ANTILEPROTIC DRUGS.

- Leprosy is caused by Mycobacterium leprae.
- It was considered incurable but now can be cured completely but defects/deformities already incurred may not reverse.
- There are 4 types of leprosy:

  1)Lepromatous leprosy

  2)Tuberculoid leprosy

  3)Intermediate leprosy

  4)Borderline leprosy.

TRANSMISSION

- Is through prolonged and intimate contact with untreated open lepromatous patients whose cutaneous lesions and mucosal discharges are full of leprosy bacilli.

DIAGNOSIS

- Supported by bacteriological evidence from smears and lesions ,nodules, earlobes or from scrapings of the oral mucosa.
- The lepromin test is of no diagnostic value because people with no exposure to leprosy but are Mantoux positive may be given a positive result.
- The lepromin test is always negative for lepromatous leprosy and weakly positive for tuberculoid leprosy.

DIFFERENCE BETWEEN TUBERCULOID NAD LEPROMATOUS LEPROSY.

TUBERCULOID LEPROSY	LEPROMATOUS LEPROSY
Anesthetic patch.	Diffuse skin and mucous membrane infiltration ,nodules.
Cell mediated immunity (CMI) is normal.	CMI is absent.
Lepromin test positive.	Lepromin test negative.
Bacilli rarely found in biopsies.	Skin and mucous membrane lesions teeming with bacilli.
Prolonged remissions with periodic exacerbations.	Progresses to anesthesia of distal parts ,atrophy, ulceration, absorption of digits e.t.c.

CLASSIFICATION OF LEPROSY FOR TREATMENT.

1.Paucibacillary leprosy(PB): Patient has few bacilli and is non infectious. Include borderline-tuberculoid ,tuberculoid and intermediate leprosy. Treatment is by use of two drugs :Rifampicin and Dapsone.

2.Multibacillary leprosy(MB): Patient has a large bacillary load and is infectious. Include lepromatous and borderline leprosy. Treatment is by use of three drugs :Rifampicin ,Dapsone and Clofazimine.

FURTHER CLASSIFICATION OF LEPROSY FOR TREATMENT.

1.Single lesion paucibacillary leprosy(SL PL): Has solitary cutaneous lesion. Test on skin smear is negative.

2.Paucibacilary leprosy(PB) : With 2-5 skin lesions. Test on skin smear is negative.

3.Multibacillary leprosy : With more than six skin lesions as well as all smear positive cases.

DIFFERENCE BETWEEN PAUCIBACILLARY AND MULTIBACILLARY LEPROSY.

PAUCIBACILLARY LEPROSY	MULTIBACILLARY LEPROSY
1-5 skin lesions	6 or more skin lesions
No nerve /only one nerve involved and subjective to number of skin lesions.	More than one nerve involved irrespective of the number of skin lesions.
Skin smear negative at all sites.	Skin smear positive at any one site.

CLASSIFICATION OF ANTILEPROTIC DRUGS.

A .Sulfone –Dapsone

B. Phenazine derivatives –Clofazimine

C .Antitubercular drugs –Rifampicin ,Ethionamide.

D .Other antibiotics –Ofloxacin ,Moxifloxacin ,Minocycline, Clarithromycin.

DAPSONE.

- It is a diamino diethyl sulfone (DDS).
- It is the simplest ,cheapest ,oldest ,most active and most commonly used member of its group.

MECHANISM OF ACTION.

- It inhibits paramino benzoic acid (PABA) incorporation into folic acid by folate synthase.
- The antibacterial action is antagonized by PABA.
- It is leprostatic at very low concentrations while it arrests bacteria sensitive to sulphonamides in high concentrations as it has the same mechanism of action as sulphonamides.
- Its specificity to *M.leprae* is due to difference in its affinity of its folate synthase enzyme.
- Doses needed for treatment of acute pyogenic bacteria are too toxic thus not used.

RESISTANCE

- Resistance was first noted in 1964 ,has spread and necessitated use of multi drug therapy (MDT).

1.Primary resistance-encountered in untreaded patient and indicates that the infection was contracted from a patient harboring resistant bacilli.

