Treatment of Tuberculosis in Children

HS Schaaf
Desmond Tutu TB Centre
Department of Paediatrics and Child Health
Stellenbosch University
Main objectives in TB Rx

Intensive phase
• To rapidly kill most bacilli in order to:
  - prevent disease progression
  - prevent transmission of infection
  - prevent development of drug-resistance

Continuation phase
• To effect cure and prevent relapse (eliminate dormant bacilli)

To do the above with minimal adverse events
Childhood TB

- Usually paucibacillary disease (less cavities than in adults)
- More extrapulmonary TB (EPTB)
- Severe and disseminated TB (TBM and miliary TB) especially in the young (<3 yr)
- Bacillary load and type of TB may influence effectiveness of Rx regimens
- Rx outcome in children generally good provided that Rx starts promptly
Current First-Line Regimen

Bacterial intensive phase
INH, RMP
PZA (EMB, SM)

Sterilising continuation phase
INH, RMP

85–95% Sputum culture negative
What has changed in first-line anti-TB regimens in children?

In 2006 WHO published a literature review on ethambutol:

- “Peak serum EMB concentrations in both children and adults increase in relation to dose, but are significantly lower in children than adults receiving the same mg/kg body weight dose.”
- Amongst 3811 children receiving EMB only 2 cases (0.05%) of optic neuritis were recorded
- EMB can probably be used with safety in children
- It was recommended that the dose for children should be 20 mg/kg (15-25 mg/kg)

PK of first-line anti-TB drugs in children

- Recent reviews and pharmacokinetic (PK) studies on the other oral first-line anti-TB drugs in children showed in general that:
  - children achieved lower serum concentrations of drugs than adults
  - eliminated drugs faster than adults at the same mg/kg body weight doses
Pharmacokinetics of INH

Several PK “benchmarks” have been associated with optimal INH efficacy (in adults):

• A 2 h serum concentration of approximately 3.0 µg/ml  
  (Mitchell & Bell 1957, Gangadharam et al 1961)

• A 2 h post-dose serum concentration of 3-5 µg/ml  
  (Peloquin 1992)

• A 2 h post-dose serum concentration of 2-3 µg/ml  
  (Donald et al 2004 & 2007)

• A 3 h post-dose serum concentration of 1.5 µg/ml  
  or between 1-2 µg/ml  
  (Vivien et al 1963 & 1986)
2-hr INH concentration vs. dose. The 2-hour INH serum concentration associated with the EBA90 is 2.19 µg/ml
INH Pharmacokinetics in Children (4-6mg/kg dose)

McIlIleron et al CID 2009
INH study results

• Studies found, taking into account the NAT2 genotype (i.e. acetylation type – fast, intermediate or slow, which is responsible for eliminating INH), that younger children eliminate INH faster than older children, and children, as a group, faster than adults.

• WHO and IUATLD previously recommend 5 mg/kg (4-6) INH for children and adults. However, AAP and BTS recommend an INH dose of 10-15 mg/kg/dose.
# Doses first-line anti-TB drugs

