TB Prophylaxis in Paediatrics

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Conflicts of Interest

Sanofi TB Advisory Group member - 2015
Overview

IPT (1 slide)

Postnatal Exposure

Perinatal Exposure
IPT

• Limited, but conflicting evidence
• Current recommendation:
  – No routine IPT to HIV-infected children
  – BUT, attempt to identify any adult TB contacts (often undiagnosed!)
  – Other children, unlikely to be source case, but may have common contact
Case 1

- John, a 3 year old HIV-uninfected boy
- Close, prolonged contact with an adult with PTB: Xpert positive, No rifampicin resistance detected
  - Recently started RHZE
- Asymptomatic
- Thriving

What would you do?
Case 1

1. Would you get a CXR?
2. Would you place a TST?
3. Would you provide chemoprophylaxis?  
   What?
4. What if he was 7 years old?
5. What if the 7 year old was HIV-infected?
6. What if the contact had no pulmonary involvement?
7. When would you see John again?
8. Whose responsibility is all of this?
Symptom Screening

Symptoms of TB disease
The commonest symptoms are chronic unpremitting cough, fever, weight loss and unusual fatigue.

- Chronic unpremitting cough
- Fever over 38°C
- Weight loss
- Failure to thrive (in the past 2 months weight should also be recorded in the past 3 months, and on the "Health" card).
- Unusual fatigue that is not improved by self-limiting health problems such as antibiotics. In HIV positive children, weight loss is not excluded.

Anything else that concerns you!!
CXR

• Many guidelines recommend it
  – But, may be an obstacle to effective preventative measures

• Seldom adds much to symptom screening

• Reasonable to do if easily accessible
  – If not, proceed without it
TST

• Some guidelines recommend it in children <5y
• May also be an obstacle to effective care
• Insufficiently sensitive
• Seldom influences management:
  – If reactive in asymptomatic child: give prophylaxis
  – If non-reactive: almost always give prophylaxis!!
Chemoprophylaxis

• Usually H x 6m
  – 7.5-15mg/kg/d
  – Also if Rif-mono resistant
    (≠ Xpert-positive, Rif-resistant – this is MDR-TB most of the time!)
• Alternative: RH x 3m
• In future: likely rifapentine + H x 12 weekly doses
• INH-resistant: R x 6m
  – Helpful to know which INH mutation(s): inhA/katG/both
Chemoprophylaxis

• MDR-TB:
  – Reasonable to refer, but often results in LTFU
    • Include as much detail as possible, esp. contact’s isolate!
  – Some guidelines → no chemoprophylaxis
  – hd-H (especially with inhA mutation): 15-20mg/kg/d
  – Quinolone + hd-H + E x 6m
  – Lfx ± E/Eto
  – Individualised
  – ?? Delamanid

• XDR-TB???

Age of Child

• <5y vs >5y
  – Natural history of TB infection

Role of HIV

• Opportunity for testing
• Give chemoprophylaxis regardless of age to all HIV-infected children & adolescents
Characteristics of Index Case

• Adult vs Child
• PTB vs EPTB
• Treated vs Untreated
• How ‘close’ is the contact?
• DR-TB, or poor response to standard treatment
Responsibility & Follow-Up

• Close clinical follow-up is vital!
• Ideally:
  – At PHC level
  – Close to home
  – Same place rest of the family access care
BUT: often forgotten!!
Figure 1: TB screening Algorithm

**DOCUMENTED TB EXPOSURE**
Close contact* with an adult, adolescent or child who has/ had smear/ culture positive PTB in the past 12 months

**ARE THERE ANY CURRENT SYMPTOMS OR SIGNS OF TB DISEASE?**
Cough of two weeks or more, wheeze, fever, lethargy, fatigue, weight loss, failure to thrive, visible mass in the neck

- No TB symptoms and signs
  - Investigate for TB
    - No TB diagnosed
      - Child is asymptomatic
        - Treat accordingly and follow up after 1 – 2 weeks
    - TB diagnosed
      - Start TB treatment and register patient
      - Child still has persistent symptoms
        - Treat for TB
          - Monitor response to treatment closely

