PHARMACOTHERAPY OF TUBERCULOSIS MANAGEMENT

Rahela Ambaras Khan
BPharm (USM), MPharm (Clin.)(UKM), BCPS(US)
PhD Student
Faculty of Medicine
University Malaya
OUTLINE

• Introduction to Tuberculosis
• Management of PTB in Adult
• Relapse, Failure & Default of Antituberculosis Drugs
• Fixed Dose Combination of Antituberculosis Drugs
• ADR of Antituberculosis & Management
INTRODUCTION
INTRODUCTION

• Tuberculosis (TB) remains an important disease both globally & in Malaysia.

• TB is a disease caused by mycobacteria.

• Number of TB cases in the country continues to increase.

• High rates of morbidity & mortality due to:
  → Delayed presentation
  → Advanced HIV
HIGH RISK GROUPS

• Close TB contacts
• Immunocompromised patients:
  - Diabetes mellitus
  - HIV
  - Chronic obstructive pulmonary disease
  - End-stage renal disease
  - Malignancy
  - Malnutrition
• Substance abusers & cigarette smokers
• Poor people living in overcrowded conditions
MANAGEMENT OF PULMONARY TUBERCULOSIS (PTB) IN ADULTS
NEW CASES

• 6-month regimen consisting of 2 months of EHRZ (2EHRZ) followed by 4 months of HR (4HR) is recommended for newly-diagnosed PTB.

• Pyridoxine 10 - 50 mg daily needs to be added if isoniazid is prescribed.

• Daily treatment is the preferred regimen.

Adopted from WHO. Treatment of Tuberculosis Guidelines (4th Ed.), 2010
# ANTITUBERCULOSIS DOSE

<table>
<thead>
<tr>
<th>DRUG</th>
<th>RECOMMENDED DOES</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Daily</td>
<td>Max in mg</td>
<td>3X a week</td>
<td>Max in mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose (range) in</td>
<td>mg/kg</td>
<td>Dose (range) in</td>
<td>mg/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>body weight</td>
<td>mg</td>
<td>body weight</td>
<td>mg</td>
<td></td>
</tr>
<tr>
<td>Isoniazid (H)</td>
<td>5 (4 - 6)</td>
<td>300</td>
<td>10 (8 - 12)</td>
<td>900</td>
<td></td>
</tr>
<tr>
<td>Rifampicin(R)</td>
<td>10 (8 - 12)</td>
<td>600</td>
<td>10 (8 - 12)</td>
<td>600</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide (Z)</td>
<td>25 (20 - 30)</td>
<td>2000</td>
<td>35 (30 – 40)*</td>
<td>3000*</td>
<td></td>
</tr>
<tr>
<td>Ethambutol (E)</td>
<td>15 (15 - 20)</td>
<td>1600</td>
<td>30 (25 – 35)*</td>
<td>2400*</td>
<td></td>
</tr>
<tr>
<td>Streptomycin (S)</td>
<td>15 (12 - 18)</td>
<td>1000</td>
<td>15 (12 – 18)*</td>
<td>1500*</td>
<td></td>
</tr>
</tbody>
</table>

*daily therapy is recommended for intensive phase

National CPG TB 2012
ROLE OF 1ST LINE ANTITUBERCULOSIS

- Isoniazid : gives a better cure rate
- Rifampicin : sterilises throughout treatment
- Pyrazinamide : Sterilises during the first 2 mth
- Ethambutol & Streptomycin : SM probably has slight sterilising activity, while EMB has none. Both probably need to be given only for the first 2 months, once the bacteria are in dormant form, the drugs are not necessary.
 ROLE OF 1ST LINE ANTITUBERCULOSIS (CONT..)

• Pyrazinamide:

The addition of PZA to an RMP-containing initial phase increases sterilising action as shown by an increase in the proportion of negative 2-month cultures and/or a reduction in the relapse rate.

ROLE OF 1\textsuperscript{ST} LINE ANTITUBERCULOSIS

- Intermittent treatment

Intermittent will only be effective if it contains HRZ, otherwise it is less effective, adding S in hong kong study improve the sputum conversion rate, but not the relapse rate.

Comparing 3 regimen of 2EHRZ4HR, 2(EHRZ)$_3$6HE and 2EHRZ6HE

- HR is better than HE, therefore vitals to have rifampicin in the treatment, even in maintenance phase.

