MANAGEMENT OF TUBERCULOSIS IN NEONATES AND YOUNG INFANTS

A Bekker

FIDSSA Conference, 2017
OUTLINE

• Case
• Perinatal TB
• Approach to the TB-exposed newborn
MOM AND BABY'S

Born by NVD at peripheral hospital

- 38 weeks - male
- 2605 g (5.7 lbs)

Developed respiratory distress and transferred to Tygerberg Children’s Hospital

MOM

18 yrs old, G1P1
Uncomplicated pregnancy
HIV - , RPR -
ARRIVAL TO NICU

GENERAL
oedematous +
pale
petechial rash

RESP  IPPV

GIT
hepatosplenomegaly
(5 cm liver; 4 cm spleen)
ascites
CONGENITAL INFECTION

- Term baby boy
- Acutely ill
- Abnormal blood results in keeping with infection

- Septic work up
- TORCH infection
- Parvovirus screen
DETERIORATION IN FIRST WEEK

- IV Pen and Gentamycin
- Broad spectrum antibiotic cover + Acyclovir
- Optimal supportive therapy – HFOV and vasopressors

- All test results were coming back negative
  .....took a week for the penny to drop...
MOM’S HEALTH?

TB screening questions

• No coughing
• No night sweats
• No fever
• Weight loss
• No other family members or close contacts with TB

• Because of high TB incidence in our area:
  – CXR
  – Sputum specimens for *M. tuberculosis*
## TB INVESTIGATIONS

<table>
<thead>
<tr>
<th>Date</th>
<th>Type</th>
<th>AFB</th>
<th>M.tb culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/08/08</td>
<td>Endometrium biopsy</td>
<td>-</td>
<td>Positive 22/09/08</td>
</tr>
<tr>
<td>30/07/08</td>
<td>Tracheal aspirate</td>
<td>+</td>
<td>Positive 04/09/08</td>
</tr>
<tr>
<td></td>
<td>Urine</td>
<td>-</td>
<td>Positive 12/09/08</td>
</tr>
<tr>
<td>01/08/08</td>
<td>Ascitic fluid</td>
<td>-</td>
<td>Positive 12/09/08</td>
</tr>
<tr>
<td>11/08/08</td>
<td>Bone marrow</td>
<td>-</td>
<td>Positive 16/10/08</td>
</tr>
</tbody>
</table>
OUTLINE

• Case
• Perinatal TB
• Approach to the TB-exposed newborn
TERMINOLOGY

• Congenital TB + Postnatal TB = Perinatal TB
Congenital TB is rare:
• transmitted *in utero* by haematogenous spread via the umbilical vein or ingestion/aspiration of infected amniotic fluid during birth

Postnatal infection much more common:
• which occurs by inhalation of bacilli spread by the airborne route from a mother or other close source case with infectious pulmonary TB
TYPES OF MATERNAL TB ASSOCIATED WITH PERINATAL TB

Bacillaemic phase – in utero transmission
Typical cavitating disease – post-natal transmission
WHEN TO CONSIDER TB IN NEONATES?

- **nonspecific symptoms** but mother (or other source case) diagnosed with TB

- **pneumonia** not responding to broad spectrum antibiotics, especially in TB endemic settings or if the mother/primary caregiver has TB

- high **lymphocyte count in CSF** with no identified pathogen;

- **fever and hepatosplenomegaly**

- abdominal distension with **ascites**
# Symptoms and signs in congenital TB: combined data from 75 cases of congenital TB

<table>
<thead>
<tr>
<th>Symptoms and signs</th>
<th>Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory distress including tachypnoea</strong></td>
<td>Common (i.e. &gt;40%)</td>
</tr>
<tr>
<td><strong>Hepatomegaly, splenomegaly</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Fever (usually low grade)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Prematurity/low birth weight</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Cough – may be acute or chronic</strong></td>
<td>Frequent (i.e. 25-40%)</td>
</tr>
<tr>
<td><strong>Poor feeding</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Failure to thrive</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Abdominal distension (including ascites)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Irritability</strong></td>
<td>Infrequent (i.e. 10-25%)</td>
</tr>
<tr>
<td><strong>Peripheral lymphadenopathy</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Sepsis syndrome</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Skin papular/pustular or ulcerative lesions</strong></td>
<td>Rare (i.e. &lt;10%)</td>
</tr>
<tr>
<td><strong>TB meningitis</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Jaundice (obstructive)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Otorrhoea/mastoiditis</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Wheeze or stridor</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Apnoea or cyanosis attacks</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Facial nervepalsy</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Shock</strong></td>
<td>Schaaf et al. Respirology 2010;15:747-763</td>
</tr>
</tbody>
</table>
Comparison of CXR features in infants with culture-confirmed congenital tuberculosis versus those <3 months of age with mainly postnatal tuberculosis

