Managing Drug-Resistant Tuberculosis in Pregnancy, Mothers and Newborns

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Postgraduate Course 31st October 2013
Epidemiology
Epidemiology

Donald et al. Lancet 2010; 375: 1852-1854
Epidemiology

• Limited data on TB in pregnancy
• TB disease in up to 8% HIV+ pregnant women in high burden countries
• TST+
  – Up to 34% HIV- women India
  – Up to 50% HIV + women SA

Effect of Pregnancy on TB

• Pregnancy suppresses Th1 response
• Increased susceptibility
  – New infections
  – Reactivation
• Reversal post-partum (IRIS)

Effect of TB on Pregnancy

- TB in pregnancy leads to increased rates
  - Maternal mortality
  - Hospitalization
  - Miscarriage

- Situation complicated by HIV
  - Increased susceptibility
  - Diagnostic challenges

Epidemiology Newborns

Congenital TB infection

High risk of infection and disease progression

Uninfected infant

High risk of disease progression

Congenital TB disease
Perfect Storm

- Epidemiology coincides
- HIV coincides
- Immunosuppression of pregnancy
- TB negative effect on pregnancy
- Intense exposure for vulnerable infants
### Studies of MDR-TB treatment in pregnancy

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Year</th>
<th>Number</th>
<th>HIV</th>
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<tbody>
<tr>
<td>Tabarsi</td>
<td>IJTLD</td>
<td>2011</td>
<td>5</td>
<td>?</td>
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<td>Palacios</td>
<td>CID</td>
<td>2009</td>
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<td>Khan</td>
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<td>Tabarsi</td>
<td>Infection</td>
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<td>Shin</td>
<td>CID</td>
<td>2003</td>
<td>7</td>
<td>?</td>
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<td>Lessnau</td>
<td>Chest</td>
<td>2003</td>
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<td>Nitta</td>
<td>CID</td>
<td>1999</td>
<td>4</td>
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</table>

Very low numbers
Drug-Resistant Tuberculosis and Pregnancy: Treatment Outcomes of 38 Cases in Lima, Peru

Eda Palacios,1,2 Rebecca Dallman,3.a Maribel Muñoz,1 Rocio Hurtado,4 Katiuska Chalco,1 Dalia Guerra,1 Lorena Mestanza,1 Karim Llaro,1 Cesar Bonilla,2 Peter Drobac,5,6 Jaime Bayona,1 Melissa Lygizos,7 Holly Anger,1 and Sonya Shin55

3089 MDR-TB patients 1996 to 2005
– 1033 (33%) women age 15–45 years
– 38 (4%) pregnant
– 14 (37%) no changes in treatment regimen
– 14 (37%) treatment suspended until after pregnancy
– Remainder suspended and restarted

## Drug-Resistant Tuberculosis and Pregnancy: Treatment Outcomes of 38 Cases in Lima, Peru

*Eda Palacios,1,a Rebecca Dallman,3,a Maribel Muñoz,1 Rocio Hurtado,4 Katiuska Chalco,1 Dalia Guerra,1 Lorena Mestanza,1 Karim Llaro,1 Cesar Bonilla,2 Peter Drobac,5,6 Jaime Bayona,1 Melissa Lygizos,7 Holly Anger,1 and Sonya Shin5,5*

<table>
<thead>
<tr>
<th>Treatment outcome</th>
<th>Healthy</th>
<th>Dead</th>
<th>In treatment</th>
<th>Unknown</th>
<th>Total</th>
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<tr>
<td>Cure</td>
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<td>2</td>
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<td>23</td>
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<tr>
<td>Death</td>
<td></td>
<td>5</td>
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<td>5</td>
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<td>Default</td>
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<td>2</td>
<td>5</td>
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<tr>
<td>Failure</td>
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<td></td>
<td>2</td>
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<tr>
<td>In treatment</td>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Not known</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>24</td>
<td>8</td>
<td>3</td>
<td>3</td>
<td>38</td>
</tr>
</tbody>
</table>
Follow up in 26/38 children