Effect of duration of and intermittency of Rifampicin on tuberculosis treatment outcomes, a systemic review and metaanalysis.

Dick Menzies, Andrea Benedetti, Anita Paydar, Ian Martin, Sarah Royce, Madhukar Pai, Andrew Vernon, Christian Lienhardt, William Burman

PLoS Med 6(9): e1000146. doi:10.1371/journal.pmed.1000146

(RCT 1965 – 2008)
Table 6. Stratified estimates of treatment failures in RCT in new cases.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Studies (N)</th>
<th>Events/Participants (M)</th>
<th>Pooled Event Rate (Across All Trials)</th>
<th>95% CI</th>
<th>I² (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of rifampin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin 1–2 mo</td>
<td>72</td>
<td>94/4,133</td>
<td>1.8</td>
<td>0.2 to 3.3</td>
<td>0.36 (0.15 to 0.52)</td>
</tr>
<tr>
<td>Rifampin 3–5 mo</td>
<td>42</td>
<td>16/2,508</td>
<td>0.3</td>
<td>0 to 0.6</td>
<td>0 (0 to 0.35)</td>
</tr>
<tr>
<td>Rifampin 6–7 mo</td>
<td>178</td>
<td>150/10,060</td>
<td>0.4</td>
<td>0.1 to 0.7</td>
<td>0 (0 to 0.19)</td>
</tr>
<tr>
<td>Rifampin 8+ mo</td>
<td>18</td>
<td>10/1,384</td>
<td>0.2</td>
<td>0 to 0.6</td>
<td>0 (0 to 0.49)</td>
</tr>
<tr>
<td><strong>Use of intermittent therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily throughout</td>
<td>159</td>
<td>179/11,510</td>
<td>0.4</td>
<td>0.2 to 0.7</td>
<td>0.07 (0 to 0.24)</td>
</tr>
<tr>
<td>Daily then thrice weekly</td>
<td>35</td>
<td>4/961</td>
<td>0.3</td>
<td>0 to 1.0</td>
<td>0 (0 to 0.38)</td>
</tr>
<tr>
<td>Daily then twice weekly</td>
<td>46</td>
<td>49/2,749</td>
<td>1.2</td>
<td>0.1 to 2.4</td>
<td>0.21 (0 to 0.45)</td>
</tr>
<tr>
<td>Thrice weekly throughout 𝑏</td>
<td>70</td>
<td>38/2,865</td>
<td>0.5</td>
<td>0 to 1.0</td>
<td>0 (0 to 0.28)</td>
</tr>
<tr>
<td><strong>Initial drug resistance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DST not done/reported</td>
<td>19</td>
<td>78/2,105</td>
<td>2.2</td>
<td>0 to 4.4</td>
<td>0 (0 to 0.48)</td>
</tr>
<tr>
<td>Sensitive to all TB drugs</td>
<td>126</td>
<td>120/14,900</td>
<td>0.3</td>
<td>0.1 to 0.4</td>
<td>0 (0 to 0.21)</td>
</tr>
<tr>
<td>Isoniazid resistance</td>
<td>67</td>
<td>25/477</td>
<td>2.8</td>
<td>0.7 to 5.0</td>
<td>0 (0 to 0.29)</td>
</tr>
<tr>
<td>Streptomycin resistance</td>
<td>54</td>
<td>6/316</td>
<td>1.3</td>
<td>0 to 2.7</td>
<td>0 (0 to 0.31)</td>
</tr>
<tr>
<td>INH+streptomycin resistant (PDR)</td>
<td>44</td>
<td>41/287</td>
<td>8.3</td>
<td>1.9 to 14.7</td>
<td>0 (0 to 0.34)</td>
</tr>
<tr>
<td><strong>Duration of pyrazinamide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No pyrazinamide</td>
<td>59</td>
<td>97/4,831</td>
<td>0.3</td>
<td>0 to 0.6</td>
<td>0.30 (0.03 to 0.49)</td>
</tr>
<tr>
<td>1–3 mo</td>
<td>139</td>
<td>124/8,287</td>
<td>0.6</td>
<td>0.2 to 1.0</td>
<td>0 (0 to 0.21)</td>
</tr>
<tr>
<td>4+ mo</td>
<td>112</td>
<td>49/4,967</td>
<td>0.5</td>
<td>0.1 to 0.8</td>
<td>0 (0 to 0.23)</td>
</tr>
<tr>
<td><strong>Duration of streptomycin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No streptomycin</td>
<td>100</td>
<td>188/7,907</td>
<td>0.6</td>
<td>0.2 to 0.9</td>
<td>0.18 (0 to 0.36)</td>
</tr>
<tr>
<td>1–3 mo</td>
<td>117</td>
<td>44/6,328</td>
<td>0.4</td>
<td>0.1 to 0.6</td>
<td>0 (0 to 0.23)</td>
</tr>
<tr>
<td>4+ mo</td>
<td>93</td>
<td>38/3,850</td>
<td>0.5</td>
<td>0 to 0.9</td>
<td>0 (0 to 0.25)</td>
</tr>
<tr>
<td><strong>Number of drugs to which strains susceptible</strong> 𝑏</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1 drugs</td>
<td>2</td>
<td>10/29</td>
<td>33.2</td>
<td>0 to 103.5</td>
<td>0 (–, –)</td>
</tr>
<tr>
<td>2 drugs</td>
<td>66</td>
<td>114/1,782</td>
<td>2.8</td>
<td>0.2 to 5.2</td>
<td>0.52 (0.36 to 0.63)</td>
</tr>
<tr>
<td>3 drugs</td>
<td>151</td>
<td>43/5,664</td>
<td>0.3</td>
<td>0 to 0.5</td>
<td>0 (0 to 0.20)</td>
</tr>
<tr>
<td>4 drugs</td>
<td>72</td>
<td>25/8,505</td>
<td>0.1</td>
<td>0 to 0.1</td>
<td>0 (0 to 0.28)</td>
</tr>
<tr>
<td>Continuation phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1 drugs</td>
<td>69</td>
<td>54/588</td>
<td>2.6</td>
<td>0 to 6.1</td>
<td>0 (0 to 0.28)</td>
</tr>
<tr>
<td>2 drugs</td>
<td>142</td>
<td>113/9,838</td>
<td>0.2</td>
<td>0.1 to 0.4</td>
<td>0 (0 to 0.20)</td>
</tr>
<tr>
<td>3 or more drugs</td>
<td>74</td>
<td>25/5,528</td>
<td>0.1</td>
<td>0 to 0.2</td>
<td>0 (0 to 0.27)</td>
</tr>
<tr>
<td><strong>Supervision of therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All doses fully supervised</td>
<td>232</td>
<td>145/10,446</td>
<td>0.4</td>
<td>0.1 to 0.7</td>
<td>0 (0 to 0.16)</td>
</tr>
<tr>
<td>None or partial DOT</td>
<td>78</td>
<td>125/7,639</td>
<td>0.4</td>
<td>0.1 to 0.7</td>
<td>0.19 (0 to 0.39)</td>
</tr>
<tr>
<td><strong>Completion of therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good (=10% dropouts)</td>
<td>181</td>
<td>102/11,837</td>
<td>0.3</td>
<td>0.1 to 0.5</td>
<td>0 (0 to 0.19)</td>
</tr>
<tr>
<td>Poor (&gt;10% dropouts)</td>
<td>129</td>
<td>168/6,248</td>
<td>0.9</td>
<td>0.3 to 1.5</td>
<td>0.25 (0.07 to 0.40)</td>
</tr>
</tbody>
</table>
Comparative evaluation of efficacy and safety profile of three anti-tuberculous regimens in Mangalore.

