Approach to managing the child exposed to tuberculosis

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GP Paediatric Update, 5+6 October 2012
Why this topic?

• Phone call yesterday from a medical officer at a local public sector clinic
  – Mother brought her 6-week old twins to clinic because they have been coughing for 3 weeks and have been in contact with a visiting family member who has TB (PCR +)
  – What should she do regarding prophylaxis for the infants?

• Other common scenarios
  – Domestic worker/child-minder with recently diagnosed TB
  – Creche / Children’s Home: staff member or patient has TB
  – Mother of newborn infant diagnosed with TB during pregnancy or after birth
  – Young children exposed to adults with drug-resistant TB
Outline

• What constitutes “exposure to TB” and “infection with TB”?  

• Who is most at risk for progression to TB disease after exposure/infection?  

• How should we screen to exclude / diagnose TB disease in children exposed to TB?  

• Chemoprophylaxis guidelines: rationale, drugs, doses, duration  

• Adherence and follow-up
Exposure to TB

- **TB exposed child** = recent contact with a person with suspected or confirmed contagious PTB, and where child has negative tuberculin skin test (TST) or interferon gamma release assay (IGRA) result, normal examination & chest radiology not compatible with TB
What constitutes significant TB exposure in a newborn infant?

- A mother with recently diagnosed TB (irrespective of type of TB or smear/culture result)
  - who has received <2 months TB treatment at the time of delivery
  OR
  - whose sputum smear or culture has not yet converted to negative or is unknown at the time of birth

- Close contact with any infectious (usually adult) TB source case

It is recommended to avoid giving BCG at birth in newborn infants with significant TB exposure
TB infection

- **Latent TB infection (LTBI)** is generally defined by a positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA) in a patient without clinical/radiographic features of TB disease.

- Exposure may or may not progress to LTBI (2-10 weeks).

- LTBI may or may not progress to symptomatic TB disease (2-12 months).

- **Exposure or LTBI** in a child < 5 years of age or an HIV-infected child of any age is an indication for chemoprophylaxis which is an effective method of preventing progression to TB disease.
Tuberculin skin test

• Indicates infection & not disease
• TST is positive if:
  – > 5mm in high risk children (HIV+ or malnourished)
  – > 10mm in all other children

• Main limitation – low sensitivity especially in HIV infected children

• Reasons for false negative TST:
  – HIV infection
  – Disseminated (miliary) TB
  – Severe malnutrition
  – Recent TB exposure – 2-3 mo delay in conversion
  – Incorrect administration
Pathogenesis of disease

- Protective immunity is critically dependent on CD4 cells
- HIV infected patients are at a significantly higher risk of disease progression
## Age Specific Risk For Disease Development Following Primary Infection

<table>
<thead>
<tr>
<th>Age at primary infection</th>
<th>Risk of pulmonary disease</th>
<th>Risk of TBM/Miliary disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>30 – 40%</td>
<td>10 -20%</td>
</tr>
<tr>
<td>1 – 2 years</td>
<td>10 – 20%</td>
<td>2 – 5%</td>
</tr>
<tr>
<td>2 – 5 years</td>
<td>5%</td>
<td>0.5%</td>
</tr>
<tr>
<td>5 – 10 years</td>
<td>2%</td>
<td>&lt; 0.5%</td>
</tr>
<tr>
<td>&gt; 10 years</td>
<td>10 -20% Adult-type disease</td>
<td>&lt;0.5%</td>
</tr>
</tbody>
</table>


- Children with HIV experience a similar risk as those under 2 years of age
- Young age and HIV infection are the most important risk factors for severe or disseminated disease. Malnutrition is an added risk factor
Diagnosis of TB disease in Children

- Accurate diagnosis of TB is a major challenge in children

- Few cases are confirmed by positive smear or culture samples
  - Pauci-bacilliary disease in children
  - Non-cavitatory disease

- Diagnosis often relies on the triad:
  - Exposure to TB &/or Positive TST
  - Screening for symptoms / signs of TB disease
  - CXR with abnormalities suggestive of TB
How should we screen to exclude TB disease in children exposed to TB?

- **Clinical assessment for symptoms and signs compatible with TB disease**
  - Thriving, playful, fever, cough, fatigue/lethargy, visible neck mass

- **Tuberculin skin test:**
  - a positive result may indicate LTBI if child is asymptomatic
  - a negative result does not exclude LTBI or TB disease

- **Ideally, chest X-ray**

- **WHO guidelines support symptom-based screening alone prior to initiation of chemoprophylaxis**
  - If asymptomatic, initiate prophylaxis (if indicated)
  - If symptomatic, investigate for TB: may require referral for TST, CXR and microbiological tests

Lack of access to or experience with TST or CXR should not be an obstacle to initiating chemoprophylaxis in asymptomatic children with TB exposure
Clinical Symptoms of TB

- Chronic cough > 14-21 days
- Fever >38°C for > 14 days
- Weight loss / Failure to thrive

- Reduced sensitivity of symptom-based diagnosis in HIV infected children
- Many other opportunistic infections and HIV itself may present with similar symptoms
Clinical signs of TB

• No pathognomonic signs confirm diagnosis

• Some suggestive signs:
  • Pneumonia unresponsive to antibiotic therapy
  • Non-painful lymphadenopathy
  • Pleural or pericardial effusion
  • Distended abdomen with ascites
  • Gibbus of the spine

