OPEN FORUM 4
KEY ISSUES IN TB DRUG DEVELOPMENT
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ADDIS ABABA, ETHIOPIA

THE ASSESSMENT OF ANTITUBERCULOSIS AGENTS IN CHILDREN

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Are Efficacy Studies of TB Drugs for Children Necessary?
The assessment of tuberculosis agents in children

- The spectrum of TB disease in childhood
- The diagnosis of TB in childhood
- Response to TB treatment in children
- Pharmacokinetics and pharmacodynamics of TB drugs

Assessment of TB agents in children should emphasize pharmacokinetics and toxicity.
“It is very difficult to assess the outcome and efficacy of any regimen for treatment of tuberculosis in children because they rarely have positive sputum and gastric washings and the best criteria would be clinical findings, such as weight gain and radiologic follow-up studies.”
Is childhood tuberculosis different from adult tuberculosis?

- Histologically and microbiologically, childhood tuberculosis lesions cannot be distinguished from those seen in adults.
Is childhood tuberculosis different from adult tuberculosis?

However:
- the spectrum of disease seen is very different,

But:
- even here one must be careful; in low incidence areas primary tuberculosis may occur in adults with similar consequences and extensive cavitating disease may be seen in infants.
The spectrum of disease in children is very different and is influenced by the age of the child.
Is childhood tuberculosis different from adult tuberculosis?

- In children the form of disease tends to be dominated by the immunological response rather than the bacteriological load.
- Enlarged mediastinal lymph nodes are intimately involved in the pathogenesis of most childhood pulmonary disease.
- Relatively benign course of many tuberculosis infections
Infection vs Disease

If evaluated shortly after infection:

- Gastric aspirate may yield a positive culture
- Culture of urine is reported positive in 20% or more of children recently infected
- Chest radiograph may show adenopathy in up to 80% of individuals
- Chest radiograph may be normal, but gastric aspirate culture positive and CT or MRI shows adenopathy!!
# Infection vs Disease

## TABLE 3

<table>
<thead>
<tr>
<th>Initial Roentgenographic Involvement</th>
<th>Total</th>
<th>Less than 4 Years</th>
<th>4–6 Years</th>
<th>More than 6 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Isoniazid</td>
<td>Placebo</td>
<td>Isoniazid</td>
<td>Placebo</td>
</tr>
<tr>
<td>Number of children*</td>
<td>1,376</td>
<td>1,335</td>
<td>827</td>
<td>788</td>
</tr>
<tr>
<td>Per cent:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative for evidence of tuberculous infection</td>
<td>41.4</td>
<td>38.7</td>
<td>45.7</td>
<td>43.7</td>
</tr>
<tr>
<td>Hilar and/or paratracheal abnormalities</td>
<td>42.5</td>
<td>45.0</td>
<td>37.7</td>
<td>39.8</td>
</tr>
<tr>
<td>Parenchymal† tuberculous lesions</td>
<td>16.1</td>
<td>16.3</td>
<td>16.6</td>
<td>16.5</td>
</tr>
</tbody>
</table>

* Does not include 18 in the isoniazid group and 21 in the placebo group whose initial roentgenograms were not satisfactory.

† With or without hilar or paratracheal involvement.
Wallgren A. Primary tuberculous infections in young adult life and in childhood. Am J Dis Child 1941; 61: 577-589

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Number infected</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>39</td>
<td>36.9%</td>
</tr>
<tr>
<td>1-3</td>
<td>64</td>
<td>15.6%</td>
</tr>
<tr>
<td>3-7</td>
<td>225</td>
<td>4.4%</td>
</tr>
<tr>
<td>7-16</td>
<td>125</td>
<td>0.8%</td>
</tr>
</tbody>
</table>
Mortality in relation to age


<table>
<thead>
<tr>
<th>Age of child</th>
<th>Mortality(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6-months</td>
<td>55</td>
</tr>
<tr>
<td>1-2 years</td>
<td>28</td>
</tr>
<tr>
<td>4-9</td>
<td>15</td>
</tr>
</tbody>
</table>
Mortality in relation to age


Mortality in relation to age
South Africa 1971-1980

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>7.1</td>
</tr>
<tr>
<td>1-4</td>
<td>2.8</td>
</tr>
<tr>
<td>5-9</td>
<td>1.1</td>
</tr>
<tr>
<td>10-14</td>
<td>1.5</td>
</tr>
</tbody>
</table>
Tuberculosis in Adolescents
Features of Childhood Tuberculosis

