Management of MDR TB

Dr Priscilla Rupali MD; DTM&H
Professor and Head
Department of Infectious Diseases
Christian Medical College Vellore
• Global epidemiology of Tuberculosis
• Epidemiology of Tuberculosis in India
• How does resistance develop
• Risk factors
• Principles of Management
Says WHO: India has highest number of multidrug-resistant TB in South East Asia

Aarti Dhar

The percentage of MDR in new TB cases in India is 2.1

India had an estimated 63,000 cases of notified multi-drug resistant tuberculosis (MDR-TB) in 2010, the highest in the South East Asia region, the World Health Organisation (WHO) has said.

The MDR-TB prevalence is estimated to be 2.3 per cent among new cases and 12-17 per cent among re-treatment cases. However, due to the size of the population and the number of TB cases reported annually, India ranks second among the 27 MDR-TB high-burden countries worldwide after China.

Extensively drug-resistant TB (XDR-TB) cases have also been reported from India, Bangladesh, Indonesia, Nepal and Thailand from the region. Considerable efforts are required to expand capacity for quality-assured drug susceptibility testing in the region in order to more accurately estimate the extent of drug-resistant TB. Given the widespread availability and use of second-line drugs, and as laboratory capacity to conduct second-line drug susceptibility testing increases, additional number of patients with XDR-TB are likely to be identified, the report warns.

The estimated percentage of the MDR in new TB cases in India is 2.1 (1.7- 2.5) per cent, while the percentage of MDR among previously treated cases was 15 (13 -17) per cent. By the end of 2009, treatment services for the MDR-TB patients were available in sites of 10 States.

Enforcement of regulations for prescription and sale of anti-TB drugs, promoting rational use of first-and second-line anti-TB drugs outside the programme to prevent MDR and XDR-TB are some of the major challenges for India, it states.
History of tuberculosis

- Pthisis, consumption and white plague was common in Europe in 17th and 18th centuries due to poor sanitation and high population density.
- Described in mummies and vedas.
- Robert Koch applied a stain to sputum of TB patients and discovered *Mycobacterium tuberculosis*.

In 1882 he presented his findings at his famous lecture “Uber tuberculose.”

Since then it is known as the [World TB Day](http://www.wtb.org/).
Globally 3.9% of new cases have drug resistant TB
Globally 21% of previously treated Tb have MDR TB
Estimated incidence of MDR/RR-TB in 2015, for countries with at least 1000 incident cases. Areas that are not applicable are in grey.
• **Drug resistant TB:** M tuberculosis resistant to one of the first line ATT (HRZES)

• **MDR TB:** *M tuberculosis* strains with *in vitro* resistance to RIF & INH at least with possibly others

• **XDR TB:** *M tuberculosis* strains with *in vitro* resistance to RIF, INH, any FQ & 1 (out of 3) injectable agent (AG)

• **TDR TB:** At present no accepted definition
Primary vs Secondary

• **Primary drug resistance**: Occurs in a patient who has never received anti-Tb therapy

• **Secondary drug resistance**: Development of resistance during or following chemotherapy in patients who previously had drug susceptible TB
>10^8 organisms in TB cavity

Likelihood of Natural Resistance

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Resistance Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>1/10^8</td>
</tr>
<tr>
<td>INH, Strep, EMB</td>
<td>1/10^6</td>
</tr>
</tbody>
</table>
If Treated with INH and RIF

- 10^8 Organisms:
  - 1 Resistant Rif
  - 10^8 Resistant INH
  - 100 Resistant Strep
  - 100 Resistant EMB

MDR-TB

- Organisms Multiply

1 organism resistant to RIF and INH
## Risk factors for failure

### Inadequate ATT

1. **Patient:** Non-adherence  
   Malabsorption

2. **Physician:** Inappropriate prescription  
   (drugs, dosage, duration)

3. **Drugs:** Poor bioavailability of  
   substandard formulations

4. **Healthcare system:** Non-availability
### Table 2. Bivariate Analysis: Risk factors for MDR.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds Ratio for MDR</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Category</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;21</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>Age 21–30</td>
<td>0.78</td>
<td>0.12–5.34</td>
</tr>
<tr>
<td>Age 31–40</td>
<td>0.12</td>
<td>0.014–1.04</td>
</tr>
<tr>
<td>Age 41–50</td>
<td>0.60</td>
<td>0.079–4.54</td>
</tr>
<tr>
<td>Age &gt;50</td>
<td>0.27</td>
<td>0.038–1.92</td>
</tr>
<tr>
<td>Female Sex</td>
<td>1.41</td>
<td>0.56–3.56</td>
</tr>
<tr>
<td>HIV infection*</td>
<td>0.19</td>
<td>0.024–1.56</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.23</td>
<td>0.063–0.81</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>0.11</td>
<td>0.014–0.82</td>
</tr>
</tbody>
</table>