- 2 IPT
- 1 MDR-TB at 19/12
- 1 died pneumonia
- 25 healthy
- 2 minor health problems unrelated to TB
Management in pregnancy

• Woman being treated for MDR-TB
  – Avoid pregnancy
  – Continue the same MDR-TB treatment
  – Stop MDR-TB treatment when pregnant
  – Adjust treatment for pregnancy
  – Terminate pregnancy

• Woman is pregnant and diagnosed with MDR-TB
  – Start normal MDR-TB treatment
  – Start a pregnancy adjusted MDR-TB treatment
  – Delay starting treatment
  – Terminate pregnancy
Management in pregnancy

Adverse effects of maternal TB treatment on foetus

Adverse effects of maternal TB on foetus
**TB Drugs in Pregnancy**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Safety class*</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Ethambutol</td>
<td>A</td>
<td>Experience in gravid patients suggests safety</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>C</td>
<td>Experience in gravid patients suggests safety</td>
</tr>
<tr>
<td>Streptomycin, Kanamycin, Amikacin, Capreomycin</td>
<td>D</td>
<td>Avoid use. Documented toxicity to developing foetal ear. Risks and benefits must be carefully considered. Avoid use when possible.</td>
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<tr>
<td>Fluoroquinolones</td>
<td>C</td>
<td>Use with caution. No teratogenic effects seen in humans when used for short periods of time (2-4 weeks). Associated with permanent damage to cartilage in weight-bearing joints of immature animals. Experience with long-term use in gravid patients is limited, but given bactericidal activity, benefits may outweigh risks.</td>
</tr>
<tr>
<td>Ethionamide, Protonamide</td>
<td>C</td>
<td>Avoid use. Teratogenic effects observed in animal studies; significantly worsens nausea associated with pregnancy.</td>
</tr>
<tr>
<td>Cycloserine, Terizidone</td>
<td>C</td>
<td>Significant experience in gravid patients: animal studies have documented toxicity.</td>
</tr>
</tbody>
</table>

A = Safety established using human studies  
B = Presumed safety based on animal studies  
C = Uncertain safety, no human studies and animal studies show adverse effect  
D = Unsafe, risk may only be justifiable under certain clinical circumstances.  

*Partners In Health 2003*
TB Drugs in Pregnancy

- Avoid treatment in first trimester if possible
- Aim to have mother culture negative by the time of birth
- Risk benefit assessment in each case
- Include mother in treatment decisions
- Include pyridoxine
TB Drugs in Pregnancy

- ‘Safe drugs’
  - Isoniazid, rifampicin, ethambutol, PZA

- Unclear
  - Fluoroquinolones, cycloserine/terizidone, PAS

- Avoid if possible
  - Injectables, ethionamide/prothionamide
Infection Control

• Challenging!!!
• Consider delivery room and postnatal wards
• Ventilation (windows)
• Best form of infection control is effective treatment
• Consider masks for breastfeeding
• Consider sleeping in separate room until smear negative
• In extreme circumstances separate (XDR-TB?)
Breast feeding

• Generally should be encouraged
• Most drugs cross in small concentrations
• Injectables will not get into the neonate
• Give pyridoxine to infant
MDR-TB in neonates

• Assessment for TB disease
  – Non-specific signs (fever, irritability, poor feeding)
  – Liver/spleen enlargement
  – Lymphadenopathy
  – Cough/respiratory distress
  – CXR changes

• Examination of placenta
MDR-TB in neonates

- If MDR-TB disease suspected clinically
  - Immediate gastric aspirate
  - Repeat gastric aspirate x 3
  - Consider LP
  - CXR
  - AUSS
  - Send samples for culture
    - Blood
    - Swabs (ears, skin) if indicated
  - Start empiric treatment based on DST of mother
MDR-TB infection in neonates

- Assessment for TB infection
  - Assume if mother culture positive in last trimester of pregnancy or after delivery
    - TST/IGRA limited use
- Close follow up
Treatment of MDR-TB in neonates

• Principles similar to older children
  – Infection
  – Disease

• Concern that in very young or premature neonates metabolism slower
  – May require lower dosages
  – May require more monitoring

