against luminal cysts so it should be used with diloxanide.
  (b)Giardiasis.
  (c)Trichomoniasis 2gm as a single oral dose.
  2.Anti-anerobe e.g dental infection,pseudomembraneous colitis and anerobic brain abscess.
- **Adverse effects**:
  1.GIT disturbances,glossitis with metalic taste in the mouth.
  2.CNS manifestations:headache,dizziness,insomnia and sensory neuropathy. 3.Dysuria and dark urine.
  4.Rash & neutropenia.
  5.Teratogenic so not used in pregnancy.
  6.Inhibits liver metabolizing enzymes potentiating warfarin and disulfiram reaction with alcohol.

Treatment of Malaria

- Malaria is a protozoal infection caused by 4 species of plasmodia (vivax,ovale,malariae & falciparum).
- The female anopheles mosqito injects **sporozoites** which can develop in the liver into **tissue schizonts →merozoites** →RBCs transformed into **blood schizonts** containing numerous merozoites Rupture of infected RBCs and release of merozoites → clinical attack,then merozoites re-enter fresh RBCs.
- Some merozoites are differentiated inside RBCs into male & female **gametocytes** (the sexual form of the parasite),where they remain until taken by female anopheles mosquito,where sexual cycle takes place to form sporozoites ,which are stored in the salivary gland of the mosquito for re-infection.

- **Hypnozoites** (resting form) formed in the liver and lasts for months or years to be reactivated and release merozoites again → relapse. This occurs with plasmodium vivax & ovale (relapsing malaria).

Antimalarial Drugs

- I.Blood schizontocides:
  (a)Chloroquine,quinine,quinidine & mefloquine).
  (b)Antifolates (pyrimethamine,proguanil,sulfadoxine & sulfone).
  II.Tissue schizontocides:Primaquine. III.Gametocytocides (prevent transmission):Primaquine.
- **CHLOROQUINE:** blood schizonticide,that kills erythrocytic forms & prevents clinical attacks. It has no effect on hepatic forms of the parasite.
- **Mechanism of action:** It is concentrated in infected RBCs →
  1.Inhibits parasite hemoglobin digestion→↓ nutrient amino acids for the parasite.
  2.Inhibits heme polymerase (converts toxic free heme into harmless hemozoin) → accumulation of toxic heme.
  Therapeutic uses of chloroquine:
  1.Antimalarial used in treatment of acute attacks,given orally,SC,IM & slow IV infusion.It is also used in chemoprophylaxis in all forms except chloroquine resistant falciparum.
  2.Amebic hepatitis or abscess.
  3.Anti-inflammatory in rheumatoid arthritis and lupus erythematosus.

- **Adverse effects:**
  1.Itching especially in africans (common).
  2.GIT disturbances (anorexia,nausea & vomiting) so given after meals.
  3.Headache,dizziness & blurring of vision.
  4.Bone marrow depression & hemolytic anemia in G6PD ↓ (rare).
  5.Ototoxicity, confusion,psychosis & seizures (rare).
  6.Hypotension & fatal arrhythmias with high IV dose.
  7.Corneal deposits & retinopathy (prolonged high dose).
  8.Myopathy & peripheral neuritis (prolonged high dose).
- **QUININE:** Its mechanism of action as chloroquine.
  It is the main drug for resistant P.falciparum strains. It is not used for chemoprophylaxis.
  Adverse effects:
  (A)Common
  1.Compliance is poor due to bitter taste & GIT irritation (nausea & vomiting).
  2.Cinchonism:nausea,tinnitus,dizziness, headache,blurred vision,hypotension & dysrhythmias.
  3.CNS:confusion,delerium & coma.

