Name of Faculty: Dr. Amit Kumar Nayak
Designation: Professor
Department: Pharmacy
Subject: Pharmacology-III (BP 602T)
Unit: III
Topic: Anti Leprotic Drugs
Leprosy is caused by a slow-growing type of bacteria called *Mycobacterium leprae* (M. leprae). Also known as Hansen's disease, after the scientist who discovered M. leprae in 1873. It primarily affects the skin and the peripheral nerves. Long incubation period (3–5 years).
Antileprotic Drugs

Sulfones – DAPSONE (DDS)-DIAMINO DIPHENYL SULFONE

Phenazine Derivative - CLOFAZIMINE

Antitubercular Drugs - RIFAMPICIN, ETHIONAMIDE

Antibiotics: OFLOXACIN, MOXIFLOXACIN, MINOCYCLINE AND CLARITHROMYCIN
Dapsone (DDS)

The simplest, oldest, cheapest

**MOA:** Leprostatic even at low concentration

Chemically related to Sulfonamides – same mechanism – inhibition of incorporation of PABA into folic acid (folic acid synthase)

Specificity to *M. leprae* – affinity for folate synthase

**Activity:** Used alone – resistance – MDT needed

Resistance – Primary and Secondary (mutation of folate synthase – lower affinity)

However, 100 mg/day – high MIC -500 times and continued to be effective to low and moderately resistant Bacilli (low % of resistant patient) Persisters. Also has antiprotozoal action (Falciparum and T. gondii)
Dapsone (DDS)

**Pharmacokinetics:** Complete oral absorption and high distribution (less CNS penetration) Half life 24-36 Hrs, but cumulative

- 70% bound to plasma protein – concentrated in Skin, liver, muscle and kidney
- Acetylated and glucuronidated and sulfate conjugated – enterohepatic circulation

**ADRs:** Generally Well tolerated drug

- Haemolytic anaemia (oxidizing property) - G-6-PD are more susceptible
- Gastric - intolerance, nausea, gastritis
- Methaemoglobinaemia, paresthesia, allergic rashes, FDE, phototoxicity, exfoliative dermatitis and hepatotoxicity etc.
Dapsone (DDS)

Active against protozoa
Combined with pyrimethamine alternative to sulfadoxine-pyrimethamine for P.falciparum and toxoplasma gondii infection
Active against Pneumocystis jirovecii
Also has anti-inflammatory property
Sulfone Syndrome

Symptoms: Fever, malaise, lymph node enlargement, desquamation of skin, jaundice and anemia
Starts after 4-6 weeks of therapy, more common with MDT
Management: stopping of Dapsone, corticosteroid therapy
Dapsone contraindications: Severe anaemia and G-6-PD deficiency
**Clofazimine**

Phenazine dye – antileprotic, anti-inflammatory and Bacteriostatic

**MOA:** Interference with template function of DNA
  - Alteration of membrane structure and transport
  - Disruption of mitochondrial electron transport

Monotherapy causes resistance in 1 – 3 years

Dapsone resistants respond to Clofazimine

**Kinetics:** absorbed orally (70%) and gets deposited in subcutaneous tissues – as crystals
  - Half life – 70 days
Clofazimine

ADRs: well tolerated

Skin: Reddish-black discolouration of skin, discolouration of hair and body secretions
Dryness of skin and troublesome itching, phototoxicity, conjunctival pigmentation

GIT: Nausea, anorexia, abdominal pain and loose stool (early and late) – dreaded enteritis

Contraindication: Early pregnancy, liver and kidney diseases
**Rifampicin**

**Rifampicin:** Cidal. 99.99% killed in 3-7 days, skin symptoms regress within 2 months

- Included in MDT to shorten the duration of treatment and also to prevent resistance
- No toxic dose as single dose only
- Should not be used in ENL and Reversal phenomenon

**Ofloxacin:** all fluoroquinolones except ciprofloxacin are active. Used as alternative to Rifampicin

**Minocycline:** Lipophillic - enters M leprae. Less marked effect than Rifampicin
ETHIONAMIDE

Anti leprotic and anti tubercular
It is a fast acting drug than dapsone
But it is more expensive and more toxic
It is orally effective and it is administered daily
Poorly tolerated –hepatotoxicity
250mg/day
Clarithromycin

Only macrolide with activity against M. leprae
Less bactericidal than rifampin
Monotherapy- 500mg daily/ 8wks- 99.9% killing
Synergistic action with minocycline
Used in alternative MDT regimen

MINOCYCLINE
High lipophilicity –penetrates into M.leprae
100mg/day
Antileprotic activity rif>mino >Clari
8 wks treatment
LEPRA REACTION

The acute exacerbation which occurs during the course of leprosy is called as lepra reaction. It occurs in LL type - after starting with chemotherapy and intercurrent infections. Jerish Hexheimer (Arthus) type reaction due to release of antigens from killed bacilli. May be mild, severe, or life threatening. ENL - erythema Nodosum Leprosum.