<table>
<thead>
<tr>
<th>Radiographic feature</th>
<th>Congenital TB n = 53 (%)</th>
<th>TB in infants (&lt;3 mo) n = 27 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphadenopathy (hilar/paratracheal)</td>
<td>4 (8)</td>
<td>14 (52)</td>
</tr>
<tr>
<td>Lobar/segmental opacification (unilateral or bilateral)</td>
<td>18 (34)</td>
<td>14 (52)</td>
</tr>
<tr>
<td>Airtrapping</td>
<td>NA</td>
<td>15 (56)</td>
</tr>
<tr>
<td>Large airway compression</td>
<td>NA</td>
<td>13 (48)</td>
</tr>
<tr>
<td>Bronchopneumonia (bilateral)</td>
<td>17 (32)</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Miliary TB</td>
<td>16 (30)</td>
<td>7 (26)</td>
</tr>
<tr>
<td>Ghon focus</td>
<td>NA</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Cavities or cystic lesions</td>
<td>4 (8)</td>
<td>NA</td>
</tr>
<tr>
<td>Lobar collapse</td>
<td>NA</td>
<td>4 (15)</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>1 (2)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Normal chest radiograph</td>
<td>4 (8)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

Schaaf et al. Respirology 2010;15:747-763
TB treatment - Factors affecting drug absorption and disposition in newborns

Figure 1. Developmental Changes in Physiologic Factors That Influence DrugDisposition in Infants, Children, and Adolescents.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>10 (7-15) mg/kg/d</td>
</tr>
<tr>
<td>RMP</td>
<td>15 (10-20) mg/kg/d</td>
</tr>
<tr>
<td>PZA</td>
<td>25 (20-30) mg/kg/d</td>
</tr>
<tr>
<td>EMB</td>
<td>20 (15-25) mg/kg/d</td>
</tr>
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</table>

Strong recommendation, moderate quality of evidence

WHO Guidance of national TB programmes on the management of TB in children 2014
ISONIAZID PHARMACOKINETICS IN 20 LOW BIRTH WEIGHT (LBW) INFANTS

• To determine the PK parameters of isoniazid (INH) given at the WHO-recommended 10 mg/kg/daily dose in LBW-infants

• To define the PK of INH in relation to the N-acetyltransferase-2 (NAT2)-genotype.

<table>
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<tr>
<th>Low Birth Weight infants</th>
<th>N=20 (%) or # median and IQR</th>
</tr>
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<tbody>
<tr>
<td>Male Sex</td>
<td>14 (70)</td>
</tr>
<tr>
<td>Postnatal age (days)</td>
<td>14 (9-29) #</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>35 (34-38) #</td>
</tr>
<tr>
<td>Term (&gt; 37 weeks)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Preterm (&lt; 37 weeks)</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>1575 (1215-2033) #</td>
</tr>
</tbody>
</table>
ISONIAZID CONCENTRATIONS IN LOW BIRTH WEIGHT INFANTS (N=20)

All 20 LBW infants obtained target INH plasma concentrations with 10 mg/kg/day
Reduced clearance was shown in slow acetylators and smaller infants
Key findings

• When dosing with INH at 10 mg/kg/day (lower range of recommended dose), all 20 LBW infants obtained target INH plasma concentrations

• Reduced clearance was shown in slow acetylators and smaller infants (caveat 15 mg/kg)

• Limited safety data reassuring
OUTLINE

• Case
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• Approach to the TB-exposed newborn
APPROACH TO THE TB-EXPOSED NEWBORN

Infectious mother

Well baby

non-infectious mother

unwell baby
WHICH MOTHERS ARE AN INFECTION RISK?

A recently diagnosed mother with TB

• Received < 2 months of TB treatment at time of delivery

OR

• Sputum smear/culture has not yet converted to negative/ results are unknown at time of delivery
APPROACH TO THE TB-EXPOSED NEWBORN

Infectious mother

Well baby

non-infectious mother

unwell baby
<table>
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<td>TB-screening</td>
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1. Well baby and non-infectious mother

- BCG at birth
- Monthly follow-up
- Ask about TB symptoms at each visit
- Screen for TB in the presence of any TB symptoms

Observe and follow-up
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</table>
2. Unwell baby

Perform TB-screening

TB Screening

- Gastric aspirates (x2)
  - Xpert and culture
- Chest radiology

- If indicated:
  - Abdominal ultrasound
  - CSF
  - Blood culture
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3. Well baby

Perform TB-screening

TB Screening

- Gastric aspirates (x2)
  - Xpert and culture
- Chest radiology
- If indicated:
  - Abdominal ultrasound
  - CSF
  - Blood culture
Perform TB screening

2. Unwell baby
3. Well baby with infectious mother

No TB
Prevention versus Observation

TB
Treatment
IPT PREVENTION

– No BCG at birth
– INH 10 mg/kg/day for 6 months -
– Monthly follow-up
– Ask about TB symptoms at each visit
– Screen for TB in the presence of any TB symptoms
– At IPT completion – BCG administration
Perform TB screening

Unwell baby

Well baby with infectious mother

No TB

Prevention

TB

Treatment
TB - TREATMENT

Intensive phase – 2 months (3/4 drugs)
- INH
- RMP
- PZA
- EMB (ETH)

Continuation phase – 4 months (2 drugs)
- INH
- RMP
KEY MESSAGES

• High index of suspicion is required in high burden TB/HIV settings
• Neonates and young infants may have an atypical TB presentation
• TB investigations in the mother can guide management of newborn
• Do not delay IPT or TB treatment when indicated
ACKNOWLEDGEMENTS

Anneke Hesseling, Simon Schaaf, Robert Gie, Mark Cotton,
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