- **(B)Rare**
  1.Hypoglycemia as it stimulates insulin release,so in patients with falciparum infection and treated with quinine we should differentiate between coma caused by cerebral malaria & hypoglycemic coma.
  2.Hypersensitivity reactions.
  3.Hemolytic anemia (black water fever) → renal failure which may be fatal.
  III.Mefloquine: Blood schizontocid effective against resistant organisms to chloroquine.In P.vivax & ovale it should be followed by a course of primaquine.Mechanism of action as chloroquine.Used in treatment of chloroquine resistant cases & in chemoprophylaxis.
- **Adverse effects & contraindications:**
  1.GIT disturbances.
  2.Teratogenic (contraindicated in pregnancy).
  3.Delayed A-V nodal conduction (contraindicated with BB & CCB).
  4.Leucocytosis,thrombocytopenia & elevated hepatic enzymes.
  5.CNS stimulation with headache,insomnia up to convulsions (contraindicated in epilepsy).
- **IV.Halofantrine:** It is a blood schizontocide active against all species of malaria,including multi-resistant P.falciparum.It is given orally.Its side effects include abdominal pain,headache,pruritus and serious cardiac problems (use limited to resistant organisms).

- **Antifolates:** (A)Drugs inhibiting folate synthesis (sulfonamides mainly sulfadoxine) inhibit conversion of PABA to folic acid (compete with PABA for the enzyme dihydropteroate synthetase). (B)Drugs inhibiting folate utilization (pyrimethamine & proguanil) inhibit conversion of folic into folinic acid by inhibiting dihydrofolate reductase.We use a combination of the two groups to inhibit two sequential steps → synergistic action.

- **Therapeutic uses of antifolates**:
  1.Antimalarial to treat chloroquine resistant P.falciparum,sulfadoxine + pyrimethamine (Fansidar),unreliable in p.ovale or p.malariae or in severe malaria.It can be also used in chemoprophylaxis in all types.
  2.Toxoplasmosis (pyrimethamine + sulfadiazine).
  3.Pneumonia due to pneumocystis carinii (fatal fungal infection in patients with AIDS ,fungus is structurally similar to protozoa)

- **Adverse effects of antifolates**:
  (a) Pyrimethamine or proguanil:
  1.GIT upset, skin rash & itching.
  2.Mouth ulcers & alopecia. 3.Megaloblastic anemia.
  (b)Sulfonamides :see before.

- **PRIMAQUINE:** Tissue schizontocide (for p.vivax & ovale) & gametocide in all species.Its mechanism of action is unknown.
- **Therapeutic uses:**
  1.Radical cure of vivax & ovale ,usually given after blood schizontocide to eradicate the hypnozoites.
  2.Prevent transmission in all species (gametocides).
- **Adverse effects:**
  1.Dose-related GIT disturbances.
  2.Methemoglobinemia with cyanosis.
  3.Hemolytic anemia in G6PD deficiency.
  4.Dysrhythmias & bone marrow depression.

- ***General adverse effects of cytotoxic drugs:***
  1.GIT nausea & vomiting followed by stomatitis,oral and intestinal ulcers with malabsorption & candidiasis with diarrhea.
  2.Bone marrow depression with neutropenia,thrombocytopenia & anemia.
  3.Immunosuppression with increased liability for infections.
  4.Reversible alopecia.
  5.Delayed wound healing.
  6.Gonadal effects sterility & teratogenicity so pregnancy should be avoided during & for several months after therapy.
  7.Hyperuricemia which may precipitate gout or urate nephropathy.
  8.Carcinogenesis.

Antifungal Drugs

- Medically important fungal infections are classified into:
  I.Superficial fungal infections :
  (a)Dermatomycosis caused by dermatophytes affecting the dead keratinous structures of the skin,nail & hair →tinea capitis,tinea pedid,tinea cruris…
  (b)Candidiasis caused by candida albicans.
  II.Deep fungal infections affecting deep layers of the skin & mucus membranes as well as internal organs e.g pneumonia,meningitis..

- **Classification of antifungal drugs** according to their route of administration
  1.**Systemic** antifungal drugs used for **systemic fungal infections** : Amphotericin-B- Azoles including imidazoles & triazoles-Flucytosine.
  2.**Systemic** antifungal drugs used for **superficial fungal infections**: Griseofulvin-Terbinafine.
  3.**Topical** antifungal drugs:Nystatin-Amphotericin B-Azoles-Terbinafine - Miscellaneous drugs.

