Multidrug-resistant tuberculosis in children

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UCL-TB and LSHTM TB Centre World TB Day 2015
24th March 2015
Outline

• Burden
• Recent studies
  • Preventive therapy
  • Disease treatment
• Planned studies
  • Preventive therapy
  • Disease treatment
• Future directions
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    • Preventive therapy
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  • Future directions
Donald PR. Curr Opin Pulm Med 2002
Zignol M et al. Eur Respir J. 2013; 42(3): 701-707

<table>
<thead>
<tr>
<th></th>
<th>All TB</th>
<th>MDR-TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Incidence</td>
<td>851,691</td>
<td>29,809</td>
</tr>
<tr>
<td>Infection Incidence</td>
<td>9,415,243</td>
<td>329,534</td>
</tr>
<tr>
<td>Infection Prevalence</td>
<td>65,254,045</td>
<td>2,283,892</td>
</tr>
</tbody>
</table>

Adapted from Dodd et al. Lancet Glob Health 2014; 2: e453-459
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Evaluation of Young Children in Contact With Adult Multidrug-Resistant Pulmonary Tuberculosis: A 30-Month Follow-up
H. Simon Schaaf, Robert P. Gie, Magdalene Kennedy, Nulda Beyers, Peter B. Hesseling and Peter R. Donald
Pediatrics 2002;109;765-771
DOI: 10.1542/peds.109.5.765

Preventive Therapy for Child Contacts of Multidrug-Resistant Tuberculosis: A Prospective Cohort Study
James A. Seddon, Anneke C. Hesseling, Heather Finlayson, Katherine Fielding, Helen Cox, Jennifer Hughes, Peter Godfrey-Faussett, and H. Simon Schaaf

Treatment for LTBI in contacts of MDR-TB patients, Federated States of Micronesia, 2009–2012
S. Bamrah, R. Brostrom, F. Dorina, L. Setik, R. Song, L. M. Kawamura, A. Heetderks, S. Mase

MANAGEMENT OF LATENT TUBERCULOSIS INFECTION IN CHILD CONTACTS OF MULTIDRUG-RESISTANT TUBERCULOSIS
Felice C. Adler-Shohet, MD, Julie Low, MD, Michael Carson, MS, Haimanot Girma, MPH, and Jasjit Singh, MD

<table>
<thead>
<tr>
<th>Year of study</th>
<th>Location</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994-2000</td>
<td>Cape Town</td>
<td>105 child MDR-TB contacts&lt;br&gt;Tailored regimen – combinations of HD-INH, Z, EMB, Eto for 6 months&lt;br&gt;Two of 41 (5%) children who received PT developed TB&lt;br&gt;13 of 64 (20%) who did not developed TB during follow-up (OR: 4.97; p = 0.05)</td>
</tr>
<tr>
<td>2010-2011</td>
<td>Cape Town</td>
<td>186 child MDR-TB contacts&lt;br&gt;Standardised regimen EMB, Ofx and HD-INH for 6 months&lt;br&gt;One child died and 6 developed incident tuberculosis&lt;br&gt;Poor adherence associated with poor outcome (RR: 7.50; p = 0.026)</td>
</tr>
<tr>
<td>2009-2012</td>
<td>Chuuk, Micronesia</td>
<td>104 treated for MDR LTBI&lt;br&gt;Tailored regimen (Lfx/Mfx and EMB or Eto) for 12 months&lt;br&gt;0 of 104 developed MDR-TB who took PT&lt;br&gt;3 or 15 who refused and an additional 15 developed MDR-TB</td>
</tr>
<tr>
<td>2014</td>
<td>California</td>
<td>27 TST+ child contacts of a teacher with MDR-TB&lt;br&gt;Children aged 6-13 years&lt;br&gt;Lfx and PZA for 9 months, none developed TB&lt;br&gt;100% adverse events, only 8 completed therapy</td>
</tr>
</tbody>
</table>

The dilemma of preventive therapy

Adverse events do occur
Unclear efficacy of treatment
Child could be infected with a susceptible strain
Low risk of disease progression if left alone

Adverse events rare
Emerging evidence for efficacy
High concordance within households
Severe consequences of developing MDR-TB
Risk of progression to disease following infection

Concordance between putative source case and child contact

Tolerability of regimen

Birth

15 years
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Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis

Dena Ettehad, H Simon Schaaf, James A Seddon, Graham S Cooke*, Nathan Ford*

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of patients</th>
<th>Number of events</th>
<th>Proportion (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schaaf et al (2003)⁷</td>
<td>South Africa</td>
<td>39</td>
<td>21</td>
</tr>
<tr>
<td>Drobac et al (2005)⁹</td>
<td>Peru</td>
<td>38</td>
<td>36</td>
</tr>
<tr>
<td>Granich et al (2005)²¹</td>
<td>USA</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Mendez Echevarria et al (2007)²¹</td>
<td>Spain</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Feja et al (2008)²²</td>
<td>USA</td>
<td>20</td>
<td>16</td>
</tr>
<tr>
<td>Lemaine et al (2009)³¹</td>
<td>Latvia</td>
<td>76</td>
<td>70</td>
</tr>
<tr>
<td>Fairlie et al (2011)²⁵</td>
<td>South Africa</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Seddon et al (2011)³⁴</td>
<td>South Africa</td>
<td>111</td>
<td>88</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
MDR-TB treatment Cape Town

