Treatment outcomes and tolerability of the revised WHO antituberculous drug dosages among children living in high HIV prevalence settings

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BACKGROUND
- In 2010, WHO revised the dosages of antituberculous drugs for children increasing rifampicin (R) to 15mg/Kg, isoniazid (H) to 10mg/Kg and pyrazinamide (Z) to 35mg/Kg.
- We assessed the treatment outcomes and safety, particularly liver toxicity of children treated with the new recommendations in Mbarara, Uganda.

OBJECTIVES
- To describe the end of treatment outcomes and the one year TB recurrence rate
- To identify factors associated with death
- To describe the occurrence of adverse events

METHODS
Eligibility criteria
- Aged 1 month to 14 years AND suspicion of tuberculosis based on:
  - At least one clinical sign suggestive of TB, OR
  - Referred with a CXR suggestive of TB, OR
  - Asymptomatic child with a recent TB contact history and abnormal chest X-ray
- Excluded if on TB treatment or had completed treatment within the past 6 months.

Study design
Prospective cohort

Procedures
- Diagnosis of TB:
  - Clinical assessment by a medical doctor
  - Antero-posterior and lateral chest X-ray
  - Sputum or induced sputum: smear, Xpert and culture
- Treatment of TB:
  - 2HRZ 4 HR
  - Addition of ethambutol (E) in HIV infected children or extensive disease or smear positive or suspicion of H resistance
  - WHO dosages-R 15mg/kg, H-10mg/kg, Z-35mg/kg and E-20mg/kg
  - Bi-weekly follow up visits for intensive phase and monthly for continuation phase
  - Alanine aminotransferase (ALT) monitoring at weeks 2, 4 and 8 of treatment
  - Six months follow-up visit after completion of treatment

RESULTS
Study profile
144 started on TB treatment
19 deaths
4 defaulters
1 transferred out
120 assessed at 6 months
2 deaths
6 loss to follow up
3 failures started on retreatment
109 assessed at 12 months

Children Characteristics
- 106 (72.2%) were <5 years and 64 (60.4%) of these were <2 years.
- 56.3% males
- 48 (33.3%) HIV infected
- Malnutrition (weight for height Z score): 33.3% moderately to severely (<-2SD)
- 20 (13.9%) microbiologically confirmed
- Of the 124 empirically treated for TB, 100 (80.6%) had CXR suggestive of TB and 11 (8.9%) had CXR abnormal non-suggestive of TB

TB Treatment Outcomes, N=144

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Success</th>
<th>Failure</th>
<th>Default</th>
<th>Death</th>
<th>Transferred out</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>117 (81.3)</td>
<td>3 (2.1)</td>
<td>4 (2.8)</td>
<td>19 (13.2)</td>
<td>1 (0.7)</td>
</tr>
</tbody>
</table>

Median time between treatment initiation and death was 12 days IQR(8-39)
After adjusting for sex, HIV status and age, moderately to severely malnourished children had a higher risk of death: aOR 2.8 (95%CI 1.07-7.35)

Post TB treatment outcomes, N= 117

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Sustained success</th>
<th>Relapse</th>
<th>Lost to follow up</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>109 (93.2)</td>
<td>0</td>
<td>6 (5.1)</td>
<td>2 (1.7)</td>
</tr>
</tbody>
</table>

Safety
Liver function test

ALT UI/mL

Serious adverse events (SAE)
- 34 hospitalizations for SAE in 30 (20.8%) children
  - 16 (47.1%) acute low respiratory tract infections
  - 4 (11.8%) acute severe malnutrition
  - 3 (8.8%) malaria
  - 1 (2.9%) increase of ALT >5xULN at week 8: resolved without treatment interruption
- 28/34 SAE (82.4%) occurred in children <5 years

CONCLUSION
- Despite increased pill burden, the new TB recommended drug dosages did not result in high proportion of defaulters and treatment was well tolerated.
- More than 80% of children achieved treatment success. However, the high proportion of deaths, especially among malnourished children is a serious concern. It highlights the importance of early and better management of comorbidities in children with TB.

Acknowledgements
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