AMPHOTERICIN-B

- It is a broad spectrum fungicidal drug given systemically as well as locally.It binds firmly & selectively to ergosterol in the fungal cell membrane → formation of pores in the cell membrane → disturbance in the cell membrane permeability & transport → leakage of intracellular ions & enzymes → fungal cell death.
- **Therapeutic uses**:
  1.The drug of choice for most systemic fungal infections.
  2.Combined with flucytosine in cryptococcal meningitis to↓resistance
  It crosses membranes poorly so injected where needed
  (a)Slow IV infusion (hospitalized patients)diluted in 5% dextrose to avoid toxicity. (b)Locally: intrathecal-intra-articular-intravesical-eye drops-tablets for GIT fungal infection ,not absorbed systemically.
- **Adverse effects:** (A)Immediate (during IV infusion)
  1.Rigors,fever,headache,vomiting and hypotension.
  2.Hypersensitivity reactions & anaphylaxis.
  (B)Delayed (high protein bound,slowly excreted in the urine and t½ 15 days).
  1.Nephrotoxicity in >80% of patients.
  2.Hypokalemia.
  3.Normochromic anemia.
  4.Thrombophlebitis.
  5.Hepatic dysfunction.
  6.CNS stimulation→convulsions (more with intrathecal).

- **AZOLES:** Broad spectrum fungistatic drugs less toxic than amphotericin-B. They have the five membered azole ring that contains either two (imidazoles) or three (triazoles) nitrogen molecules.
- **Mechanism:**Inhibit synthesis of fungal cell membrane by inhibition of fungal cytochrome P450-dependent 14 α demethylase enzyme which is essential for conversion of lanosterol to ergosterol.
- **Imidazoles (Ketoconazole):** It is the 1st oral broad spectrum antifungal drug.
  Therapeutic uses:
  1.Broad spectrum antifungal drug for superficial & systemic fungal infection (ineffective in fungal meningitis since it doesn`t cross BBB).
  2.Advanced androgen-dependent cancer prostate.It is available topically (cream & shampoo)as well as tablets.
- **Adverse effects:**
  1.Liver toxicity (may progress after stopping the drug & may be fatal). 2.Blocks synthesis of adrenal & gonadal steroids due to inhibition of human cytochrome P450 enzyme resulting in:
  (a)Gynecomastia,↓libido and infertility.
  (b)Menstrual irregularity in females.
  3.GIT disturbances (nausea,vomiting & diarrhea).
  4.Pruritus & skin rash.
  5.Enzyme inhibition in the liver → drug interactions.

- **(B)TRIAZOLES:**

- **I.ITRACONAZOLE:** It is a broad spectrum antifungal drug given orally after meal or IVI.Its absorption is increased by low gastric PH.It doesn`t penetrate to the CSF.
  Advantages: More potent with less side effects than ketoconazole & no effect on mammalian steroids (high selectivity against fungi).
  Adverse effects:
  1.GIT disturbances as nausea & vomiting.
  2.Headache,hypokalemia & hypersensitivity reactions.
- II.**FLUCONAZOLE:** It is a broad spectrum antifungal drug given orall or IV.
  Advantages:
  1.Excellent bioavailability independent of food intake.
  2.Reaches high concentration in CSF & occular fluid.
  3.Less inhibition of hepatic microsomal enzymes.
  4.Better GIT tolerance.
  Adverse effects (mild):
  1.Nausea & intestinal colic.
  2.Skin reactions.
  3.Headache.
  4.Hepatitis (rare).