S Beena, KN Rao, MR Pai
Comparing 3 different centres that used 3 different regimes

<table>
<thead>
<tr>
<th></th>
<th>Before Treatment</th>
<th>During Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean weight (kg) ± S.D.</td>
<td>Mean weight (kg) ± S.D.</td>
</tr>
<tr>
<td><strong>Group I</strong></td>
<td>42.37±5.41</td>
<td>45.93±5.23</td>
</tr>
<tr>
<td><strong>Group II</strong></td>
<td>42.27±5.48</td>
<td>43.80±5.47</td>
</tr>
<tr>
<td><strong>Group III</strong></td>
<td>43.03±5.75</td>
<td>45.03±5.87</td>
</tr>
</tbody>
</table>

Group I* vs Group II* at 3rd follow up P<0.05

Gp I: 2EHRZ4HR
Gp II: 2SHRZ4HR
Gp III: 2SHRZ4HE
Efficacy of ethambutol better than S in terms of weight gain, cough and sputum conversion, p<0.05
‘The early bactericidal activity of anti-tuberculosis drugs: A literature review’

P.R. Donald; A.H. Diacon

Tuberculosis (2008) 88 Suppl. 1, S75-S83
Isoniazide has the highest EBA in the first 2 days (faster onset) then its effect becomes much lower.