- Cavitation is uncommon, lesions are thus usually paucibacillary
- Organisms are dormant or intermittently active
- Frequently culture negative
- Seldom smear-positive
- Radiological extent of disease is not necessarily related to bacteriological burden
Culture of *M. tuberculosis*, Detection of Acid-fast Bacilli

- Gastric aspirate/lavage is the usual manner to seek culture or microscopy confirmation of childhood TB
- Success will depend upon the extent of disease and the presence of cavitation
- Confusingly a positive culture may often be obtained early in a primary infection
Sputum/Gastric aspirate Culture-positive


- Mulago Hospital, Uganda.
- **750** children with suspected TB evaluated
- **121** probable cases evaluated by tuberculin testing, chest radiography, sputum induction or lymph node biopsy
Sputum/Gastric aspirate Culture-positive

- Mantoux test-positive 55/121 (45%)
- Negative Mantoux associated with HIV-infection
- Induced-sputum -
  - 12/101 (12%) pos smears,
  - 30/101 (30%) pos cultures
Sputum/Gastric aspirate
Culture-positive


Prospective community-based study

- All children reporting a non-remitting cough >2 weeks in duration
- 1024 children referred for evaluation
- Symptoms resolving in 596 children, and 428 investigated
Sputum/Gastric aspirate Culture-positive


PTB diagnosed in 197 (46%) children
- 96 (49%) bacteriologically proven
- 75 (38%) radiologically certain
- 26 (13%) probable TB

<table>
<thead>
<tr>
<th>Clinical &amp; radiographic features</th>
<th>N</th>
<th>Fl Microsoc + (%)</th>
<th>GAsp Culture + (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miliary TB</td>
<td>13</td>
<td>54</td>
<td>69</td>
</tr>
<tr>
<td>Far-advanced cavitary TB</td>
<td>13</td>
<td>62</td>
<td>69</td>
</tr>
<tr>
<td>Far-advanced non-cavitary TB</td>
<td>26</td>
<td>73</td>
<td>65</td>
</tr>
<tr>
<td>Moderately advanced TB</td>
<td>21</td>
<td>14</td>
<td>43</td>
</tr>
<tr>
<td>Minimal or negative TB</td>
<td>24</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>No TB</td>
<td>81</td>
<td>1</td>
<td>5</td>
</tr>
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</table>
Radiological features of childhood tuberculosis

Radiology

- the radiological extent of disease may bear no relationship to the microbiological burden
- Radiological changes persist long after successful treatment is completed
- Radiological changes may undergo spontaneous remission
Assessment of response to antituberculosis agents

In children:

- Seldom microscopy smear-positive
- Often culture negative
- Tendency, especially in children 5-10 years of age, for ‘spontaneous’ recovery; “The safe school age”
- Hilar adenopathy may remain present for up to 2 years and may increase in size despite ‘successful’ treatment
Assessment of response to treatment


- Radiological improvement is used as an objective criterion of success.
- Graded as:  
  I. Complete clearance  
  II. Moderate to significant clearance  
  III. Mild clearance  
  IV. No clearance or deterioration

The response to treatment was judged by:

- Elimination of symptoms
- Negative sputum cultures. Cultures became negative within 3-months in all 5 patients with positive cultures to start with.
- Disappearance of extra-pulmonary findings
Clearing of chest radiograph findings.

- **Lymphadenopathy** resolved slowly. In 12 children (50% of those with nodes) nodes did not clear for 2-3 years.

- **Pulmonary infiltrates**: Of 23 patients 4 (17%) had residual infiltrates after 9 months of treatment.

Criteria used to assess response to treatment pulmonary tuberculosis:

- General improvement
- Normalization of temperature
- Improvement in appetite
- Weight gain.
The radiological response was graded as:

*Marked* if the lesions cleared within 3-months and no new lesions appeared,

*Moderate* if there was partial clearance of the radiological lesions within 3-months and no fresh lesions or

*Poor* if there was no radiological clearance or an increase in the size of pulmonary lesions or the appearance of new lesions.
All children had radiological improvement after 6-months of treatment, but

- Chest radiographs were completely normal in only 21 (22%).
- Mediastinal nodes persisted until the end of treatment in 31 children (32%)
- Residual parenchymal changes were present in 12 patients (24% of those who presented with such lesions)
Assessment of treatment response:

- **Parents assessment:** worse, not better, better or much better
- **Clinical symptoms:** worse, unchanged, better, much better
- **Weight gain:** lost weight, unchanged, gained weight, significant gain
- **Chest radiograph:** worse, unchanged, some clearing, definite clearing
Assessment of response to treatment:

- Improvement in symptoms (if present initially)
- Weight gain
- Improvement on examination in particular with regard to lymph nodes
- Chest radiograph

- In only 29% of cases were all clinical and radiographic findings normal at the completion of therapy.
- In 66% of cases the CR was improved, but not normal.
- In 6% there was minimal or no improvement. In all cases, however, good weight gain was noted and all clinical symptoms had resolved. Only one child relapsed and later admitted to non-compliance.
At the end of treatment mediastinal nodes were still seen in 23 (39%) of children who had adenopathy at the start of treatment, but by 60 months all but one had resolved.

At the end of 1 year: 55% of chest radiographs were normal and 71% at the end of 2 years; at 60 months after starting treatment 8% of radiographs were still abnormal.
Assessment of response to antituberculosis agents in adults

- Sputum smear for AFB
- Sputum culture for *M. tuberculosis*
- Other features such as radiological changes or weight gain are interesting, but not necessarily associated with the all important microbiological measures of response to treatment
Assessment of response to antituberculosis agents in adults

Sputum culture can then be further refined:

- Early bactericidal activity (EBA)
- Serial colony counting (SCC)
- Time to culture negativity (TTP)
- Treatment failure measured microbiologically
- Relapse rates measured microbiologically
- Emergence of resistance
Assessment of response to antituberculosis agents in adults

- All of these require the culture of \textit{M} \textit{tuberculosis}, with or without the enumeration of bacilli.
The Pharmacokinetics of Antituberculosis Agents in Children

<table>
<thead>
<tr>
<th>NAT2 genotype</th>
<th>Adults N (%)</th>
<th>Children N (%)</th>
<th>AUC0-5 (μg/ml/hr)</th>
<th>Mean INH 2 h concentration (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adults</td>
<td>Children</td>
<td>Adults</td>
<td>Children</td>
</tr>
<tr>
<td>SS</td>
<td>21 (35)</td>
<td>25 (39)</td>
<td>24.9</td>
<td>18.4</td>
</tr>
<tr>
<td></td>
<td>10.9</td>
<td>8.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FS</td>
<td>27 (45)</td>
<td>24 (38)</td>
<td>15.3</td>
<td>8.2</td>
</tr>
<tr>
<td></td>
<td>8.7</td>
<td>5.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FF</td>
<td>12 (20)</td>
<td>15 (23)</td>
<td>8.1</td>
<td>5.4</td>
</tr>
<tr>
<td></td>
<td>6.0</td>
<td>4.0</td>
<td></td>
<td></td>
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</tbody>
</table>
INH serum concentrations 2 h after an INH dosage of 10 mg/kg in relation to age and N-acetyltransferase 2 genotype. Homozygous rapid acetylators
INH serum concentrations 2 h after an INH dosage of 10 mg/kg in relation to age and N-acetylates-2 genotype Heterozygous rapid acetylators
INH serum concentrations 2 h after an INH dosage of 10 mg/kg in relation to age and N-acetyltransferase 2 genotype. Homozygous slow acetylators
RMP $C_{\text{max}}$ concentrations in adult and patients and paediatric patients established and not established on RMP
PZA $C_{\text{max}}$ concentrations in adults and children
PZA \( C_{\text{max}} \) (\( \text{ug/mL} \)) related to PZA dosage
How then best to assess an antituberculosis agent for a paediatric indication?
How then best to assess an antituberculosis agent for a paediatric indication?

Utilize clinical features and radiology:

- Be careful about what is being assessed
- Hilar adenopathy alone does not have the same implications as extensive lobar opacification
- Classify extent of disease on radiological grounds
- Radiological improvement, deterioration
- Relapse, recurrence, regression
- Microbiology if positive
- General ‘well-being’ especially weight
Alternatively

- Accept the findings from adult studies of efficacy regarding the pharmacokinetic parameters associated with the recommended dosage in adults.
- Study the pharmacokinetics and toxicity of the relevant drug in children.
- Pharmacokinetics across age groups
- **Toxicity** across age groups
- Suitable forms for administration