- **FLUCYTOSINE:**
  ●It is converted within the fungal (not human cells) into 5-fluorouracil ,then to cytotoxic phosphorylated metabolites which inhibit DNA & RNA synthesis.
  ●Used in candidiasis & cryptococcal meningitis.
  ●It given orally or intravenously.
  ●It is excreted unchanged in the urine & the dose should be adjusted in renal dysfunction.
  Adverse effects:
  1.Enterocolitis. 2.Long term use with large doses results in (a)Bone marrow depression with neutropenia,anemia and thrombocytopenia. (b)Alopecia. (c)Hepatitis (rare).
- **Systemic antifungal drugs for superficial infections:**
- **I.Griseofulvin:** It is a narrow spectrum gungistatic drug given orally. Its absorption is affected by the presence of food.It prevents fungal growth by inhibiting microtubular function→inhibition of mitosis.
  It also inhibits nucleic acid synthesis.It is used in treatment of dermatophytosis of the skin,hair and nail.
  Adverse effects: 1.Hypersensitivity reactions (rashes & fever).
  2.Photosensitivity. 3.Mental confusion. 4.Headache.
  5.Hepatotoxicity. 6.GIT disturbances (nausea,vomiting & diarrhea).
  7.Induction of liver metabolizing enzymes.

- **II.Terbinafine:**
  It is highly lipophilic & keratophilic fungicidal drug given orally & topically where it is taken up by the skin ,nail and adipse tissue.
  Mechanism: It selectively inhibits squaline epoxidase enzyme which is involved in ergosterol synthesis from squaline in fungal cell membrane → accumulation of toxic squaline within the cell → cell death.
  Uses: It has a narrow spectrum for dermatophytosis of skin & nail.
  Adverse effects:
  1.GIT disturbances. 2.Pruritus & skin rash.
  3.Headache & dizziness. 4.Joint & muscle pain.
  5.Rarely hepatitis.
- **Topical antifungal drugs:**
  1.Polyene antibiotics
  (a)NYSTATIN: Pore formation similar to amphotericin-B.
  ●It is a narrow spectrum fungicidal against candidiasis of the skin & mucous membranes (vagina or GIT) & oral thrush (1stchoice).
  ●Preparations given locally as it is too toxic for systemic use. Suspension & tablets act locally in the GIT(not absorbed systemiclly) ,pessaries applied vaginally and cream or powder for the skin.
  (b)Amphotericin-B: discussed before.

- **II.Azoles** (broad spectrum):
  (a)Clotrimazole & miconazole are used in candidiasis & dermatophytosis.
  (b)Ketoconazole effective in seborrheic dermatitis.
  (c)Isoconazole for vaginal candidiasis.
  (d)Ticonazole for fungal nail infection.
- **III.Terbinafine:** discussed before.
- **IV.Miscellaneous:**
  1.Cyclopirox olamine inhibits cell membrane protein synthesis.
  2.Haloprogin (both 1&2 used for candida & dermatophytes.
  3.Whitefield ointment (benzoic acid [fungistatic] +salicylic acid [keratolytic]).
  4.Tolnaftate: inhibits squaline epoxidation.
  NB.3 & 4 are used in treatment of dermatophytosis.

Antiviral Drugs

- Viruses are obligate intracellular parasites without metabolic machinery.In ordrer to replicate they have to enter a living host cell and use its metabolic processes.
- Virus replication consists of the following steps:
  1.Adsorption to and penetration of susceptible cells.
  2.Uncoating & the nucleic acid of the virus then uses the cell machinery for synthesis of non structural proteins e.g nucleic acid polymerase,structural proteins of the coat and RNA&DNA synthesis.
  3.Assembly of the viral particles and their release from the cell.
- **Mechanism of action of antiviral drugs:**
  1.Inhibition of adsorption & penetration:gamma globulin.
  2.Inhibition of uncoating of the virus:amantadine & remantadine.
  3.Inhibition of DNA polymerase:acyclovir,ganciclovir & ribavirin.
  4.Inhibition of reverse transcriptase:zidovudine,didanosine and lamivudine.
  5.Inhibition of protease: saquinavir,indinavir & ritonavir.
  6.Inhibition of assembly of viral particles:rifampicin.
  7.Modulation of the host immune system **(immunomodulators): Interferon.**