<table>
<thead>
<tr>
<th>Drug (Abbrev)</th>
<th>Recommended dose in mg/kg BW (range)</th>
<th>Daily (new WHO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (H)</td>
<td>10 (7-15)</td>
<td>max 300/d</td>
</tr>
<tr>
<td>Rifampicin (R)</td>
<td>15 (10-20)</td>
<td>max 600/d</td>
</tr>
<tr>
<td>Pyrazinamide (Z)</td>
<td>35 (30-40)</td>
<td>max 2000/d</td>
</tr>
<tr>
<td>Ethambutol (E)</td>
<td>20 (15-25)</td>
<td>max 1600/d</td>
</tr>
<tr>
<td>Weight</td>
<td>Intensive phase 2 months</td>
<td>Continuation phase 4 months</td>
</tr>
<tr>
<td>----------</td>
<td>--------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td></td>
<td>RH</td>
<td>PZA</td>
</tr>
<tr>
<td>60,60</td>
<td>500mg</td>
<td>400 mg tablet OR 400mg/8mL* solution</td>
</tr>
<tr>
<td>2–2.9 kg</td>
<td>½ tablet</td>
<td>Expert advice on dose</td>
</tr>
<tr>
<td>3–3.9 kg</td>
<td>¾ tablet</td>
<td>¼ tablet</td>
</tr>
<tr>
<td>4–5.9 kg</td>
<td>1 tablet</td>
<td>¼ tablet</td>
</tr>
<tr>
<td>6–7.9 kg</td>
<td>1½ tablet</td>
<td>½ tablet</td>
</tr>
<tr>
<td>8–11.9 kg</td>
<td>2 tablets</td>
<td>½ tablet</td>
</tr>
<tr>
<td>12–14.9 kg</td>
<td>3 tablets</td>
<td>1 tablet</td>
</tr>
<tr>
<td>15–19.9 kg</td>
<td>3½ tablets</td>
<td>1 tablet</td>
</tr>
<tr>
<td>20–24.9 kg</td>
<td>4½ tablets</td>
<td>1½ tablet</td>
</tr>
<tr>
<td>25–29.9 kg</td>
<td>5 tablets</td>
<td>2 tablets</td>
</tr>
</tbody>
</table>
## CHILDREN > 8 YEARS AND ADOLESCENT

<table>
<thead>
<tr>
<th>Pre treatment body weight</th>
<th>Two months initial phase given daily</th>
<th>Four months continuation phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RHZE 150,75,400,275</td>
<td>RH 150,75</td>
</tr>
<tr>
<td></td>
<td>RH 300,150</td>
<td>RH 300,150</td>
</tr>
<tr>
<td>30–37 kg</td>
<td>2 tabs</td>
<td>2 tabs</td>
</tr>
<tr>
<td>38–54 kg</td>
<td>3 tabs</td>
<td>3 tabs</td>
</tr>
<tr>
<td>55–70 kg</td>
<td>4 tabs</td>
<td>2 tabs</td>
</tr>
<tr>
<td>≥71 kg</td>
<td>5 tabs</td>
<td>2 tabs</td>
</tr>
</tbody>
</table>
TB diagnostic categories for Rx

Category I (Regimen I = 2HRZE/4HR)
- New smear-pos pulmonary TB
- New smear-neg pulmonary TB with extensive parenchymal involvement
- Severe forms of EPTB (abdominal TB or bone/joint TB)
- Severe concomitant HIV disease
- Not TBM – special category

Category III (Most children) (Regimen III = 2HRZ/4HR)
- New smear-negative pulmonary TB other than in Cat I;
- Less severe forms of EPTB
TB diagnostic categories for Rx

Category II (Regimen II = 2HRZES/1HRZE/5HRE)
- Not used in SA anymore – was used for previously treated cases (usually smear+ PTB)
  - relapse
  - treatment after interruption (default >2 months)
  - treatment failure
- In children ALWAYS consider possible drug-resistant TB in retreatment cases

Category IV = Chronic and MDR-TB
- This needs specially designed regimens and should be referred to a specialised clinic/expert
TB meningitis and osteo-articular TB

TBM – need drugs that penetrate blood-brain-barrier. EMB and SM penetration poor, but ethionamide good penetration

New Standard Treatment Guidelines & Essential Medicines List Paediatrics 2013: TBM – 6HRZEth (slow response 9 months)
Miliary TB – 6HRZEth

Osteo-articular TB
WHO current recommendation 2HRZE/10HR
Hepatotoxicity on TB treatment

- Recognition:
  - new onset vomiting on TB treatment
  - abdominal pain
  - jaundice (late sign)
- STOP all hepatotoxic drugs (which are they?)
- If treatment needs to continue, give non-hepatotoxic drugs
- Wait until ALT/AST normal – reinstitute first-line drugs
  - one by one
  - watch LFTs (ALT especially)
Corticosteroids

- TBM – 2 mg/kg/d x 4 weeks, reduce dose over 2 weeks and stop. Improves survival and decreases morbidity
- Large airway compression due to lymph nodes and TB pericarditis – 2 mg/kg/d X 4 weeks, reduce dose over 2 weeks and stop.
- Usually prednisone. Maximum dose 60 mg/day
Other drug treatment