• Less sensitive in HIV infected children
Chest X-Ray

• Commonly relied upon to make a diagnosis

• Limitations:
  – Wide observer variation in interpretation
  – May not be available in poorly-resourced settings
  – Overlap with other HIV-related lung diseases
    • Lymphocytic interstitial pneumonitis
    • Recurrent pneumonia
    • Bronchiectasis
Parenchymal disease
Widened mediastinum
Hilar lymphadenopathy
Repeated exposure to TB

- Previous chemoprophylaxis does not protect the child against subsequent TB exposure/infection

- Re-exposure: repeat chemoprophylaxis

- Re-exposure while on chemoprophylaxis: continue chemoprophylaxis for as long as the index case remains infectious
Chemoprophylactic regimens: Rationale

• Pathogenesis
  – High risk of disease progression following exposure/infection
  – Low organism load

• Drug choice
  – Isoniazid
    • High early bactericidal activity killing actively dividing bacteria, well absorbed, well tolerated, penetrates body fluids well
  – Rifampicin
    • Bactericidal, sterilizing agent, well absorbed, good penetration. Critical treatment drug, resistance issues, drug interactions
## Chemoprophylactic regimens: Children <5 yrs of age

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Drug</th>
<th>Dose mg/kg/dose once daily</th>
<th>Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SA EDL (2012 draft); SA NDOH TB guidelines (2011 draft)</strong></td>
<td>INH</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td><strong>American Academy of Pediatrics (2012)</strong></td>
<td>INH</td>
<td>10-15 mg/kg/dose once daily OR 20-30 mg/kg/dose twice weekly as DOT</td>
<td>9</td>
</tr>
<tr>
<td><strong>WHO (2006)</strong></td>
<td>INH</td>
<td>5</td>
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Alternative regimens

• Children
  – Prospective evaluation in randomised controlled trials:
    • INH only for 6-mths or more
    • 9 months optimal (Comstock 1999)
    • Adherence concerns (Alperstein 1998, Marais 2006)
  – Retrospective observational cohort studies:
    • INH + Rif for 3 months as good as longer with same regimen (Ormerod 1998)

• Adults
  – INH + Rif for 3 months as effective as INH for 6 months compared to placebo
  – Rif + PZA effective but not recommended due to toxicity
## Chemoprophylactic regimens:
### Perinatal TB exposure

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<tr>
<td>SA EDL (2012 draft)</td>
<td>INH, Rif</td>
<td>10, 10</td>
<td>3 mths followed by TST &amp; review. TST neg: stop INH &amp; Rif, give BCG (if HIV neg); TST pos: full TB Rx</td>
</tr>
<tr>
<td>SA NDOH TB guidelines (2011 draft)</td>
<td>INH</td>
<td>10</td>
<td>6 mths OR TST available, TST at 3 mths &amp; review . TST neg: stop INH, give BCG (if HIV neg)</td>
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Definitions of drug-resistant TB

• Isoniazid mono-resistant TB
  – Resistance to isoniazid only

• Multidrug resistant TB (MDR-TB)
  – resistance to isoniazid and rifampicin

• Extremely drug resistant TB (XDR-TB)
  – resistance to isoniazid and rifampicin as well as to any member of the quinolone family and at least one of the following second-line anti-TB injectable drugs: kanamycin, capreomycin, or amikacin

who.int/mediacentre/factsheets/fs104/en/print.html
# Chemoprophylactic regimens:

Children <5 yrs of age or HIV-infected children exposed to drug-resistant TB

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<th>Duration (months)</th>
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<tr>
<td>SA EDL (2012 draft); SA NDOH TB guidelines (2011 draft)</td>
<td>INH mono-resistance: Rif</td>
<td>15</td>
<td>4</td>
<td></td>
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<td></td>
<td>Rif mono-resistance: INH</td>
<td>10</td>
<td>6</td>
<td></td>
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<tr>
<td></td>
<td>MDR or XDR-TB: High-dose INH</td>
<td>15-20</td>
<td>?</td>
<td>Close follow-up for two years</td>
</tr>
<tr>
<td>Handbook of Paediatrics 7th edition, OUP 2010</td>
<td>INH mono-resistance: Rif</td>
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<td>Pre-XDR-TB or XDR-TB: High-dose INH</td>
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<td></td>
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<tr>
<td>American Academy of Pediatrics (2012)</td>
<td>INH mono-resistance: Rif</td>
<td>10-20</td>
<td>6</td>
<td>If daily Rx not possible, DOT twice a week</td>
</tr>
</tbody>
</table>
Chemoprophylaxis for children exposed to drug-resistant TB

• No standardised international recommendations for MDR, pre-XDR, XDR-TB

• High dose INH is recommended in case source case is INH-susceptible, and close follow-up for 2 years

• Recognised that INH chemoprophylaxis is unlikely to prevent TB if a patient is infected with INH-resistant TB
  • Sneag DB, Schaaf HS, Cotton MF, Zar HJ. Failure of chemoprophylaxis with standard antituberculosis agents in child contacts of multidrug-resistant tuberculosis cases. Pediatr Infect Dis J 2007;26:1142-1146
Does INH chemoprophylaxis promote development of INH drug-resistance?

• A meta-analysis showed that INH chemoprophylaxis is not associated with production of INH resistance

• Development of resistance is a concern if patients have active disease before commencing INH chemoprophylaxis
Adherence & follow-up

• Chemoprophylaxis often neglected in high TB incidence, low resource settings: treatment is priority

• Poor adherence rates noted with 6 months of chemoprophylaxis

• Unsupervised treatment (DOT)

• Alternative prophylactic regimens & mechanisms for improving adherence are required