- **Immunoglobulins:**
  ●Contain antibodies against viral envelop which can neutralize some viruses and prevent their adsorption to host cells.
  ●If used before the onset of the signs & symptoms may attenuate or prevent measles,infectious hepatitis,rabies and poliomyelitis.
  ●It produce passive immunization and the protective effect lasts for 2-3 w.
  ●It is given IM or IV once,may be repeated 2-3 weeks later accord- ing to the incubation period.
- **Amantadine:**
  Inhibits virus penetration & uncoating → inhibition of viral nucleic acid release into the cytoplasm of the cell → inhibition of replication.
- Therapeutic uses:
  1.Antiviral against influenza A for treatment & prophylaxis.
  2.Treatment of parkinsonism (↑ release of dopamine in the basal ganglia).
- Side effects:
  Insomnia,slurred speech,ataxia & excitement up to convulsions.
- **Remantadine** is similar but it has longer t½ and fewer side effects.
- **ACYCLOVIR:**
  It is a prodrug taken up by the infected hodt cells to be phosphorylated (activated) by virus kinase to acyclovir-MP and then to the active triphosph- ate by host cell`s kinases. The triphosphate inhibits viral DNA polymerase & terminates biosynthesis of viral DNA strand.

- Therapeutic uses:
  1.Varicella-zoster infections (Herpes zoster & chickenpox).
  2.Herpes simplex (mucocutaneous,genital and H.encephalitis).
- Adverse effects: (mild & tolerated)
  1.GIT disturbances as nausea & vomiting.
  2.IV route → local inflammation if there is extravasation,or renal dysfunction due to crystalluria (adequate hydration & slow infusion).
  3.Headache,confusion,tremors or seizures.
  4.Topically in the eye → stinging sensation.
  5.Resistance.
- **GANCICLOVIR:**
  ●A prodrug with a mechanism similar to acyclovir.
  ●It is the drug of choice in life-threatening cytomegalovirus (CMV) pneumonia (oral or IV) or retinitis (intraoccular implant) in immuno-compromized patients.
- Adverse effects: (serious)
  1.Anemia,granulocytopenia & thrombocytopenia.
  2.Potential carcinogenicity.
  3.Vitreous hemorrhage and retinal detachment (intraocular implant).
- **RIBAVIRIN:** It has a mechanism of action similar to acyclovir.
- Therapeutic uses:
  1.Respiratory syncytial viral infection in infants (aerosol).

- 2.Influenza A & B viral infection.
  3.Viral hepatitis.
  4.Lassa fever (drug of choice).
  Adverse effects:
  1.Mild GIT disturbances if given orally.
  2.Respiratory irritation,rash & conjunctivitis with aerosol.
  3.Teratogenicity & mutagenicity.
- **ZIDOVUDINE:** phosphorylated to triphosphate which inhibits viral reverse transcriptase.Resistance develops due to rapid mutation in the reverse transcriptase. It is used in treatment of HIV (human immune deficiency virus) infection (orally & IV).
  Adverse effects:
  1.Megaloblastic anemia, thrombocytopenia & neutropenia (most common with long term use).
  2.GIT upset and severe hepatomegaly.
  3.Insomnia,headache up to convulsions.
  4.Flue-like syndrome.
  5.Nail hyperpigmentation and myopathy.
- **PROTEASE INHIBITORS** (saquinavir-indinavir-ritonavir): During replication in HIV the mRNA is translated into inert polypeptides which require a virus specific protease to cleave them into structural & functional proteins of the mature virus.Protease inhibitors disrupt this essential process.

