Childhood Tuberculosis - Treatment

KPA Annual Scientific Conference
Boma Inn - Eldoret
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Outline

• Disease categories
• Anti-TB drugs
• FDCs
• Drug Resistant TB
• TB/HIV co infection
• Peri-natal TB
• Hepatotoxicity
• BCG Disease
• Airway Compression
TB in children vs TB in adults

- Severe, rapidly progressive
- Higher mortality
- Low bacillary load
- Good Rx outcome
- Handle anti-TB drugs better
- Adherence issues (3rd party)
- Diagnostic difficulties
- Epidemiological significance
- Availability of child friendly medicines
Shoe 4 Africa Children Hospital- MTRH
Disease categories

• Non severe disease
• Severe Disease
• Drug Resistant TB
• ? Retreatment
Treatment Phases

• Intensive Phase
  – Rapidly eliminate majority of the bacilli
  – Prevent emergence of resistant strains
  – Prevent relapse
  – Decrease transmission

• Continuation Phase
  – Eliminate dormant organisms from the lesions
  – Effect cure
The science

- Liver size in proportion to total body weight
- Genetic Polymorphism that affect INH metabolic
- Children eliminate INH faster than adults
- **Children require higher doses of anti-TB drugs to achieve same serum concentrations as in adults**
- RMP induction of cytochrome P450 seems to affect metabolism of some anti-TB drugs
- HIV +ve children have lower anti-TB drug serum concentrations.
- EMB. and Optic neuritis
The practice

• Previous anti-TB doses for children were extrapolated from adult studies.

• Anti-TB drug doses have since been increased by 25 to 70%.

• Current Paediatric FDCs don’t support the new recommendations even with the dispersible tablets.

• Too many tablets given to get correct dose
“A decision to treat any child for TB should be carefully evaluated and once decided the child should receive a full course of treatment unless an alternative diagnosis can be established unequivocally”
## Anti-TB drugs

### 1<sup>st</sup> line
- Isoniazide
- Rifampicin
- Prynaminade
- Ethambutol
- Streptomycin

### 2<sup>nd</sup> line
- Ethionamide
- Fluoroquinolones
- Aminiglycosides
- Capreomycin
- Cycloserine
- Terizidone
- PAS
## Recommended Regimen

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>Intensive phase</th>
<th>Continuation phase</th>
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</thead>
<tbody>
<tr>
<td>All forms of TB except TBM and osteoarticular TB</td>
<td>2 RHZE</td>
<td>4RH</td>
</tr>
<tr>
<td>TB Meningitis and Osteoarticular TB</td>
<td>2RHZE</td>
<td>10RH</td>
</tr>
<tr>
<td>Drug Resistant TB</td>
<td>Refer to DR TB specialist</td>
<td></td>
</tr>
<tr>
<td>DRUG</td>
<td>DOSE range mg/Kg</td>
<td>Mean dose Mg/Kg</td>
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<tr>
<td>------</td>
<td>------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>INH</td>
<td>7-15</td>
<td>10</td>
</tr>
<tr>
<td>RIF</td>
<td>10-20</td>
<td>15</td>
</tr>
<tr>
<td>PZA</td>
<td>30-40</td>
<td>35</td>
</tr>
<tr>
<td>EMB.</td>
<td>15-25</td>
<td>20</td>
</tr>
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</table>
## FDCs

<table>
<thead>
<tr>
<th>FDC/ Formulation</th>
<th>Currently available</th>
<th>Awaited</th>
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</thead>
<tbody>
<tr>
<td>RHZ - dispersible</td>
<td>60/30/150</td>
<td>75/50/150</td>
</tr>
<tr>
<td>RH  - dispersible</td>
<td>60/30 and 60/60</td>
<td>75/50</td>
</tr>
<tr>
<td>EMB  - dispersible</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>RHZE- Adult</td>
<td>150/75/275/400</td>
<td>N/A</td>
</tr>
<tr>
<td>RH  - Adult</td>
<td>150/75</td>
<td>N/A</td>
</tr>
</tbody>
</table>
New FDCs RHZ 75/50/150 and RH 75/50
Who to Hospitalize?

- Severe forms of TB
- TB Meningitis
- Severe Malnutrition
- Other significant co-morbidities
- Severe Pneumonia
- Difficult social circumstances
- Severe adverse reactions
Corticosteroids

- TB meningitis
- PTB with pulmonary distress
- PTB with airway obstruction
- Severe miliary TB
- Pericardial effusion

*Prednisone 2mg/kg od for 4 weeks the 1mg/kg for one week and .5mg/Kg for one week*
Follow up

- Symptom assessment
- Adherence assessment
- Drug Toxicity assessment
- Weight gain
- Sputum for those who were smear positive at the start of treatment at months 2, 5 and 6
Poor Response

• Good response usually visible within 4-8 wks
• Wt gain is a good indicator of response to Rx
• Reasons for poor response
  – Poor adherence
  – HIV infection
  – Drug resistance
  – Wrong diagnosis
  – Other concurrent lung diseases
Drug Resistant TB