• Pyridoxine – with INH in adults. Indicated in the following children:
  - Malnourished children
  - HIV-infected children, especially if on HAART
  - Breastfeeding infants (vitamin suppl)
  - Adolescents

• Acetazolamide (50 mg/kg/day 3-4 divided doses) and furosemide (1mg/kg/dose 6 hrly) in children with TBM.
Additional management options

• Mediastinal lymph node enucleation (by bronchoscopy or by thoracotomy) if severe airway compression – do early
• Ventricoperitoneal shunts: mainly for non-communicating hydrocephalus in TBM (air-encephalogram)
• Thalidomide for TB brain abscesses (anti-inflammatory)
Follow-up of pulmonary TB

- If sm+ PTB, repeat sputum smear (culture) at 2 and 5 months of treatment
- At 2 weeks and then 2-monthly – symptom assessment, adherence, adverse events, weight.
- Request follow-up CXR only if clinically indicated.
- If not responding – need further assessment and management
- Classify: Rx completed, cured, lost to follow-up (previously defaulter), treatment failure, transferred out, died
Treatment of TB and HIV infection

• Current SA and WHO guidelines: 6-month RMP-based Rx regimen for HIV-infected and -uninfected cases
• Several studies show slower response to Rx and increased recurrences in HIV-infected children
• New STG & EML 2013 Recommend: 2HRZ(E)/4-7HR, but with clinical, radiologic and bacteriologic follow-up of cases to decide on extended treatment duration
• Alternative regimens without RMP not recommended – significantly inferior in RCTs
Treatment of TB and HIV infection

• Cotrimoxazole prophylaxis in HIV-infected adults co-infected with TB has been shown to reduce mortality. Probably indicated in children as well.

• Pyridoxine supplementation may be beneficial, especially if administered in conjunction with HAART (highly active antiretroviral therapy).
Co-Treatment TB and HIV

cART (combination ART) reduced HIV related TB by 80% in one adult study; In children – 3-10 X reduction in TB

TB Rx and cART – issues to consider:

• Pharmacokinetic issues, e.g. drug-drug interactions and drug-malabsorption
• Overlapping drug toxicities
• Immune reconstitution inflammatory syndrome (IRIS)
• Adherence with multiple medications
• Timing of initiation of cART
Drug-Drug Interactions

• Rifampicin induces the cytochrome P450 system and decrease serum concentrations of PIs and NNRTIs.
• Serum concentrations of all PIs, except ritonavir (35%) reduced by 75-95%, rendering them ineffective and increasing the risk for developing drug resistance
• NNRTIs: AUC for efavirenz reduced by 22% and that of nevirapine by 37-58%
• Urgent need for pharmacokinetic data for children on TB Rx and cART
cART for children on RMP-based TB Rx

- <3 years of age: ABC (or d4T) + 3TC + Lopinavir/ritonavir
- However, Lopinavir/ritonavir needs to be boosted – ritonavir to same dose as Lpv
- >3 years of age: ABC + 3TC + efavirenz; currently no change in doses recommended
Drug malabsorption

- Concern has been expressed about malabsorption of TB drugs in HIV-infected patients
- Similar INH serum concentrations in HIV+/- children
- RMP – concentrations lower in some HIV-infected adults
- Previously concern about relatively low dosages of INH and RMP in NTP guidelines, but this has changed
# Overlapping Toxicities

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Anti-TB Drugs</th>
<th>ARV Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rash</td>
<td>PZA, RMP, INH</td>
<td>NVP, EFV, ABC</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
<td>ETH, EMB, PZA, RMP, INH</td>
<td>AZT, RTV, Kaletra</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>PZA, RMP, INH, ETH</td>
<td>NVP, all PIs, EFV paradox reactions</td>
</tr>
<tr>
<td>Leukopenia, anemia</td>
<td>INH, RMP</td>
<td>AZT</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>INH</td>
<td>d4T, ddI</td>
</tr>
</tbody>
</table>
TREATMENT ISSUES