2.Secondary resistance-Develops during monotherapy and caused by selective propagation of resistant bacilli over time.

Dapsone resistance *M. leprae have mutated folate synthase which has a low affinity of dapsone.*

CONT`D

- Peak serum concentration of dapsone after 100 mg/day dose exceeds minimum inhibitory concentration(MIC) by nearly 500 times thus dapsone continues to be active against low and moderate resistant *M. leprae* and the risk of relapse due to dapsone resistance is reported to be only 2-3%.
- There is the problem of `persisters' ;drug sensitive bacilli that become dormant ,hide in some tissues and are not affected by any drug They come back after the drug is withdrawn.

PHARMACOKINETICS.

- It is completely absorbed after oral administration and is widely distributed in the body but CSF penetration is poor.
- It is 70% protein bound and high concentration in skin (especially in lepromatous skin ,muscle ,liver and kidney.
- It is acetylated as well as glucuronide and sulphate conjugated in the liver.
- Metabolites are excreted in bile and reabsorbed in the intestine thus is ultimately secreted in urine.

HALF-LIFE.

- Half life is variable although is often higher than 24 hours.
- The drug is cumulative due to retention in the tissues and enterohepatic circulation.
- Elimination takes place in 1-2 weeks or longer.

INDICATIONS.

- It is used in paucibacillary leprosy and in multibacillary leprosy in combination with other antileprotic drugs.
- Dapsone is active against certain protozoa e.g Combined with pyrimethamine and is an alternative to sulfadoxine-pyrimethamine for *P. falciparum* and *Toxoplasma gondii* infections as well as for the fungus *Pneumocystis jirovecii*.
- An anti-inflammatory property has also been detected in dapsone.

CONTRAINDICATIONS.

- Patients with known hypersensitivity to sulfones.
- Patients with severe anemia (Hb of less than 7g/dl).
- Patients with G-6-PD deficiency.

ADVERSE EFFECTS.

- Dapsone is generally well tolerated at 100mg/day or less.
- Mild hemolytic anemia and dose related toxicity- reflects oxidizing property of the drug with patients with G-6-PD deficiency being more susceptible; doses of more than 50mg/day produces hemolysis in such subjects.
- Gastric intolerance- nausea and anorexia are frequent in the begin but decrease later.
- Methaemoglobinaemia, headache, paresthesias, mental symptoms, drug fever and eosinophilia are also seen.
- Cutaneous reactions include itching, allergic rashes, fixed drug eruption, hypermelanosis, phototoxicity and rarely exfoliative dermatitis.
- Hepatitis and agranulocytosis are rare complications.

SULFONE SYNDROME

- It develops 4-6 weeks after start of dapsone treatment and symptoms consist of fever, malaise, lymph node enlargement, desquamation of skin, jaundice and anemia.
- It is seen in malnourished patients and more frequently after introduction of MDT.
- Treatment is by stopping of dapsone and instituting a corticosteroid therapy with supportive measures.

DRUG INTERACTIONS.

- Probenicid interacts with dapsone reducing the rate of its excretion resulting in increased side effects.

CLOFAZIMINE.

- It is a dye with leprostatic and anti-inflammatory properties.
- It is also a sulfone.

MECHANISM OF ACTION.

- It interferes with the template function of DNA.
- It alters the membrane structure and its transport function.
- Disruption of mitochondria electron transport chain.
- It is slow when used alone and resistance develops in 1-3 years.
- Dapsone resistant *M. leprae* respond to clofazimine but after a lag period of two months.

PHARMACOKINETICS.

- It is orally active; 50-70% is absorbed.
- Accumulates in macrophages and gets deposited as needle shaped crystals in many tissues including subcutaneous fat and reticuloendothelial system.
- It shows poor CSF entry.
- It has a half life of 70 days so that intermittent therapy is possible.
- It is excreted in urine unchanged over a period of several weeks.

INDICATIONS AND CONTRAINDICATIONS.

Indications.

~Used in multibacillary leprosy in combination with dapsone and rifampicin.

~It is a component of a combination regimen for extensive drug resistant tuberculosis(XDR-TB).