Rifampicin maintains its moderate EBA up to 14 days studied.
Table 3: The early bactericidal activity of fluoroquinolones (dose mg)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Days 0–2</th>
<th></th>
<th>Authors</th>
<th>Days 0–5a, 0–7b or 2–7c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sirgel et al</td>
<td>11</td>
<td>0.21</td>
<td>(SD 0.17)</td>
<td>Kennedy et al</td>
</tr>
<tr>
<td>(1997)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitchison &amp; Sturm</td>
<td>10</td>
<td>0.32</td>
<td>(SD 0.36)</td>
<td>Chambers et al</td>
</tr>
<tr>
<td>(1997)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chambers et al</td>
<td>10</td>
<td>0.32</td>
<td>(SD 0.05)</td>
<td>Pletz et al</td>
</tr>
<tr>
<td>(1998)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sirgel et al</td>
<td>11</td>
<td>0.38</td>
<td>(SD 0.31)</td>
<td>Johnson et al</td>
</tr>
<tr>
<td>(2000)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gosling et al</td>
<td>8</td>
<td>0.53</td>
<td>(SD 0.31)</td>
<td></td>
</tr>
<tr>
<td>(2003)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johnson et al</td>
<td>9</td>
<td>0.33</td>
<td>(SD 0.39)</td>
<td></td>
</tr>
<tr>
<td>(2006)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CFX=ciprofloxacin, OFX=ofloxacin, MFX=moxifloxacin, LFX=levofloxacin, GFX=gatifloxacin.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*In the study of Chambers et al 1998 an OFX dose of 600 mg was used.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Moxi > Levo  > Oflox > Gati > Cipro in the first 2 days
Table 4  The early bactericidal activity of aminoglycosides

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>n</th>
<th>Streptomycin</th>
<th>n</th>
<th>Streptomycin</th>
<th>n</th>
<th>Amikacin</th>
<th>n</th>
<th>Paromomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>8</td>
<td>0.133 (SD 0.09)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>4</td>
<td>0.094</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>9</td>
<td>0.043 (SD 0.10)</td>
<td>15</td>
<td>0.052 (SD 0.10)</td>
<td>15</td>
<td>0.092 (SD 0.14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td>13</td>
<td>0.045 (SD 0.14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.5</td>
<td>10</td>
<td>-0.133 (SD 0.16)</td>
<td>12</td>
<td>0.041 (SD 0.10)</td>
<td>7</td>
<td>0.066 (SD 0.22)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AMG – The higher the dose, the better the EBA
IMPORTANT POINTS

• Rifampicin
  → should be used for the whole duration of treatment
  → whenever possible, rifampicin dosage should not be lower than recommended dosage (10 - 12 mg/kg).

• Pyrazinamide beyond 2 months during the intensive phase does not confer further advantage if the organism is fully susceptible.
DAILY VS TWICE WEEKLY VS THrice WEEKLY

• WHO recommends daily dosing throughout the course of antiTB treatment.

• A daily intensive phase followed by thrice weekly maintenance phase is an option.

• A maintenance phase with twice weekly dosing is not recommended since missing one dose means the patient receives only half the total dose for that week.
PREVIOUSLY TREATED WITH ANTITUBERCULOSIS (FAILURE, RELAPSE, DEFAULT)

New case who have taken treatment for more than one month & are currently smear or culture positive again.
### DEFINITION

<table>
<thead>
<tr>
<th>Previously treated</th>
<th>Patient previously treated for TB including relapse, failure &amp; default cases.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relapse</strong></td>
<td>A patient whose most recent treatment outcome was “cured” or “treatment completed”, &amp; who is subsequently diagnosed with bacteriologically positive TB by sputum smear microscopy or culture.</td>
</tr>
<tr>
<td><strong>Failure</strong></td>
<td>A patient who has received First Line treatment for TB &amp; in whom treatment has failed.</td>
</tr>
<tr>
<td><strong>Default</strong></td>
<td>A patient who returns to treatment, bacteriologically positive by sputum smear microscopy or culture, following interruption of treatment for 2 or more consecutive months.</td>
</tr>
</tbody>
</table>
PREVIOUSLY TREATED TB

• Recommend: retreatment regimen containing first-line drugs 2HRZES/1HRZE/5HRE if country-specific data show low or medium levels of MDR-TB in these patients or if such data is not available.