Immune Reconstitution Inflammatory Syndrome (IRIS)
Can occur when introducing ARVs (unmasking TB-IRIS) or when introducing ARVs soon after initiating anti-TB Rx (paradoxical TB-IRIS)

Unmasking IRIS: aggressive onset of TB in previously undiagnosed case

Paradoxical IRIS: Temporary exacerbation of symptoms (e.g. fever), signs (e.g. lymph node enlargement) or XR-appearance

Can be quite severe. Generally subsides spontaneously, not Rx failure. Severe cases may need steroids

Distinguish from MDR-TB
When to start HAART in relation to TB Rx

TB newly diagnosed: New HIV-diagnosis/Not on HAART
- TB treatment is the priority
- Recent data shows benefit starting cART early in ALL TB cases. Urgent in infants, stage 4 disease and in MDR-TB cases – in these cases start cART within 1-2 weeks of starting anti-TB Rx
- In all other cases start within 2-8 weeks (to prevent majority of overlapping drug toxicities and IRIS)
When to start HAART in relation to TB Rx

Child already on cART:

- Patient stable and antiretroviral drugs compatible with RMP-based TB regimen – continue cART and start TB treatment: close follow-up for adverse events
- cART with nevirapine – hepatotoxicity possible – do monthly LFTs. Ensure NVP dose $200\text{mg/m}^2\text{body surface area}$
- Likelihood for IRIS probably low if child’s immune response has already been considerably restored
Recurrence of TB

CAUSES TO CONSIDER

• Poor adherence to Rx or incorrect Rx regimen
• Drug-resistant TB
• Progressive immune suppression
• Reinfection
• Impaired drug absorption (HIV related?)
• Insufficient duration of treatment

Second episode of TB is possible!
Management of MDR-TB in children

- Confirm MDR-TB if possible - use the index case’s isolate DST pattern if no isolate from child is available
- If MDR-TB is confirmed, also do DST for 2\textsuperscript{nd}-line drugs
- Management – at a specialized MDR-TB clinic
- DOT with daily treatment only is essential
- Give $\geq 4$ drugs to which the patient’s isolate is susceptible and/or naïve (extent of disease)
- Know drug adverse effects and screen regularly
- Counsel patients/parents at every visit for support, about adverse events, and importance of adherence
- Follow-up is essential; clinical, radiological and cultures
Drugs in M/XDR-TB Rx

• 1\textsuperscript{st} line drugs to which isolate still susceptible (EMB, PZA)
• A FQN in MDR-TB (ofloxacin, levofloxacin, moxifloxacin)
• 2-nd line injectable drug
  - Kanamycin or amikacin (prefer amikacin in children)
  - Capreomycin
• Other oral 2\textsuperscript{nd}-line drugs in combination:
  - Ethionamide/prothionamide (inhA/katG mutation?)
  - Terizidone/cycloserine
  - PAS
• INH high dose – as added drug in low-level INH resistance (or inhA promoter region mutation)
• Reserve drugs for XDR-TB (especially linezolid, clofazimine)
11-month-old Morning tablets MDR-TB Rx

No child-friendly drugs!
Difficult to accurately break tablets to correct dosage. Also receives an injectable
REVIEW

Paediatric use of second-line anti-tuberculosis agents: A review

James A. Seddon\textsuperscript{a,b,*}, Anneke C. Hesseling\textsuperscript{a}, Ben J. Marais\textsuperscript{c}, Helen McIlleron\textsuperscript{d}, Charles A. Pelloquin\textsuperscript{e}, Peter R. Donald\textsuperscript{f}, H. Simon Schaaf\textsuperscript{a,f}
### Drugs for treatment of MDR-TB