- Adverse effects:
  1.Redistribution of body fat with cushingoid appearance.
  2.Hyperlipidemia,glucose intolerance & insulin resistance.
  3.Inhibit liver metabolizing enzymes.
  4.GIT disturbances as nausea & vomiting (they are all given orally).
- **IMMUNOMODULATORS:**
  Interferons(IFN) which are classified into 3 types α,β & gamma.
  ●α&β IFN are produced by B&T lymphocytes, macrophages and fibroplasts in response to virus infection → antiviral action.
  ●Gamma IFN is produced only by T lymphocytes in response to viral & nonviral organisms as bacteria & protozoa.
- Mechanism of action:
  IFNs bind to a specific receptors on the host cell membrane and induce the synthesis of enzymes (in the host cell ribosomes) that inhibit the translation of viral mRNA into viral proteins and thus stop the viral replication.
- Therapeutic uses of IFNs:
  1.Antiviral in Chronic active hepatitis (B,C and D),HIV infection and herpes infection.
  2.Cytotoxic in hairy cell leukemia,Kaposi sarcoma in AIDS & genital warts.

- Adverse effects of IFNs:
  1.Flue-like symptoms as fever,headache,malaise and myalgia.
  2.Granulocytopenia & thrombocytopenia (common due to bone marrow depression).
  3.Cardiac dysrhythmias & hypotension.
  4.Elevated serum hepatic transaminases.
  5.Nausea and anorexia sufficient to induce weight loss.
  6.Alopecia.
  7.Thyroid dysfunction (due to induction of autoantibodies).
  8.Severe neuropsychiatric side effects may occur as convulsions & depression.

Cytotoxic Drugs

- ***Classification:***
  1.Alkylating agents:
  As cyclophosphamide-thiotepa-busulfan, melphalan,carmustine, lomustine & cisplatin.They act by transfering their alkyl groups to DNA resulting in either DNA strand breakage or cross linking of the two strands so that normal replication is prevented.
  2.Antimetabolites:
  As methotrexate,6-mercaptopurines, fluorouracil and cytarabine. They compete with natural metabolites blocking one or more of the metabolic pathways involved in DNA synthesis.
  3.Antibiotics:
  As actinomycin D ,bleomycin, mitomycin & adriamycin.They bind to DNA & block synthesis of DNA & RNA thus interfering with cell replication.
  4.Mitotic Inhibitors:
  Vinca alkaloids (vinblastine & vincristine).They bind to the microtubule protein tubulin and thus inhibit spindle formation resulting in mitotic arrest.

- ***5.Hormones & Antihormones:***
  Tumors derived from hormone-sensitive tissues can be inhibited by:-
  (a)Hormones with opposing action e.g estrogen for treatment of cancer prostate.
  (b)Hormone receptor antagonist e.g tamoxifen (block estrogen receptors) for treatment of cancer breast.
  (c)Hormone synthesis inhibitors e.g aminoglutethimide (inhibits steroid hormones synthesis.
  (d)Glucocorticoids for leukemias & lymphomas.
- ***6.Radioactive isotopes:***
  As phosphorus (P^{32}) and iodine (I^{131}) emit β irradiations intracellularly → release of free (toxic) radicals → necrosis of tumor cells.

- ***Important notes:***
  1.A given dose of cytotoxic drug kills a constant fraction of cells, therefore in late presentation it is necessary to use combination of drugs & to repeat administration.
  2.Combination chemotherapy is more effective than a single agent because:
  (a)Less toxic by using small doses of each drug.
  (b)Reduces resistance which develops with repeated use of a single drug.
  (c)More efficacy by synergism of drugs acting on different phases of the cell cycle.
  3.Cytotoxics adversely affect all rapidly dividing normal tissues as bone marrow,GIT epithelium,hair follicles and germ cells but all these normal tissues recover rapidly. So repeated courses of high dose chemotherapy with intervals for recovery of normal tissue are better than continuous low dose therapy.

- ***General adverse effects of cytotoxic drugs:***
  1.GIT nausea & vomiting followed by stomatitis,oral and intestinal ulcers with malabsorption & candidiasis with diarrhea.
  2.Bone marrow depression with neutropenia,thrombocytopenia & anemia.
  3.Immunosuppression with increased liability for infections.
  4.Reversible alopecia.
  5.Delayed wound healing.
  6.Gonadal effects sterility & teratogenicity so pregnancy should be avoided during & for several months after therapy.
  7.Hyperuricemia which may precipitate gout or urate nephropathy.
  8.Carcinogenesis.

Thank you….