### Table 3. Bivariate Analysis: Risk factors for XDR.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds Ratio for XDR</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Category (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt;21</td>
<td>reference</td>
<td></td>
</tr>
<tr>
<td>Age 21–30</td>
<td>1.04</td>
<td>0.16–6.97</td>
</tr>
<tr>
<td>Age 31–40</td>
<td>0.49</td>
<td>0.072–3.27</td>
</tr>
<tr>
<td>Age 41–50</td>
<td>0.90</td>
<td>0.13–6.46</td>
</tr>
<tr>
<td>Age &gt;50</td>
<td>0.31</td>
<td>0.044–2.15</td>
</tr>
<tr>
<td>Female Sex</td>
<td>1.64</td>
<td>0.76–3.55</td>
</tr>
<tr>
<td>HIV infection*</td>
<td>0.29</td>
<td>0.081–1.05</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.43</td>
<td>0.18–1.03</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>0.21</td>
<td>0.060–0.74</td>
</tr>
</tbody>
</table>

### Table 4. Multivariate Analysis: Risk factors for XDR.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio for XDR</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous treatment with a fluoroquinolone and an injectable agent (other than streptomycin)</td>
<td>7.00</td>
<td>1.14–43.03</td>
</tr>
<tr>
<td>Initial treatment regimen did not follow national guidelines</td>
<td>5.68</td>
<td>1.24–25.96</td>
</tr>
</tbody>
</table>

Including smoking, alcohol, HIV, TN state, payment, regimen 1 adequate, extrapulmonary TB, cavitary, number of regimens, previous treatment with fluoroquinolone and injectable.
Only significant associations shown.
Model based on 69 cases with complete data.
Case
History

• 50 year old lady from Shillong in North East India presented with a history of a lump in the right breast gradually increasing in size with no associated pain or discharge
• She also complained of low grade fever, cough with mucoid expectoration on and off
• Diagnosed to have pulmonary tuberculosis in November 2 years ago and given TB treatment for 6 months (Category I – 2 HRZE + 4 HR)
• She was still smear positive at the end of 6 months and hence started on Cat II ATT in March 2010.

• She had been on 18 months of treatment when she presented to us

• We were called in for a consultation as General Surgery wanted to perform a modified radical mastectomy
General examination

- She was afebrile
- No pallor/icterus/cyanosis/clubbing/pedal edema.
- Pulse rate: 76 per minute
- Blood pressure: 120/90 mmHg
- RS: Normal vesicular breath sounds, no added sounds.
- CVS: S1S2 normally heard, no murmurs.
- PA: Soft and non-tender, No hepato-splenomegaly.
- CNS: No neurological deficit
- Spine and joints: Normal
Local examination

• Right breast 4x4 cms lump in the upper aspect hard in consistency with restricted mobility
• 2x1 cm LN in Right axilla
• Left breast and axillae were normal.
Investigations

- Haemoglobin 10.6 gm%
- Platelet count 176000 cc.Mm
- WBC total 4800 /cu mm
- Differential – N 60%, L 21%, E 11%, M 8%
- Creatinine 0.8 mg %
- Sodium 143 m mol/L
- Potassium 3.6 m mol/L
- AFB SMEAR 3+ AFB/FIELD
Investigations

• Liver Function Test
  – Bilirubin total 0.4 mg%
  – Direct 0.1 mg%
  – Protein total 7.1 g%
  – Albumin 3.6 g%
  – SGOT 20 U/L
  – SGPT 14 U/L

• Biopsy –
  Infiltrating duct carcinoma, tru-cut biopsy, right breast.
  The tumour cells are negative for oestrogen and progesterone receptors.
### MYCOBACTERIA CULTURE & SENS 1ST LINE (MGIT AUTO)

**Smear:** 3+ >100 AFB/FIELD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofloxacin</td>
<td>Resistant</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Resistant</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Resistant</td>
</tr>
<tr>
<td>Sparfloxacian</td>
<td>--</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Resistant</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Resistant</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Resistant</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Resistant</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Resistant</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>--</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Susceptible</td>
</tr>
</tbody>
</table>
Probable diagnosis

- Carcinoma breast

- Open pulmonary Tuberculosis- Extensively drug resistant tuberculosis
Management of drug resistant tuberculosis
Challenges
Diagnosis