Treatment - clofazimine - 200mg
Dapsone temporary withdrawal
Severe reaction - prednisone - 40-60 mg. Tapered in 2-3 months
Thalidomide - alternative to prednisolone in ENL.
Reversal reaction

TT and BL cases
Manisfestation of delayed hypersensitivity to M.leprae antigens
Cutaneous ulceration, multiple nerve involvement with tender nerves
Treatment-Clofazimine/ corticosteroids
Classification-Ridley and Jopling - 1966

Lepromatous-LL
Borderline –BL
Borderline tubercular-BT
Tuberculoid TT

Conventional monotherapy
MT-Dapsone 100-200m- 5/7 days in week
TT-4-5 yrs
LT- 8-12 yrs or life long
<table>
<thead>
<tr>
<th>Tuberculoid</th>
<th>Lepromatous</th>
</tr>
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<tbody>
<tr>
<td>Anaesthetic patch</td>
<td>Diffuse skin and mucous membrane, nodules</td>
</tr>
<tr>
<td>CMI-cell mediated immunity is normal</td>
<td>CMI is absent</td>
</tr>
<tr>
<td>Lepromin test is positive</td>
<td>Lepromin test is negative</td>
</tr>
<tr>
<td>Bacilli rarely found in biopsy</td>
<td>Skin and mucous membr biopsy +ve for bacilli</td>
</tr>
<tr>
<td>Prolonged remission with periodic exacerbations</td>
<td>Prognosis to anaesthesia of distal parts, atrophy</td>
</tr>
</tbody>
</table>
Monotherapy - 1982 and since then MDT
Elimination achieved in India in 2005 (prevalence rate ?)
Leprosy classified as LL, BL, BB, BT and TT
For operational purposes:
Paucibacillary: few bacilli and non-infectious – TT and BT
Multibacillary: large bacilli load and infectious – LL, BL and BB types
   Single lesion Paucibacillary: single lesion
<table>
<thead>
<tr>
<th></th>
<th>MULTIBACILLARY</th>
<th>PAUCIBACILLARY</th>
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<tbody>
<tr>
<td><strong>RIFAMPIN</strong></td>
<td>600mg OD/once per month</td>
<td>600mg OD/once per month</td>
</tr>
<tr>
<td><strong>Dapsone</strong></td>
<td>100mg daily</td>
<td>100mg daily</td>
</tr>
<tr>
<td><strong>Clofazimine</strong></td>
<td>300mg once/month 50mg-OD</td>
<td></td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>12 months</td>
<td>6 months</td>
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<td></td>
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<tr>
<td>Alternative regimens</td>
<td>Rifampin 600mg +</td>
<td>Oflox 400mg +</td>
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<td>----------------------</td>
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<tr>
<td>Intermittent ROM</td>
<td>Oflox 400mg</td>
<td>Minocycline 100</td>
</tr>
<tr>
<td>Once/month</td>
<td>PBL</td>
<td>3-6months</td>
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<tr>
<td>MBL</td>
<td>12-24 months</td>
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<thead>
<tr>
<th>Clofazimine 50mg + (any 2) 6months</th>
<th>Ofoxacin 400mg</th>
<th>Minocycline 100mg</th>
<th>Clarithromycin 500mg</th>
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<tr>
<th><strong>RMMx regimen</strong></th>
<th>Moxiflox 400mg +</th>
<th>minocycline 200mg</th>
<th>Rifampin 600mg</th>
<th>PBL- 6doses MBL-12 doses</th>
</tr>
</thead>
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<thead>
<tr>
<th>Clofazimine 50mg (any 1)</th>
<th>Ofloxacin 400mg Minocycline 100mg</th>
<th>18 months</th>
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<tr>
<th><strong>4 drug regimen</strong></th>
<th>Sparfloxacin 200mg</th>
<th>Clarithromycin 500mg</th>
<th>Minocycline 100mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin 600mg</td>
<td>For 12wks is similar to standard MDT for</td>
<td></td>
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