• Drug sensitivity test (DST) must be done for patients. When results become available, drug regimen should be adjusted appropriately.

WHO Recommendation 2010.
FIXED DOSE COMBINATIONS
ANTITUBERCULOSIS
FIXED-DOSE COMBINATION (FDC) IN MALAYSIA

• Forecox-Trac Film Coated Tab: isoniazid, rifampicin, ethambutol & pyrazinamide
• Rimactazid 300 Sugar Coated Tab: isoniazid, & rifampicin
• Rimcure 3-FDC Film Coated Tab: isoniazid, rifampicin & pyrazinamide
• Akurit-Z Tab: isoniazid, rifampin (rifampicin) & pyrazinamide
• Akurit Tab: isoniazid & rifampin (rifampicin)
• Akurit-Z Kid Dispersible Tab: isoniazid, rifampin (rifampicin) & pyrazinamide
• Akurit-4: ethambutol, isoniazid, rifampin (rifampicin) & pyrazinamide
FDC IN MOH

• 4-Drug combination: isoniazid 75 mg, rifampicin 150 mg, pyrazinamide 400 mg & ethambutol 275 mg tablet

• 3-Drug combination: isoniazid 75 mg, rifampicin 150 mg & pyrazinamide 400 mg tablet
RECOMMENDED DOSES

• 30 - 37 kg body weight: 2 tablets daily

• 38 - 54 kg body weight: 3 tablets daily

• 55 - 70 kg body weight: 4 tablets daily

• More than 70 kg body weight: 5 tablets daily
EFFECTIVENESS OF FDC

• FDCs compared to separate-drug regimens significantly reduce risk of non-compliance by 17% & consequently improve effectiveness of therapy.\(^1\)

• In term of bioavailability, FDCs are proven to be bioequivalent to separate-drugs formulations at the same dose levels.\(^2\)

\(^1\)Bangalore S et al., Am J Med, 2007
\(^2\)Agrawal S et al., Int J Pharm, 2002
OTHER ADVANTAGES

• Smaller number of tablets to be ingested may also encourage patient adherence.

• Prescription errors are likely to be less frequent for FDCs due to easy adjustment of dosage according to patient weight.
ADVERSE DRUG REACTIONS OF ANTITB
DEFINITION OF ADVERSE DRUG REACTION (ADR)

• A response to a medicine which is unintended or harm which occurs at a normal dosage during normal use.

ONSET OF ADR FOR ANTITB

• ADRs occur within early stage of the treatment compared to the later stage.

Kishore PV et al., Pa J Pharm Sci, 2008
CLASSIFICATION OF ADR FOR ANTITB

Troublesome but NOT SERIOUS
- Nausea
- Tiredness
- Pruritus
- Minor rashes

Treat symptomatically WITHOUT treatment interruption

Need IMMEDIATE DISCONTINUATION
- Severe skin reaction (Steven-Johnson Syndrome, Toxic Epidermal Necrolysis & Drug Rash with Eosinophilia & Systemic Symptoms)
- Hepatitis

Treat symptomatically WITHOUT treatment interruption
RISK FACTORS OF ADR FOR ANTITB

- Age >40 years
- Overweight/obesity
- Smoking
- Alcoholism
- Anaemia
- Baseline ALT more than twice upper limit of normal
- Baseline aspartate aminotransferase more than twice upper limit of normal

- EPTB
- MDR-TB medication
- HIV infection
- CD4 count <350 cells/mm$^3$
- Hepatitis B virus infection
- Hepatitis C virus infection
- Concomitant use of other hepatotoxic drugs

$^1$Chung-Delgado K et al., PLoS ONE, 2011
$^2$Vilarica AS et al., Rev Port Pneumol, 2010
$^3$Khalili H et al., Factors DARU, 2009
SYSTEM MOST AFFECTED BY ANTITB DRUGS

- Hepatobiliary
- Skin
- Gastrointestinal tract
- Skeletal system
- Renal

1 Shang P et al., PLoS ONE, 2011
2 Teleman MD et al., Int J Tuberc Lung Dis, 2002
DRUG-INDUCED RASHES

Algorithm

Severe Cutaneous ADRs

Discontinue antiTB until the rashes subside

Reintroduce individual drug sequentially to identify the offending drug

Provide suitable regimen when an offending drug is identified
(If possible, regimen should include 2 most potent drugs namely isoniazid & rifampicin)

Drug-Induced

Pyrazinamide (MOST)

Yee D et al., Am J Respir Crit Care Med, 2003
Desensitisation?