• History that suggests DR-TB
  - Previous ATT
  - TB treatment failure due to intermittent ATT in HIV infection
  - Acquisition of TB in an area of high resistance
  - DR TB contacts
  - Failure to respond to empiric treatment
  - Quinolone treatment for any previous indication
Diagnosis

• **Culture and Susceptibility** – sputum positivity at 60 days has a 67% PPV for diagnosis of MDR TB

• **Rapid diagnostic tests:**
  - Gene Xpert MTb/rif – sensitivity 98%, detection of rifampicin resistance was 98%
  - MTBDRplus – inhA for Isoniazid and rpoB for rifampicin resistance
  - MTBDRsl – detects resistance to second line fluoroquinolones and injectable drugs
### WHO categories of drugs for MDR-TB

<table>
<thead>
<tr>
<th>Classification</th>
<th>Medicines</th>
<th>Abbreviations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Fluoroquinolones</strong></td>
<td>Levofloxacin, Moxifloxacin, Gatifloxacin</td>
<td>Lfx, Mfx, Gfx</td>
</tr>
<tr>
<td><strong>B. Second-line injectable agents</strong></td>
<td>Amikacin, Capreomycin, Kanamycin, Streptomycin</td>
<td>Am, Cm, Km, (S)</td>
</tr>
<tr>
<td><strong>C. Other core second-line agents</strong></td>
<td>Ethionamide / Prothionamide, Cycloserine / Terizidone, Linezolid, Clofazimine</td>
<td>Eto / Pto, Cs / Trd, Lzd, Cfz</td>
</tr>
<tr>
<td><strong>D. Add-on agents</strong></td>
<td><strong>D1</strong> Pyrazinamide, Ethambutol, High-dose isoniazid</td>
<td>Z, E, H&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>D2</strong> Bedaquiline, Delamanid</td>
<td></td>
<td>Bdq, Dlm</td>
</tr>
<tr>
<td><strong>D3</strong> p-aminosalicylic acid, Imipenemcilastatin, Meropenem, Amoxicillin-clavulanate, Thioacetazone</td>
<td>PAS, Ip, Mpm, Amx-Clv (T)</td>
<td></td>
</tr>
</tbody>
</table>
Composition of a 2\textsuperscript{nd} line regimen

- Uncertainty re the DST for Z and E – in vitro resistance ≠ in vivo resistance hence Z should be used in.
- At least 5 drugs should be used – Z+ including 4 second line TB drugs- 1 from group A, 1 from group B and 2 from group C.
- All aminoglycosides are = efficacy.
- Use of later generation quinolones is associated with cure.
- Cure greater if Ethionamide > Cycloserine > Linezolid > Clofazimine.
- Add an agent from D2 or D3 to bring the total to 5 if other groups cannot be used.
The development pipeline for new TB drugs, August 2015

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Preclinical development</th>
<th>Clinical development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead optimization</td>
<td>TBI-166</td>
<td>Sutezolid (PNU-100480)</td>
</tr>
<tr>
<td>Diarylquinolines</td>
<td>CPZEN-45, SQ609</td>
<td>SQ109, Rifapentine for DS-TB</td>
</tr>
<tr>
<td>DprE Inhibitors</td>
<td>PBTZ169</td>
<td>AZD5847, Bedaquiline-Pretomanid-Pyrazinamide Regimen</td>
</tr>
<tr>
<td>InhA Inhibitor, Indazoles</td>
<td>DC-159a, Q203</td>
<td>Bedaquiline (TMC-207) with OBRb for MDR-TB</td>
</tr>
<tr>
<td>LeuRS Inhibitors, Ureas</td>
<td></td>
<td>Delamanid (OPC-67683) with OBRb for MDR-TB</td>
</tr>
<tr>
<td>Macrolides, Azaindoles</td>
<td></td>
<td>Rifapentine for LTBI</td>
</tr>
<tr>
<td>Mycobacterial Cynase Inhibitors</td>
<td></td>
<td>Pretomanid-Moxifloxacin-Pyrazinamide Regimen</td>
</tr>
<tr>
<td>Pyrazinamide Analogs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruthenium(II) Complexes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spectinamides SPR-113</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Translocase-1 Inhibitors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone
Bedaquiline in MDR-Tb

• Patients: 160 age 18-65 with newly diagnosed MDR pulmonary TB from 15 sites –India, Peru, Brazil, Philippines, Latvia, Russian Federation, South Africa and Thailand

• Intervention: Bedaquiline vs placebo as well as 5 anti-Tb drugs (Ags, FQs, PZA, Ethionamide, Ethambutol and/or Cycloserine/Terizidone

• Results: Medium time to culture conversion 83 days (B) vs 125 days (P); HR=2.44.
- Cure at 120 weeks was 57.6%(B) vs 31.8% (P)
Delaminid in MDR-Tb