- TB symptoms and signs present
  - Child is <5 years or HIV positive
    - Give Isoniazid for 6 months
      - Regular follow up
        - Screen for TB symptoms
        - Evaluate or refer if symptoms recur
  - Child is >25 years or HIV negative
    - No preventive therapy
      - Regular follow up

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*Close contact is defined as any household contact or contact outside the household that is of sufficient duration and proximity to pose a high risk of infection.
Contact Tracing

WHO recommends that for all TB patients:
- Screen household contacts
- Offer INH preventive therapy to children < 5 years and all HIV-infected

Risk of infection greatest when contact is close and prolonged

Risk of progression to TB disease greater in children < 5 years:
- Most progression to disease occurs in first 2 years after infection
Any questions?
Case 2

• Well, asymptomatic, term newborn baby
  – Born to HIV-negative mother
  – Pulmonary TB, diagnosed 1 year ago, completed 6 months treatment
  – Symptoms resolved
  – CXR normal

• What would you do?
Case 3

- Well, asymptomatic, term newborn baby
  - Born to HIV-negative mother
  - Pulmonary TB, diagnosed 3 months ago, completed 12 weeks treatment
  - Symptoms resolved
  - CXR improved, no cavities

- What would you do?
Case 4

- Well, asymptomatic, term newborn baby
  - Born to HIV-negative mother
  - Pulmonary TB, diagnosed today, starting treatment today
  - CXR: RUL fibro-cavitatory changes

- What would you do?
Case 5

- Well, asymptomatic, term newborn baby
  - Born to HIV-negative mother
  - TB arthritis (right knee), diagnosed today, starting treatment today
  - CXR: clear
  - Sputum Xpert: negative

- What would you do?
Case 6

- Well, asymptomatic, term newborn baby
  - Born to HIV-positive mother
  - Miliary TB, diagnosed today, starting treatment today
  - CXR: Miliary infiltrate

- What would you do?
Case 7

• Well, asymptomatic, term newborn baby
  – Born to HIV-negative mother
  – Pulmonary TB, diagnosed today, starting treatment today
  – CXR: RUL fibro-cavitatory changes

• Presents at 2 weeks of age with respiratory distress, generalised lymphadenopathy, hepato-splenomegaly, poor weight gain

• What would you do?
Case 8

• Well, asymptomatic, term newborn baby
  – Born to HIV-negative mother
  – Pulmonary MDR-TB, diagnosed today, starting treatment today
  – CXR: RUL fibro-cavitatory changes

• What would you do?
Case 9

- Well, asymptomatic, term newborn baby
  - Born to HIV-negative mother
  - Pulmonary XDR-TB, diagnosed today, starting treatment today
  - CXR: RUL fibro-cavitatory changes

- What would you do?
History of Perinatal TB

- Hippocrates
  - Believed pregnancy to protect against TB
- Grisolle (19th Century)
  - Less favourable course during pregnancy
  - Until recently, abortion recommended
  - Still apparently persists in MDR/XDR

- Diagnostic criteria
  - Beitzke (1935)
  - Cantwell (1994)

- < 300 cases reported by 1994, not many since then
Epidemiology

- ‘Exceedingly rare’ – though underdiagnosed
- Median age of incident TB cases < 30 years
- Increasing proportion of females
- Therefore, increasingly babies born to parents with TB disease
- Also, expanded families, resulting in exposure to elderly etc.
- HIV → increase in extra-pulmonary TB
- Often (60-70%) undiagnosed/unsuspected maternal TB
- Mortality: 20-40% - improved with treatment
Pathogenesis

• Genital tract TB → contiguous spread

• TB bacillaeemia → placental infection

• Placental granulomas
  – Haematogenous spread via umbilical vein
  • 1° focus in liver
  – Rupture in amniotic fluid, then inhaled or ingested
  • 1° focus in lung/GIT/upper respiratory tract

• Direct contact with lesions during birth

Don’t forget the placenta!
Clinical Features

• Median age at presentation = ~24d
• Almost all TST-negative, though often convert later
• ± half with normal CXR
• Often non-specific
  – May mimic acquired infections, congenital cardiac disease, inborn errors, other congenital infections, etc.
Table 1. Presenting Signs and Symptoms in 29 Cases of Congenital Tuberculosis Reported since 1980.

