Management of patients with rifampicin resistance

Dennis Falzon, MD

Workshop for Early Implementers

Implementation and roll-out of the Xpert MTB/RIF system for rapid diagnosis of tuberculosis and multidrug-resistance

Geneva, Switzerland

8 April 2011
Topics of presentation

• R-resistant cases post Xpert MTB/RIF algorithm
• The new PMDT guidelines
• MDR-TB regimens & duration
• Recommendations on monitoring
A. Individuals at risk of MDR-TB
- Diagnosed with TB or
- Suspected of having TB

B. HIV (+) individuals
(or HIV unknown in high HIV settings)
suspected of having TB

HIV (-) individuals not at risk of MDR-TB with either:
- Abnormal CXR
- Sputum smear (-) but still suspected of having TB

Xpert MTB/RIF

- TB, Rif resistance
  - Enrol on MDR-TB regimen
  - DST FLD and SLD
  - ART if HIV +

- TB, no Rif resistance
  - Treatment regimen based on patient history
  - ART if HIV +

- No TB detected
  - Appropriate further clinical management
  - IPT if HIV +
Positive predictive values for R-resistance using Xpert MTB/RIF, at different prevalence of R-resistance (N=1000)

<table>
<thead>
<tr>
<th>% Prevalence of rifampicin resistance</th>
<th>True Positives*</th>
<th>False Positives*</th>
<th>False Negative*</th>
<th>True Negative*</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>9.5</td>
<td>19.8</td>
<td>0.5</td>
<td>970.2</td>
<td>32.4%</td>
<td>99.9%</td>
</tr>
<tr>
<td>2%</td>
<td>19</td>
<td>19.6</td>
<td>1</td>
<td>960.4</td>
<td>49.2%</td>
<td>99.9%</td>
</tr>
<tr>
<td>3%</td>
<td>28.5</td>
<td>19.4</td>
<td>1.5</td>
<td>950.6</td>
<td>59.5%</td>
<td>99.8%</td>
</tr>
<tr>
<td>4%</td>
<td>38</td>
<td>19.2</td>
<td>2</td>
<td>940.8</td>
<td>66.4%</td>
<td>99.8%</td>
</tr>
<tr>
<td>5%</td>
<td>47.5</td>
<td>19</td>
<td>2.5</td>
<td>931</td>
<td>71.4%</td>
<td>99.8%</td>
</tr>
<tr>
<td>6%</td>
<td>57</td>
<td>18.8</td>
<td>3</td>
<td>921.2</td>
<td>75.2%</td>
<td>99.7%</td>
</tr>
<tr>
<td>7%</td>
<td>66.5</td>
<td>18.6</td>
<td>3.5</td>
<td>911.4</td>
<td>78.1%</td>
<td>99.6%</td>
</tr>
<tr>
<td>8%</td>
<td>76</td>
<td>18.4</td>
<td>4</td>
<td>901.6</td>
<td>80.5%</td>
<td>99.6%</td>
</tr>
<tr>
<td>9%</td>
<td>85.5</td>
<td>18.2</td>
<td>4.5</td>
<td>891.8</td>
<td>82.4%</td>
<td>99.5%</td>
</tr>
<tr>
<td>10%</td>
<td>95</td>
<td>18</td>
<td>5</td>
<td>882</td>
<td>84.1%</td>
<td>99.4%</td>
</tr>
<tr>
<td>11%</td>
<td>104.5</td>
<td>17.8</td>
<td>5.5</td>
<td>872.2</td>
<td>85.4%</td>
<td>99.4%</td>
</tr>
<tr>
<td>12%</td>
<td>114</td>
<td>17.6</td>
<td>6</td>
<td>862.4</td>
<td>86.6%</td>
<td>99.3%</td>
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<tr>
<td>13%</td>
<td>123.5</td>
<td>17.4</td>
<td>6.5</td>
<td>852.6</td>
<td>87.7%</td>
<td>99.2%</td>
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<tr>
<td>14%</td>
<td>133</td>
<td>17.2</td>
<td>7</td>
<td>842.8</td>
<td>88.5%</td>
<td>99.2%</td>
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<tr>
<td>15%</td>
<td>142.5</td>
<td>17</td>
<td>7.5</td>
<td>833</td>
<td>89.3%</td>
<td>99.1%</td>
</tr>
</tbody>
</table>

* Sensitivity (95%) and specificity (98%) for Xpert MTB/RIF rifampicin resistance, compared with reference method
Second test for R-resistance
Re-testing

In "low MDR prevalence" setting

(THRESHOLD determined by country)

• Recommended to confirm new cases by LPA or conventional DST
• Sample is also referred for SLD testing
• MDR-TB regimen started immediately and modified if necessary based on second DST
Revised regimens for MDR regimens (1)

• Guidelines on PMDT updated between 2009-2011

• Key questions on MDR regimen composition and duration of treatment

• Systematic review with individual patient data

• 32 case series with >9,000 treatment episodes

• No RCTs
Revised regimens for MDR regimens (2)

Regimen composition for treatment of MDR-TB (1)

1) a fluoroquinolone should be used (strong recommendation / very low-quality evidence)
2) a higher generation fluoroquinolone rather than a lower generation fluoroquinolone should be used (conditional recommendation, very low-quality evidence)
3) ethionamide (or prothionamide) should be used (strong recommendation, very low-quality evidence)

/...
Revised regimens for MDR regimens (3)

4) four second-line anti-TB drugs likely to be effective (including a parenteral agent), as well as pyrazinamide, should be included in the intensive phase (conditional recommendation, very low-quality evidence).

5) regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and either cycloserine or PAS (p-aminosalicylic acid) if cycloserine cannot be used (conditional recommendation, very low-quality evidence).
Revised regimens for MDR regimens (3)

Odds of success by duration of intensive phase (left) and total treatment (right)

<table>
<thead>
<tr>
<th>INTENSIVE PHASE</th>
<th>TOTAL TREATMENT*</th>
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<tbody>
<tr>
<td><strong>Duration in months</strong></td>
<td><strong>Observations</strong></td>
</tr>
<tr>
<td>1- 2.5</td>
<td>308</td>
</tr>
<tr>
<td>2.6 -4.0</td>
<td>1406</td>
</tr>
<tr>
<td>4.1 -5.5</td>
<td>481</td>
</tr>
<tr>
<td>5.6 -7.0</td>
<td>377</td>
</tr>
<tr>
<td>7.1- 8.5</td>
<td>172</td>
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<tr>
<td>8.5 -20</td>
<td>792</td>
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</table>

* only in patients without prior treatment for MDR

** adjusted for age, sex, HIV, past TB treatment, past MDR treatment, and extent of disease
Shorter regimen for MDR : Bangladesh

- Also observational study
- The most effective regimen was 9 months (minimum) with gatifloxacin, clofazimine, E and Z throughout treatment + prothionamide, Km, and high-dose H during intensive phase (minimum of 4 months)
- Relapse-free cure of 88% (95% CL: 82.7–91.6) in 206 patients
- RCTs recommended especially in settings with high prevalence of HIV & resistance to SLDs

Monitoring of response to second line treatment

- The use of sputum smear and culture over smear alone is recommended for monitoring patients with MDR-TB during treatment (conditional recommendation/very low quality evidence).
- Recommendation based on data pooled from 10 observational studies
- Modelling different testing strategies
- Sputum smear and culture monthly until conversion performed best at identifying failures earlier