- If the offending drugs are both isoniazid & rifampicin
- If a suitable drug combination is available, it is not necessary to perform desensitisation
- It is done by careful administration of increasing doses of the drug under close supervision
- Complex Cutaneous ADRs requires specialists consultation
DRUG-INDUCED HEPATITIS

**Risk Factors**
- Slow acetylators
- Old age
- Extensive TB disease
- Malnutrition
- Alcoholism
- Chronic viral hepatitis B & C infections
- Pregnancy until 90 days postpartum
- HIV
- Organ transplant recipients

**Drug-Induced**
- Pyrazinamide (MOST)
- Isoniazid
- Rifampicin (LEAST)

**Monitoring**
At least for the first 2 - 4 weeks is recommended among all patients with antiTB treatment as DIH usually occurs within the initial 2 months of treatment.

---

1. Yew WW et al., Respirology, 2006
2. Centers for Disease Control & Prevention (CDC)
Restarting?

• Depends on whether hepatotoxicity sets in during the initial or the continuation phase of treatment & the amount of treatment received prior to the onset of such toxicity.
When to Stop AntiTB?

- Serum transaminase level reaches 3 x ULN for patients with symptoms suggestive of hepatitis
- Serum transaminase level reaches 5 x ULN for those without symptoms

Restarting

The patient can then be retreated with a regimen containing fewer potentially hepatotoxic drugs such as streptomycin, ethambutol, isoniazid & fluoroquinolones.
REFERENCES


• MOH. 2012. CPG on Management of Tuberculosis3rd edition.
ACKNOWLEDGEMENT

• Dr Wong Jyi Lin
  Respiratory Physician, Hosp Umum Sarawak

• Dr Irfan Ali Hyder Ali
  Respiratory Physician, Penang Hospital

• CPG Development Group on Management of Tuberculosis 2011
THANK YOU
MANAGEMENT OF MULTIDRUG RESISTANT (MDR) TB
DRUG RESISTANT TB

• Monodrug resistant
  → MTB resistant to any one of antiTB drugs

• Polydrug resistant
  → MTB resistant to 2 or more antiTB drugs

• Multidrug resistant
  → MTB resistant to both isoniazid & rifampicin with or without resistant to other antiTB drugs
DRUG RESISTANT TB CONT..

• Extensively drug-resistance (XDR)
  → MDR TB with resistance to at least one injectable second-line antiTB drugs & any fluoroquinolone

• Extremely/Total drug-resistance TB
  → not well-defined
  → MTB resistant to all tested first-line & second-line antiTB drugs

Inadequate treatment or improper use of the antiTB medications remains an important cause of drug-resistant TB!
### SECOND-LINE ANTITB DRUGS

<table>
<thead>
<tr>
<th>Group Name</th>
<th>AntiTB Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
<td>All the first line antiTB drugs which are the most effective. If laboratory evidence and clinical history suggests that a drug from this group is effective, it should be used. If a Group 1 drug was used in a previous regimen that fails, its efficacy should be questioned even if the DST result suggests susceptibility. The newer rifamycins, such as rifabutin, have very high rates of cross-resistance to rifampicin.</td>
</tr>
<tr>
<td>Group 2 - Injectable drugs</td>
<td>kanamycin, amikacin</td>
<td>Group 2 - 5 (except streptomycin) are second line or reserve drugs. All patients should receive a Group 2 injectable agent if susceptibility is documented or suspected. Kanamycin or amikacin is the first choice of an injectable agent. Amikacin and kanamycin have high frequency of cross-resistance. Hence if there is a resistance to both streptomycin and kanamycin, capreomycin should be used.</td>
</tr>
<tr>
<td>Group 3</td>
<td>levofloxacin, moxifloxacin, ofloxacin</td>
<td>The newer generation fluoroquinolones, such as levofloxacin or moxifloxacin, is the fluoroquinolone of choice.</td>
</tr>
<tr>
<td>Group 4</td>
<td>ethionamide, cycloserine, p-aminosalicylic acid (PAS)*</td>
<td>Drugs in this group can be added.</td>
</tr>
<tr>
<td>Group 5</td>
<td>clofazimine, linezolid, amoxicillin/clavulanate, clarithromycin, imipenem</td>
<td>Group 5 drugs are not use routinely as their efficacy is uncertain. They may be needed in patients with XDR-TB.</td>
</tr>
</tbody>
</table>