<table>
<thead>
<tr>
<th>Symptom or Sign*</th>
<th>No. (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatosplenomegaly</td>
<td>22 (76)</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>21 (72)</td>
</tr>
<tr>
<td>Fever</td>
<td>14 (48)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>11 (38)</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>7 (24)</td>
</tr>
<tr>
<td>Lethargy or irritability</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Ear discharge</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Papular skin lesions</td>
<td>4 (14)</td>
</tr>
</tbody>
</table>

*The following symptoms and signs occurred in 10 percent of patients or less: vomiting, apnea, cyanosis, jaundice, seizures, and petechiae.
Prevention

- Variety of similar approaches
- Largely expert-opinion based
- Predominantly INH x 6m
  - Alternative = Rifampicin + INH x 3m
  - ? Rifapentine + INH weekly x 12 doses
- Some guidelines suggest TST at 3-6m
- Always require close clinical follow-up
- Aggressive investigation and treatment if symptomatic

Principles very similar to postnatal exposure!
Prevention

• Historically, concern over increased risk of death in pregnant women receiving INH
  – Best estimate = 0.001% risk

• BCG
  – Usually deferred
  – May interfere with TST interpretation
  – May have reduced immunogenicity in presence of INH (±Rif)
  – Consider HIV status of infant
## Managing asymptomatic neonates

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Action 1</th>
<th>Action 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic neonates born of mother’s with infectious drug-susceptible tuberculosis</td>
<td>Treat with daily rifampicin (15 mg/kg), isoniazid (10 mg/kg), PZA (35mg/kg) for 6 months.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>At the end of the treatment period,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Screen the infant for TB again</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If negative, BCG must be given after 2 weeks¹.</td>
</tr>
<tr>
<td>Asymptomatic neonates born of mother’s with infectious drug-resistant tuberculosis</td>
<td>Give prophylaxis with high dose INH (15-20 mg/kg) daily for 6 months and followed up monthly to exclude clinical tuberculosis disease (usually drug-resistant) and to monitor side effects. Consider adding pyridoxine when INH is given.</td>
<td>If child is well and does not develop signs of TB whilst on prophylaxis, Continue prophylaxis until end of 6 months stop prophylaxis and BCG given 2 weeks later.</td>
</tr>
<tr>
<td>Asymptomatic neonates born of mother’s with non infectious drug-susceptible tuberculosis²</td>
<td>Screen the infant for TB clinically, radiologically and bacteriologically (gastric aspirates)</td>
<td>If no tuberculosis is confirmed (negative), give prophylaxis with Isoniazid (10 mg/kg/d) for 6 months. If child is well and has no signs of TB at 6 months, prophylaxis can be stopped and BCG given 2 weeks later.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If TB is confirmed or infant has signs suggestive of TB,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A complete course of TB treatment must be given</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BCG must be given 2 weeks after completing treatment.</td>
</tr>
</tbody>
</table>

¹ BCG is a life vaccine, which is affected by the use of TB drugs (including INH)

² Non infectious means the mother has completed at least 2 months of anti-tuberculosis therapy prior to delivery of the baby with confirmed negative smear microscopy/ culture
## Table 2. Use of antituberculosis drugs in pregnancy, lactation, and in the newborn baby