Contraindications.

Early pregnancy.

Patients with kidney or liver damage.

ADVERSE EFFECTS.

- It is well tolerated in doses for MDT.
- **Skin-**Reddish- black discoloration of skin especially on exposed parts. Discoloration of hair and body secretions may occur but harmless. Dryness of skin, itching and scaling. Acneform eruptions and phototoxicity. Conjuctival pigmentation may create cosmetic problem.
- **G.I.T-**Nausea, anorexia, abdominal pain, weight loss and enteritis with intermittent loose stools can occur in high doses and subsides with dose adjustments and taking drugs with meals. G.I.T effects caused by deposition of clofazimine crystals in intestinal submucosa may produce late start to G.I.T symptoms.

RIFAMPICIN

- Is a semisynthetic derivatives of rifamycin which is a complex macrocylic antibiotic. It is the most potent.
- Active against mycobacteria, gram-positive organism and Neisseria species

MECHANISM OF ACTION

- Inhibits ribonucleic acid synthesis
- Not satisfactory used as some bacilli persist even after prolonged treatment and resistance develops .

PHARMACOKINETICS

- Lipids soluble and well absorbed after administration
- Maximum serum levels achieved in two hours
- Best taken on an empty stomach
- Distributed widely in the body fluids , tissues and therapeutics effects achieved in cerebrospinal fluid and pleural fluids
- Extensively recycled in enterohepatic circulation and metabolites formed by deacetylation in liver are biological active
- Excreted in feces.

PHARMACODYNAMICS

- Up to 99.99% *M.leprae* killed in 3-7 days by 600mg/day dose
- Clinical effects are rapid; nasal symptoms in lepromatous leprosy subside in 2-3 weeks and skin lesions start to regress by 2 months but nerve damage already incurred is little benefited.

INDICATIONS

- Used in bath PB and MB leprosy in combination with other anti-leprosy drugs
- Treatment of TB in combination with other effective antimycobacterial agents.

CONTRAINDICATIONS

- Pots with the renal or hepatic dysfunction
- During erythema nodosum leprosum (ENL) or reversal reaction in leprosy pots because it can release large quantities of mycobacterial antigens by inducing rapid bacillary killing known hypersensitivity to the drug.

ADVERSE EFFECTS

- May cause skin rashes , fever , influenza-like symptoms and thrombocytopenia. Exfoliative may occur ,especially in HIV positive and TB patients.
- Others are temporary. Eg; oliguria , dyspnea , hemolytic anemia and gastrointestinal discomfort.
- Body secretions(urine ,tears) become deep orange-red.
- Dose related hepatitis can occur and is potentially fatal.

DRUG INTERACTIONS

- Is a potent liver enzyme inducer and vary cause interactions with oral anticoagulants , anticonvulsants , oral hypoglycemic agents, corticosteroids and steroids contraceptive.
- It reduces effectiveness of the oral contraceptives pill; it is necessary to switch the patient to a higher dose of estrogen or to a non-normal contraceptive method.

ETHIONAMIDE.

- This antitubercular drug has significant antileprotic activity but is poorly tolerated and causes hepatotoxicity in ~10% patients.
- It has been used as an alternative to clofazimine but other substitutes are preferred.
- Ethionamide 250mg/day may be used only when absolutely necessary.

OFLOXACIN.

- Many fluoroquinolones (FQs) like ofloxacin ,pefloxacin ,oxifloxacin and sparfloxacin are highly active against *M .leprae* are but ciprofloxacin has poor activity.
- Clinically ,ofloxacin has been used to the largest extent and found to hasten bacteriological and clinical response in MDT.
- It is cidal to *M. leprae* but is not yet included in the standard treatment protocols but can be used in alternative regimens incase rifampicin can not be used or to shorten treatment duration or to reduce chances of drug resistance.
- Safety in long term use is not documented.
- DOSE: 400mg/day.
- Moxifloxacin is the most potent against *M. leprae*.

MINOCYCLINE.

