Treatment of drug-susceptible TB in children

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Objectives of TB Treatment

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
Current First-Line Regimen

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

Sterilising continuation phase
INH, RMP

85–95% Sputum culture negative

Percentage organisms killed

Percentage patients cured

Time (months)
TB in children differ from adult type TB

- Mainly paucibacillary disease in young children (less extensive/cavitary pulmonary disease than in adults)
- Children have more extrapulmonary TB (EPTB)
- Disseminated TB (TB meningitis and miliary TB) especially in the young (<3 yr) – both of these involve the brain
- Bacillary load and type of TB may influence effectiveness of treatment regimens
- Treatment outcome in children generally good provided that it starts promptly and adherence is maintained until completion
Current DS-TB Regimens in children

- Different regimens are recommended by the WHO based on:
  - Type and extent of disease
  - HIV status of the child or HIV prevalence in the community
  - Prevalence of isoniazid resistance in the community

- The main differences in the regimens are the inclusion of ethambutol (or not) and the duration of the continuation phase

- Summary of recommended regimens/indications:
  - 2HRZ/4HR: PTB and peripheral lymph node TB in settings with low HIV prevalence and/or low prevalence of isoniazid resistance and children who are HIV-negative
  - 2HRZE/4HR: Extensive PTB (HIV-negative) or ALL TB in settings with high HIV prevalence and/or where the prevalence of isoniazid resistance is high (>4%)
  - 2HRZE/10HR: TB meningitis and osteoarticular TB
Ethambutol dosage for the treatment of children: literature review and recommendations

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Ethambutol serum conc. in adults and children

![Graph showing the concentration of Ethambutol in adults and children versus dose.](image-url)
Ethambutol’s role and risk?

• At the current dose of 15-25mg/kg/day in children, EMB is **bacteriostatic** and most likely does not play a major role in the killing of *M. tuberculosis* bacilli.

• It’s role in the 4-drug regimen is as a **companion drug** to protect against development of resistance to INH and rifampicin.

• **Risk** – mainly optic neuritis, causing visual acuity disturbance, visual field fall-out and loss of colour vision. These are mainly reversible, **uncommon in children** (but difficult to evaluate) and dose dependent (do not use more than recommended).
Alternative regimens

- 4-month fluoroquinolone-containing regimens have shown NOT to be non-inferior to the standard 2HRZE/4HR regimen in adult trials therefore not recommended (REMoxTB; OFLOTUB; RIFQUIN trials)

- A large study is in progress (SHINE-trial) in children with non-severe TB disease comparing 2HRZ/2HR vs. 2HRZ/4HR with 72-week follow-up

- Efficacy trials are usually done in adults and, if effective in adults, dose finding and safety studies are done in children. However, there is a place for childhood TB efficacy studies
The following dosages of anti-TB medicines should be used daily for the treatment of TB in children:

<table>
<thead>
<tr>
<th>Drug (Abbrev)</th>
<th>Recommended daily dose in mg/kg body weight (range)</th>
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<tbody>
<tr>
<td>Isoniazid (H)</td>
<td>10 (7-15) max 300/d</td>
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<tr>
<td>Rifampicin (R)</td>
<td>15 (10-20) max 600/d</td>
</tr>
<tr>
<td>Pyrazinamide (Z)</td>
<td>35 (30-40) (not provided)</td>
</tr>
<tr>
<td>Ethambutol (E)</td>
<td>20 (15-25) (not provided)</td>
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</tbody>
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NEW Fixed dose combination dispersible tablet was launched in December 2015: H/R/Z = 50/75/150 mg
This is to achieve above dosages with FDC tablets
LBW infants receiving 10 mg/kg of INH had desirable blood drug concentrations, .... However, a prolonged half-life and reduced elimination of INH were noted in smaller and younger infants, especially in ... slow acetylators. ...we caution against exceeding a dosage of 10 mg/kg in this population.
Thee S et al. Pharmacokinetics of isoniazid, rifampicin and pyrazinamide in children younger than two years of age with tuberculosis: evidence for the implementation of revised World Health Organization recommendations. Antimicrob Agents Chemother 2011; doi1128/AAC.05429-11

Rifampicin

15 mg/kg

10 mg/kg
Rifampicin concentrations with 2 RIF suspensions in infants: Low concentrations achieved even with higher dose RIF according to WHO recommendations.

Pharmacokinetics of Rifampin, Isoniazid, Pyrazinamide, and Ethambutol in Infants Dosed According to Revised WHO Recommended Treatment Guidelines. Bekker et al. AAC 2016;60:2171

FIG 1 Mean plasma rifampin (RMP) concentrations (µg/ml) after the intake of a mean dose of 12.9 mg/kg for RMP formulation 1 (n = 14) and of a mean dose of 16.7 mg/kg for RMP formulation 2 (n = 25). C_{max} adult target values, 8 to 24 µg/ml when RMP is administered at 600 mg daily in American adults (23); C_{max} 5.9 µg/ml when RMP is administered at 10.9 mg/kg in South African adults (24).
Is current Rifampicin dose sufficient?

- Variable bioavailability in different formulations and high inter- and intra-individual concentration variability
- Current dose probably not optimal: Early Bactericidal Activity (EBA) at maximum adult dose of 600mg not optimal – EBA increases linearly with higher dose of 1000mg in >1 study. In adults looking at PK and safety of RIF up to 40mg/kg – planning similar study in children
TB Meningitis – which regimen?

- WHO 2010: 2HRZE/10HR
- ATS/CDC 2016: 2HRZE/7-10HR
- AAP: 2HRZEto or E or injectable/7-10HR
- South Africa 2013: 6HRZEto (Ethionamide to replace ethambutol because of better CSF penetration
- Outcome in South African study in 184 children with TBM: 80% good outcome, mortality 3.8% and approximately 16% with severe neurologic sequelae
- No RCTs yet! New study comparing WHO regimen to HRZ + Levofloxacin for 6 months – Also higher dose RIF initially – only recently started enrolling
Other drugs in DS-TB treatment

- Corticosteroids: (dexametazone or prednisone)
  - TB meningitis (RTC confirmed benefit)
  - Lymph node compression of airways (observational)
  - Pericarditis (mixed evidence)
- Pyridoxine (Vit B6):
  - not generally needed in children on INH
  - recommended in: adolescents, breastfeeding infants, malnourished and HIV-infected children
- Co-trimoxazole: prophylaxis in all HIV-infected children on anti-TB treatment (based on adult studies)
Anti-TB and ART drug-drug interactions (DDIs)

• DDIs mainly because of rifampicin induction of cytochrome P450 isoenzymes

• Protease inhibitors – lopinavir/ritonavir, darunavir/ritonavir, atazanavir/ritonavir – all significantly reduced (>90%): **In young children (<10 years)** double-dose lopinavir/ritonavir given with RIF results in inadequate concentrations – **super-boosted lopinavir/ritonavir is advised** (increase RTV-dose to same as LPV-dose)

• NNRTIs – also reduced by RIF, but currently not recommended to increase nevirapine or efavirenz dose

• No data in children on newer ARVs such as integrase inhibitors – data urgently needed (in adults – dose increase of raltegravir and dolutegravir with RIF)
Conclusions

• Although DS-TB treatment in children is well-established and has high success rate, many questions remain regarding optimal treatment:
  - Pharmacokinetics of drugs in different age groups
  - Optimal RIF dose (especially TBM, infants)
  - Shorter treatment duration especially in non-severe TB disease
  - DDIs with RIF and newer ARVs
  - Optimal treatment regimen for TBM

• As new shorter regimens are developed for adults with existing or new drugs, these should also be tested and used in children