• Trial 204,208,116: 481 patients Delamanid + OBR vs P+ OBR. Culture conversion at 2 months was 45.4% vs 29.6%

• Combined long term efficacy
  - 90.9% of patients who received Delamanid + OBR for 6 months achieved culture negativity vs 70.9% of patients who received D+ OBR for < 2 months
New drugs and regimens - Trials underway

- Bedaquiline – STREAM 6 months/9 months vs standard WHO MDR TB treatment
- Delaminid – Short course + OBR vs placebo + OBR
- Pretomanid
- SQ109 – used instead of ethambutol showed no benefit
- Pa200mgMZ: 6 months for drug resistant TB as part of STAND trial
- Bedaquiline, Pretomanid, Pyrazinamide, Moxifloxacin combinations – NC -005
- Nix-TB/PRACTEAL: Six month combination of bedaquiline, pretomanid and linezolid WITH or WITHOUT Moxifloxacin
Bangladeshi regimen

- 515 patients enrolled from 2005-2011
- Short course of MDR TB treatment
- **Intensive regimen: 4-6 months** – Gatifloxacin (or Moxifloxacin), Kanamycin, Prothionamide, Clofazimine, high dose Isoniazid, Pyrazinamide and Ethambutol
- **Continuation phase: 5 months** - Gatifloxacin (or Moxifloxacin), Clofazimine, Ethambutol, Pyrazinamide
- Results: 84.4% had a favourable outcome
- Only ½ completed a 9 month treatment regimen but 95% completed a 12 month regimen
- Unfavourable outcome was noted if FQ resistance ± PZA resistance
Cameroon

- Patients: 323 eligible but only 150 enrolled in a prospective observational cohort study
- Intensive phase 4 months: Kanamycin, Gatifloxacin, Prothionamide, Clofazimine, INH, EMB (25mg/kg) and PZA (30-40mg/kg)
- Continuation phase 8 months: As above without INH and Kanamycin
- By 3/12 99.2% of patients were culture negative
- 89.3% had a successful treatment outcome with no relapse
- 1 failure and no relapses
Shorter vs Longer conventional MDR-TB regimens

Table 5. Treatment success in patients treated with a shorter MDR-TB regimen versus conventional MDR-TB regimens

<table>
<thead>
<tr>
<th>Resistance pattern</th>
<th>Shorter MDR-TB regimen</th>
<th>Conventional MDR-TB regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases regardless of pyrazinamide and fluoroquinolone susceptibility</td>
<td>N: 1008/1116, % (95% CI): 90.3% (87.8%-92.4%)</td>
<td>N: 4033/5850, % (95% CI): 78.3% (71.2%-84%)</td>
</tr>
<tr>
<td>Pyrazinamide resistant; fluoroquinolone resistant</td>
<td>N: 19/28, % (95% CI): 67.9% (47.6%-84.1%)</td>
<td>N: 81/137, % (95% CI): 59.1% (50.6%-67.1%)</td>
</tr>
<tr>
<td>Pyrazinamide resistant; fluoroquinolone susceptible</td>
<td>N: 90/100, % (95% CI): 88.8% (47.3%-98.6%)</td>
<td>N: 840/1075, % (95% CI): 81.4% (71.6%-88.4%)</td>
</tr>
<tr>
<td>Pyrazinamide susceptible; fluoroquinolone resistant</td>
<td>N: 12/15, % (95% CI): 80.0% (50.0%-94.1%)</td>
<td>N: 72/120, % (95% CI): 64.4% (49.6%-76.9%)</td>
</tr>
<tr>
<td>Pyrazinamide susceptible; fluoroquinolone susceptible</td>
<td>N: 121/125, % (95% CI): 96.8% (77.3%-99.6%)</td>
<td>N: 890/1119, % (95% CI): 83.5% (75.7%-89.2%)</td>
</tr>
</tbody>
</table>
Shorter regimen reduced MDR-Tb incidence from 15.2 to 9.7 cases per 100,000

MDR-Tb mortality from 3.0 to 1.7 deaths per 100,000 per year
Treatment outcomes MDR TB

• Successful completion of treatment = 50%, 16% died, 16% lost to follow up, treatment failure in 10% and 8% had no outcome information.
Summary

• Conventional MDR-Tb regimens for adults and children
  - Intensive phase 4-6 months – PZA with 1 drug from group A, 1 drug from group B and at least 2 from group C
  - Add on agents from D2 or D3 if required
  - Add on high dose INH/Ethambutol if required

• **Shorter regimen for MDR-Tb:** Only if resistance to FQ or AGs excluded and have not been previously treated