- Because of high lipophilicity ,this tetracycline penetrates into *M. leprae* and is active against them.
- A dose of 100mg/day produces peak blood levels that exceeds MIC against *M. leprae* by 10 to20 times.
- Antileprotic activity is less marked than rifampicin but more than clarithromycin. Good clinical response in terms of relief of lepromatous symptoms and the bacilli has been reported.
- Vertigo is the only serious complication in long term use.

CLARITHROMYCIN.

- It is the only macrolide antibiotic with significant activity against *M. leprae*.
- It is less bactericidal than rifampicin.
- Monotherapy of 500mg/day causes 99.9% killing in 8 weeks with rapid clinical improvement.
- Synergic action has also been demonstrated.

MULTIDRUG THERAPY OF LEPROSY.

DRUG	MULTIBACILLARY	PAUCIBACILLARY
Rifampicin	600mg once a month supervised.	600mg once a month supervised
Dapsone	100mg daily self administered.	100mg daily self administered.
Clofazimine	300mg once a month supervised+ 50mg daily self administered.	-
DURATION	12 months	6 months

CHILD DOSAGE.

- RIFAMPICIN: 10mg/kg once a month.
- CLOFAZIMINE: 1mg/kg daily + 6mg/kg once monthly.
- DAPSONE: 2mg/kg daily.

SPECIAL CAUSES FOR TREATMENT.

- **Relapse of leprosy:** Same MDT is started on confirmation of relapse.
- **Leprosy and TB infection:** MDT for leprosy continued but rifampicin given daily as for treatment of TB.
- **Leprosy in HIV patients:** No association of leprosy with HIV infection thus MDT with ARVs.

ALTERNATIVE REGIMENS.

- **Intermediate ROM:** Rifampicin 600mg+ofloxacin 400mg +minocycline 100mg once a month for 3-6 months(PBL) and 12-24 months (MBL) without any drug in between.
- Clofazimine 50mg+ any two(ofloxacin 400mg /minocycline 100mg /clarithromycin 500mg) daily for 6 months followed by clofazimine 50mg+ any ofloxacin 400mg /minocycline 100mg daily for 18 additional months.
- **Four drug regimen:** Rifampicin 600mg+ sparfloxacin 200mg+ clarithromycin 500mg+ 100mg daily for 12 weeks.

CONT`D

- **Incase of refusal to accept clofazimine:** Ofloxacin 400mg or minocycline 100mg daily can be substituted for it in the standard MDT butvethionamide use is not recommended.
- **Intermittent RMM:** Mixofloxacin 400mg+ minocycline 200mg+ rifampicin 600mg once a month; 6 months for PBL and 12 months for MBL.

REACTIONS IN LEPROSY.

LEPRA REACTION.

- Occurs in LL, usually coincides with institution of chemotherapy and/or intercurrent infection.
- It is a Jarish Herxheimer (Arthus) type of reaction due to release of antigens from the killed bacilli and may be mild, severe or life threatening .i.e. erythema nodosum leprosum(ENL).
- Lepra reaction is of abrupt onset; existing lesions enlarge, become red, swollen and painful; several new lesions may appear.
- Malaise, fever and other constitutional symptoms may generally accompany and be marked.
- Temporary discontinuation of dapsone is recommended only in severe cases. Clofazimine(200mg daily) is effective in controlling the reaction(except in severe one), probably because of anti inflammatory property.

- For severe, prednisole 40-60mg/day is started immediately and continued till the reaction subsides. The dose is the tapered over 2-3 months.
- Thalidomide(anti inflammatory, cytokine modulating drug with anxiolytic, antiemetic property) used as an alternate to prednisole and plays n important role in cancer-associated cachexia and multiple myeloma treatment.
- Other drugs used to treat are analgesics, antipyretics, antibiotics e.t.c according to symptoms and need. Chloroquine is also used to suppress lepra reaction.

REVERSAL REACTION.

- Seen in TT and BL cases and its manifestation is delayed hypersensitivity to M. *leprae* antigens.
- Cutaneous ulceration, multiple nerve involvement with swollen, painful and tender nerves occur suddenly even after completion of therapy.
- It is treated with clofazimine or corticosteroids in the same way as ENL but thalidomide is ineffective.