• Mono, Poly, MDR, XDR and TDR
• After TB diagnosis possibility of DR-TB should always be considered
• Suspect DR-TB if
  – Contact of House hold MDR TB
  – Contact died while on Rx
  – Bacteriologically proven TB with poor response to RX
MDR-TB treatment

• **Use minimum of 4 drugs isolate is sensitive to**
  - Any 1\textsuperscript{st} line drugs isolate is susceptible to
  - One injectable
  - One Fluoroquinolone
  - 2-3 2\textsuperscript{nd} line agents \((ETH, CS, TR, PAS, High dose INH)\)

• **Duration of therapy 18-24 months**

• **Adherence is critical (DOTS)**
TB/HIV coinfection

- Rate of primary infection is higher
- Progression of LTBI to active disease is higher
- Disseminated TB common
- ? Higher chances of developing DR-TB
- Relapse/Re-infection is higher
- Adherence is an issue
- Overlapping clinical presentation (delayed or missed diagnosis)
TB/ HIV coinfection

• Poor drug absorption problems
• Response to Rx may be slower
• Drug Interactions are common
• Overlapping drug toxicities
• Risk of IRIS
• Higher mortality

• HAART has greatly reduced the incidence of TB in HIV infected children
TB/HIV Treatment

- TB treatment is priority
- Drug regimen are same
- When to initiate ARV treatment?
  - CD4 levels
  - TB Meningitis
  - Overlapping toxicities
  - Survival vs IRIS risk
  - ? Pill burden
  - Within 2-8 wks or as soon as the anti-TB drugs are well tolerated
IRIS

• Usually self limiting
• Presents 3 mo. Within starting ARVs
• Higher prevalence in those with low CD4 counts
• Out come - mild morbidity to death
• Poor outcome in TBM
• Rx
  – Both ARVs and anti-TB Rx continues
  – Anti-inflammatory drugs

• IPT and IRIS ?
Peri-natal TB

• Source usually Maternal TB
  – Poor adherence
  – Late 3rd trimester diagnosis
  – Post-natal diagnosis
• Risk of infection and active disease is very high
• Pathogenesis
  – Transplacental (Haematogenous)
  – Ingestion or aspiration of infected amniotic fluid
  – Ingestion or aspiration of infected cervicovaginal secretions
  – Postpartum inhalation most common
Perinatal TB

• Symptomatic neonate
  — Hepatosplenomegaly, jaundice, N/Sepsis, Lymphadenopathy, disseminated TB, LBW, poor growth, lethargy, poor feeding, unresolving pneumonia, skin lesions, jaundice, seizures, ear discharge, parevertebral abscess.

• Rule out other differentials
  — HIV
  — The Torches

• Start on Anti-TB Rx

• Neonatal doses
Perinatal TB

Asymptomatic neonate

- Maternal infectious state and drug susceptibility
- Defer BCG
- Screen for active TB disease
- Start IPT
- Follow up with regular evaluation for active TB
- Mantoux test at 3-6 months (if +ve thoroughly re-evaluate for active TB)
- BCG 2 weeks after IPT completion

• If mother has MDR TB?
Riley Mother Baby Hospital-MTRH
TB Meningitis treatment

• Usually presents with late disease
• Issue of CSF penetration of some drugs
• Initiate Rx as soon as diagnosis of disseminated TB or TBM is made
• Regimen 2RHZE /10RH
  – Alternatives: 2RHZEth./10RH or 6RHZEth or 6RHZE
• Corticosteroids
• IRIS can be devastating in TBM
BCG and the HIV infected infant

- Risk of dBCG disease is 1%
- HIV infection impairs BCG specific T-cell responses. **Protective effect**
- No BCG in HIV infected infants
- Close follow up of the HIV infected who have already received BCG to identify and treat BCG related complications
- BCG disease is difficulty to treat and mortality is high
Hepatotoxicity

- Rare in children
- Liver Transaminases elevated > 5 the baseline
- Tender Hepatomegaly Jaundice signs of liver failure
- Management
  - Differential diagnosis
  - Stop all possible offending drugs
  - Holding regimen for severe TB
  - Reintroduce drugs 1 at a time 2wks after liver enzymes have normalized H> R> ? Z
Airway compression

• May be 1\textsuperscript{ST} sign of intrathoracic TB
• CXR
  – Hilar adenopathy
  – reduced airway calibre
• Unilateral Wheeze in child with features of TB
• May be a feature of IRIS
• Broncho- dilator nonresponsive
• Treat with oral corticosteroids
  – Predinisone 2mg /Kg
Retreatment

• Failure or relapse?
• Very rare in children
• Reason?
  – Incorrect regimen/dose, non-adherence, severe immunocompromise, reinfection, drug resistance, wrong diagnosis
• Mycobacterial culture and DST
• In the meantime re-start on RHZE
• Never add a single drug to a failing regimen
Summary

- Disease in children is often disseminated and can be rapidly progressive.
- Children metabolize anti-TB drugs faster and need to have enhanced doses.
- Children tolerate anti-TB drugs very well.
- Child friendly anti-TB medications are now available.
Thank you