*Drug not registered in Malaysia
STANDARD MDR-TB REGIMEN

- Consist of **4 second-line antiTB drugs** that are most likely to be effective in the intensive phase

- Regimens should include:
  - Fluoroquinolone*
  - Parenteral agent (aminoglycosides)
  - Ethionamide &
  - Either **cycloserine** or **PAS** (if cycloserine cannot be used) &
  - Pyrazinamide

*Later-generation fluoroquinolone (e.g. levofloxacin & moxifloxacin) should be used
MONITORING

• Monthly sputum smears & cultures until smear & culture conversion occur
  ➔ “Conversion” - 2 consecutive negative smears & cultures taken 30 days apart

• Monthly monitoring by clinician until sputum conversion, then every 2 - 3 monthly.

• At each visit, patient’s weight & side effects to antiTB drugs should be monitored.
DURATION OF TREATMENT

Newly MDR-TB (i.e. not previously treated for MDR-TB), a total treatment duration is 20 months for most patients.

May be modified according to the response to treatment based on patient’s cultures, smears, CXR & clinical status.
MANAGEMENT OF EXTRAPULMONARY TUBERCULOSIS (EPTB) IN ADULTS
DURATION OF EPTB TREATMENT - NICE RECOMMENDATION\textsuperscript{1}

- Meningeal TB – 2 months S/EHRZ+10HR*
- Peripheral lymph node TB – should normally be stopped after 6 months
- Bone & joint TB – 6 months
- Pericardial TB – 6 months

\textsuperscript{1}National Collaborating Centre for Chronic Conditions and the Centre for Clinical Practice. Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control. 2011
DURATION OF EPTB TREATMENT - WHO RECOMMENDATION

• Regimen should contain 6 months of rifampicin: 2HRZE/4HR*
• Duration of treatment for TB meningitis is 9 - 12 months & bone & joint TB is 9 months

CORTICOSTEROIDS IN EPTB

- Corticosteroid therapy may benefit patients with some forms of EPTB.
# TB MENINGITIS

<table>
<thead>
<tr>
<th>Severity</th>
<th>Regime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I disease</td>
<td>Week 1: IV dexamethasone sodium phosphate 0.3 mg/kg/day&lt;br&gt;Week 2: 0.2 mg/kg/day&lt;br&gt;Week 3: Oral dexamethasone 0.1 mg/kg/day&lt;br&gt;Week 4: Oral dexamethasone a total of 3 mg/day, decreasing by 1 mg each week</td>
</tr>
<tr>
<td>Grade II &amp; III disease</td>
<td>Week 1: IV dexamethasone sodium phosphate 0.4 mg/kg/day&lt;br&gt;Week 2: 0.3 mg/kg/day&lt;br&gt;Week 3: 0.2 mg/kg/day&lt;br&gt;Week 4: 0.1 mg/kg/day, then oral dexamethasone for 4 weeks, decreasing by 1 mg each week</td>
</tr>
</tbody>
</table>

Prasad K et al., Cochrane, 2008
TB PERICARDITIS

Week 1 - 4: Oral prednisolone 60 mg daily
Week 5 - 8: Oral prednisolone 30 mg daily
Week 9 - 10: Oral prednisolone 15 mg daily
Week 11: Oral prednisolone 5 mg daily
IV hydrocortisone can be used if patients cannot take orally: IV hydrocortisone 300 mg bolus, then 100 mg daily for 1 - 2 weeks b, continued with oral prednisolone as above

INTERRUPTION OF THERAPY
INTERRUPTION OF INTENSIVE PHASE

– If ≥14 days, to restart from beginning i.e. Day 1

– If <14 days, to continue from last dose
INTERRUPTION OF MAINTENANCE PHASE

– After patient receives 80% of total planned doses:
  ➔ If sputum AFB smear was negative at initial presentation, tx may be stopped
  ➔ If sputum AFB smear was positive,
    treatment should be continued to achieve total number of doses.
– If total doses <80% & interruption lapse is ≥2 months, restart treatment from beginning.
– If total doses is <80% & interruption lapse is <2 months, continue treatment from date it stops to complete full course.