• Remember BCG

• Close follow up
## Pharmacokinetics in neonates

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal and year</th>
<th>Drug</th>
<th>Age</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Thee</td>
<td>AAC 2011</td>
<td>INH, RMP, PZA</td>
<td>&lt; 2 years</td>
<td>INH concentrations ↑ in &lt; 12 months</td>
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<tr>
<td>Pullen</td>
<td>T Drug Mon 2006</td>
<td>RMP</td>
<td>29/40</td>
<td>RMP concentrations low with 8.5mg/kg</td>
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<tr>
<td>Tan</td>
<td>AAC 1993</td>
<td>RMP</td>
<td>35/40</td>
<td>RMP concentrations low with 10mg/kg</td>
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<tr>
<td>Le Doare</td>
<td>BMJ CR</td>
<td>RMP</td>
<td>26+2/40</td>
<td>&gt;10mg/kg required for RMP dosing</td>
</tr>
</tbody>
</table>
a. INH serum concentrations

Mean INH serum conc. in μg/ml (95% CI)

Target >8μg/ml

b. PZA serum concentrations

Mean PZA serum conc. in μg/ml (95% CI)

Target >35μg/ml

c. RMP serum concentrations

Mean RMP serum conc. in μg/ml (95% CI)

Target 3-5μg/ml

Thee et al. AAC. 2011; 55(12): 5560-5567
<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
<th>Dose</th>
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<tbody>
<tr>
<td>Group 1</td>
<td>Isoniazid</td>
<td>15-20mg/kg</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>30-40mg/kg</td>
</tr>
<tr>
<td></td>
<td>Ethambutol</td>
<td>20-25mg/kg</td>
</tr>
<tr>
<td>Group 2</td>
<td>Amikacin</td>
<td>15-22.5mg/kg</td>
</tr>
<tr>
<td></td>
<td>Capreomycin</td>
<td>15-30mg/kg</td>
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<tr>
<td>Group 3</td>
<td>Ofloxacin</td>
<td>15-20mg/kg</td>
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<tr>
<td></td>
<td>Levofloxacin</td>
<td>7.5-10mg/kg daily or bd</td>
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<td>Moxifloxacin</td>
<td>7.5-10mg/kg</td>
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<tr>
<td>Group 4</td>
<td>Ethionamide</td>
<td>15-20mg/kg</td>
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<tr>
<td></td>
<td>Terizidone</td>
<td>15-20mg/kg</td>
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<tr>
<td></td>
<td>PAS</td>
<td>150mg/kg</td>
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<tr>
<td>Group 5</td>
<td>Clofazimine</td>
<td>3-5mg/kg</td>
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<tr>
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<td>Linezolid</td>
<td>10mg/kg daily or bd</td>
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<tr>
<td></td>
<td>Thiacetazone</td>
<td>5-8mg/kg</td>
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<tr>
<td></td>
<td>Augmentin</td>
<td>15mg/kg tds</td>
</tr>
<tr>
<td></td>
<td>Clarithromycin</td>
<td>7.5mg/kg bd</td>
</tr>
</tbody>
</table>
The injectables

- Unclear which drug to use
- IM vs. IV
- Effect of lignocaine
- $C_{\text{max}}$ dose-dependent

Fluoroquinolones

Ethionamide

Thee et al. AAC 2011; 55: 4595-4600
Other drugs

- Cycloserine / Terizidone
  - Poorly studied and unstable
  - No PK data to guide dosing in children of different ages and +/- HIV

- PAS
  - One study of 4 children
  - $C_{max}$ 6.25-12μg/ml after 300mg/kg/day given 5 times/day

Other drugs

- **Clofazimine**
  - No paediatric PK data

- **Linezolid**
  - Limited data in children

- **Thiacetazone**
  - No PK data in children

- **Amoxicillin/carbapenems + clavulanic acid**

- **Clarithromycin**

- **New agents**
  - TMC-207, OPC-67683, PA-824

*Santos et al. Ped Pulmonology 2009; 44: 148-154

Thank You!

baby

ice cream