**Group 3: Fluoroquinolones – PK data still needed in all**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dosage (mg/kg)</th>
<th>Maximum (mg)</th>
<th>Unit size (in mg (SA))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones: ↔</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ofloxacin</td>
<td>15-20</td>
<td>800</td>
<td>200/400</td>
</tr>
<tr>
<td>- Levofloxacin* (&lt;8 yrs)</td>
<td>15-20</td>
<td>750</td>
<td>250/500</td>
</tr>
<tr>
<td>- Moxifloxacin (&gt;8 yrs)</td>
<td>7.5-10</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>- Ciprofloxacin</td>
<td>30-40</td>
<td>2.0g</td>
<td>250/5ml</td>
</tr>
<tr>
<td>(Ciprofloxacin <strong>NOT recommended</strong>)</td>
<td></td>
<td></td>
<td>250/500</td>
</tr>
</tbody>
</table>
## Adverse effects 2\textsuperscript{nd}-line drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse effects</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin/</td>
<td>ototoxicity,</td>
<td>hearing test,</td>
</tr>
<tr>
<td>Kanamycin/</td>
<td>nephrotoxicity</td>
<td>creatinine, K+ levels</td>
</tr>
<tr>
<td>Capreomycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethionamide</td>
<td>GIT disturbance</td>
<td>(split dose, escalate)</td>
</tr>
<tr>
<td></td>
<td>hepatotoxicity,</td>
<td>ALT?</td>
</tr>
<tr>
<td></td>
<td>hypothyroidism</td>
<td>TSH (T4)</td>
</tr>
<tr>
<td>Fl-quinolones</td>
<td>GIT disturbance\pm</td>
<td>clinical observation</td>
</tr>
<tr>
<td></td>
<td>insomnia, arthralgia</td>
<td></td>
</tr>
</tbody>
</table>
## Adverse effects 2\textsuperscript{nd}-line drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse effects</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycloserine/</td>
<td>psychosis, depression, parasthesias</td>
<td>more common in adults</td>
</tr>
<tr>
<td>Terizidone</td>
<td></td>
<td>add pyridoxine</td>
</tr>
<tr>
<td>PAS</td>
<td>GIT disturbance hypothyroidism</td>
<td>TSH (T4)</td>
</tr>
<tr>
<td>Linezolid</td>
<td>myelosuppression periph neuropathy lactic acidosis pancreatitis</td>
<td>FBC clinical lactate clinical, amilase?</td>
</tr>
</tbody>
</table>
What about the new drugs?

Bedaquiline (TMC207): Janssen Pharmaceutical

- A diarylquinoline – unique mechanism of action – inhibits ATP synthesis - results in bactericidal activity
- Provisionally approved by FDA for use in MDR-TB – in addition to current MDR-TB regimen
- ONLY adults >18 years for now. Strange drug with $t_{1/2}$ of >5 months – no dosage established for children
- Now phase 3 studies and planning child PK studies

Delamanid (OPC-67683)

- A new Nitro-dihydroimidazo-oxazole derivative
- No cross-resistance with any current used anti-TB drugs
- Phase 2 b trials done – trying for registration Europe
- Dose finding and safety studies in children ongoing
Prevention of TB in children

- Role of BCG limited; important in high TB burden countries. Also give to HIV-exposed infants – start ART early in infancy – this will prevent severe IRIS and dissemination of BCG
- Identify infectious TB cases early and start anti-TB treatment immediately (usually adults)
- Child contacts of infectious TB cases – exclude TB disease. Once TB disease excluded, provide preventive therapy (even if TST/IGRA negative) especially in high risk cases (children <5 years of age and HIV-infected children, irrespective of age)
Prophylaxis for DS and DR-TB contacts

- DS-TB contacts: 6 to 9 months INH (or 3HR)
- INH monoresistance: RMP x 4 months
- RMP monoresistance: INH x 6-9 months (Line-Probe test – could miss INH resistance in some cases)
- Failure of INH or INH/RMP to prevent MDR-TB reported.
- MDR-TB: 2 drugs to which source case strain is susceptible for 6-12 months (no studies)
- XDR-TB – high-dose INH (15mg/kg) as may have low-level INH resistance (inhA mutation)
- In MDR and XDR-TB regular follow-up for a minimum of 12 months (WHO recommends 2 yrs) is most important