- 149 children
- Median age: 36 months (IQR: 16-66)
- Male gender: 69 (46.3%)
- HIV-infected: 32 of 146 tested (21.9%)
- Confirmed diagnosis: 59 (40%)

Thorax 2014; 69: 458-464
# Treatment and Outcome

<table>
<thead>
<tr>
<th></th>
<th>Severe disease (n=45)</th>
<th>Non-severe disease (n=104)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admission</td>
<td>42 (93.3%)</td>
<td>61 (58.7%)</td>
<td>9.87 (2.64-36.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Injectable TB drug use</td>
<td>39/41 (95.1%)</td>
<td>55/101 (54.5%)</td>
<td>16.3 (3.27-81.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median duration of injectable drug (months)</td>
<td>6 (4-6)</td>
<td>4 (3-5)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median total duration of therapy (months)</td>
<td>18 (18-20)</td>
<td>12 (10-16)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mortality</td>
<td>3 (6.7%)</td>
<td>0</td>
<td></td>
<td>0.008</td>
</tr>
</tbody>
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# Preventive Therapy Trials

<table>
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<tr>
<th>Trial</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>TB-CHAMP</strong></td>
<td>Double blind randomised controlled trial: levofloxacin vs. placebo</td>
</tr>
<tr>
<td></td>
<td>Children &lt;5 years</td>
</tr>
<tr>
<td></td>
<td>South Africa</td>
</tr>
<tr>
<td><strong>ACTG 5300</strong></td>
<td>Double blind randomised controlled trial: levofloxacin and isoniazid vs. isoniazid</td>
</tr>
<tr>
<td>(Phoenix)</td>
<td>All contacts (adults and children)</td>
</tr>
<tr>
<td></td>
<td>ATCG sites</td>
</tr>
<tr>
<td><strong>V-QUIN</strong></td>
<td>Double blind randomised controlled trial: levofloxacin vs. placebo</td>
</tr>
<tr>
<td></td>
<td>All contacts (adults and children)</td>
</tr>
<tr>
<td></td>
<td>Vietnam</td>
</tr>
</tbody>
</table>
Children < 5 years
(aged 1-5 years TST positive or < 12 months regardless of TST)
with known MDR-TB adult contact in the household
N=988 households

Randomise
(1:1)

INTERVENTION ARM
Treatment Phase:
6 months daily dosing of levofloxacin
Follow-up phase:
18 months post-treatment

CONTROL ARM
Treatment Phase:
6 months daily dosing of placebo
Follow-up phase:
18 months post-treatment
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</table>
| **STREAM I**  | OBT vs. 4MfxCfzEZKmHPto/5MfxCfzEZ  
Will evaluate standardized shortened 9-month regimen for MDR-TB                                                                                     |
| **STREAM II** | 9 month all oral regimen including bedaquiline vs. 6 month regimen including both an injectable and bedaquiline  
Will evaluate the addition/substitution of bedaquiline to the experimental regimen from STREAM I                                                    |
| **PRACTECAL** | JPaLzdMfx vs. JPaLzdCfz vs. JPaLzd  
Will evaluate three experimental regimens                                                                                                             |
| **ACTG 5319** | Will evaluate shortened regimens with novel drug (pending drug sponsor collaboration).  
[TBD: bedaquiline, delamanid, Pa-824]                                                                                                              |
| **NiX-TB**    | 6–9 month all oral regimen: Pa100mg  
Will evaluate shortened regimens with novel drugs for XDR-TB in adults and adolescents down to 14 years old.                                      |
| **End-TB**    | Various 9 month combinations of: bedaquiline/delamanid, levofloxacin/moxifloxacin, pyrazinamide, clofazimine  
Will evaluate whether novel and repurposed drugs can improve outcomes for people with M/XDR-TB.                                                  |
| **NeXT**      | Bedaquiline, linezolid, levofloxacin, pyrazinamide, ethionamide/high dose isoniazid  
Will evaluate whether 6–9-month regimen with novel drugs can improve outcomes for people with M/XDR-TB.                                          |
| **NC-006**    | 2HRZE/4HR vs. 4Pa100mg MfxZ vs. 4Pa200mg MfxZ. Includes open-label exploratory MDR-TB arm  
Will evaluate treatment-shortening regimen including Pa-824, moxifloxacin and pyrazinamide.                                                   |
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Future Directions

• Confirmed vs. clinical MDR-TB
• Children can be treated with novel regimens if individual drugs safe in children
• Limited treatments for limited disease
• If drug efficacy demonstrated in adults then efficacy can be assumed in children
• Paediatric specific drug requirements
  • Formulations
  • Adverse effects
  • Pharmacokinetics
Adults

1. PK and tolerability in healthy adults
2. EBA and PK studies adults with TB
3. Sputum culture-conversion over 2-4 months; Consider inclusion of adolescents
4. RCT with TB outcomes as primary outcome
5. On-going evaluation

Children

None

Formulation development

Initial PK studies in children with TB

RCT with tolerability and PK as primary outcomes; Compassionate use

Studies in key sub-groups; Validation of PK

Conclusions

• Childhood TB likely underestimated
• Limited evidence base for preventive therapy and MDR-TB treatment
• Clinical trials for MDR-TB preventive therapy are soon to start
• New drugs and regimens are being developed
• Children needed to be included at an appropriate time in clinical trials for new drugs
Questions?