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pregnancy</th>
<th>Lactation</th>
<th>Newborn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifamycins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Safe</td>
<td>0·05% of adult dose can be detected</td>
<td>Safe 10–20 mg/kg/day</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Congenital defects in animal studies</td>
<td>Use not established</td>
<td>Use not established</td>
</tr>
<tr>
<td>Rifapentine</td>
<td>Rarely causes bleeding in mother and newborn if administered in last few weeks of pregnancy</td>
<td>Use not established</td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Safe, supplement with pyridoxine to avoid peripheral neuropathy</td>
<td>0·75–2·3% of adult dose can be detected</td>
<td>Safe 5–10 mg/kg/day</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Limited data but recommended</td>
<td>Use not established</td>
<td>Safe 20–30 mg/kg/day</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Safe in human beings, cleft palate, skull and spine defects</td>
<td>Yes, in minute amounts</td>
<td>Retrobulbar neuritis, Not recommended</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Premature labour, congenital abnormalities</td>
<td>Use with caution</td>
<td></td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Ototoxicity in fetus, renal damage</td>
<td>Use with caution</td>
<td></td>
</tr>
<tr>
<td>Quinolones</td>
<td>Bone developmental abnormalities in animals</td>
<td>Use with caution</td>
<td></td>
</tr>
</tbody>
</table>
"Is it contagious, doctor?"
Case 2

• Well, asymptomatic, term newborn baby
  – Born to HIV-negative mother
  – Pulmonary TB, diagnosed 1 year ago, completed 6 months treatment
  – Symptoms resolved
  – CXR normal

• What would you do?
  – Clinical examination, no prophylaxis if well, close clinical follow-up
Case 3

• Well, asymptomatic, term newborn baby
  – Born to HIV-negative mother
  – Pulmonary TB, diagnosed 3 months ago, completed 12 weeks treatment
  – Symptoms resolved
  – CXR improved, no cavities

• What would you do?
  – Clinical examination, investigate if clinically indicated, probably no need for prophylaxis, close clinical follow-up
Case 4

• Well, asymptomatic, term newborn baby
  – Born to HIV-negative mother
  – Pulmonary TB, diagnosed today, starting treatment today
  – CXR: RUL fibro-cavitatory changes

• What would you do?
  – Clinical examination, initiate INH, close clinical follow-up, strongly consider investigating, withhold BCG, infection control
Case 5

• Well, asymptomatic, term newborn baby
  – Born to HIV-negative mother
  – TB arthritis (right knee), diagnosed today, starting treatment today
  – CXR: clear

• What would you do?
  – Clinical examination, prophylaxis probably not indicated, close clinical follow-up
Case 6

• Well, asymptomatic, term newborn baby
  – Born to HIV-positive mother
  – Miliary TB, diagnosed today, starting treatment today
  – CXR: Miliary infiltrate

• What would you do?
  – Clinical examination, placental histology & TB DST ± other specimens, withhold BCG, initiate PMTCT, initiate INH, close clinical follow-up, BCG once PCR-negative and off anti-TB drugs, infection control
Case 7

- Well, asymptomatic, term newborn baby
  - Born to HIV-negative mother
  - Pulmonary TB, diagnosed today, starting treatment today
  - CXR: RUL fibro-cavitatory changes

- Presents at 2 weeks of age with respiratory distress, generalised lymphadenopathy, hepato-splenomegaly, poor weight gain

- What would you do?
  - Investigate and treat as congenital TB, notify, consider other diagnoses, consider drug-resistance, close clinical follow-up
Case 8

• Well, asymptomatic, term newborn baby
  – Born to HIV-negative mother
  – Pulmonary MDR-TB, diagnosed today, starting treatment today
  – CXR: RUL fibro-cavitatory changes

• What would you do?
  – Clinical examination, consider placental histology & TB DST, withhold BCG, try avoid undue separation of mother & baby, if in contact with mother: chemoprophylaxis, infection control, close clinical follow-up
Case 9

• Well, asymptomatic, term newborn baby
  – Born to HIV-negative mother
  – Pulmonary XDR-TB, diagnosed today, starting treatment today
  – CXR: RUL fibro-cavitatory changes

• What would you do?
  – Clinical examination, placental investigations, infection control, currently no prophylaxis recommended, very close follow-up, ??consider separating until non-infectious
Any Questions?
Figure 1. The morning pill burden for a teenage boy on ART and treatment for MDR-TB. (Photographer: Damien Schumann).
In the dark days, before doctor-patient confidentiality.