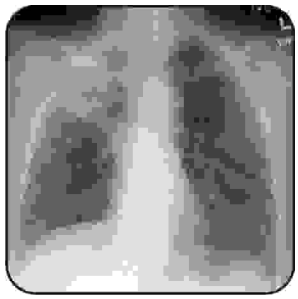
REVIEW PROF-1290

# CHILDHOOD TUBERCULOSIS;
## CHEMOTHERAPY IN PAKISTAN



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**ABSTRACT...** drarehman100@yahoo.com This article reviews the treatment of tuberculosis regimens and dosage schedule recommended by different organizations and guidelines.

## INTRODUCTION

It is estimated that 11% (1 million) of the annual TB cases occur in children less than 15 years of age. Of these childhood cases, 75% occur annually in 22 high-burden countries[1]. Pakistan is one of the countries with high burden[2]. Hussain A et al showed that there is lack of knowledge about standardized TB treatment protocols among doctors in Pakistan[3]. The study done in Lahore[4] showed that only ten percent of doctors were giving anti-tuberculosis chemotherapy according to body weight. Another study done in Gujrat (Pakistan) showed that only thirty two percent of the doctors knew the correct regimen for treatment of childhood tuberculosis[5].

Pakistan has recently published national policy for the management of tuberculosis in children[6]. The treatment regimens, their duration and dosages in children recommended by World Health Organization [WHO], International Union against Tuberculosis and Lung Disease [IUATALD][7], American Academy of Pediatrics [AAP][8], Pakistan National TB Control Programme[6] and NICE Guidelines UK[9] are not exactly the same. The purpose of review of this paper is to discuss treatment regimens of different organizations to give awareness for the latest protocols for childhood tuberculosis management and to compare these with Pakistan National TB Control Programme for the management of tuberculosis in children.

## ANTI-TUBERCULOSIS REGIMENS

Anti-TB treatment is divided into two phases: an intensive phase and a continuation phase. The purpose of the intensive phase is to rapidly eliminate the majority of organisms and to prevent the emergence of drug resistance. This phase uses a greater number of drugs than the continuation phase. The purpose of the continuation phase is to eradicate the dormant organisms. Fewer drugs are generally used in this phase because the risk of acquiring drug resistance is low, as most of the organisms have already been eliminated.

## STANDARD CODE

There is a standard code for anti-TB treatment regimens, which uses an abbreviation for each anti-TB drug, e.g. isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E). A regimen consists of two phases: the

initial and continuation phases. The number at the front of each phase represents the duration of that phase in months[1].

## TREATMENT REGIMENS

The Treatment regimen issued by WHO is shown in table-I. Pakistan National TB Control Prgramme[6] has divided children with tuberculosis into two categories: Pulmonary tuberculosis and Extra pulmonary tuberculosis while the WHO categories are I – IV[1]. The treatment duration recommended by AAP[8], IUATALD[7], Pakistan National TB Control Prgramme[6] and NICE Guidelines from UK[9] are the same (6 month) as that by WHO[1] except in cases of disseminated (miliary) tuberculosis and tuberculosis meningitis (TBM). The reason to give drugs for longer duration in TBM by all other agencies is based on the fact of rare relapse of the disease on 6 month regimen[10,11]. The treatment regimens in TBM and disseminated tuberculosis (including miliary) are shown in Table-II.

The recommendation of IUATALD[7] and Pakistan National TB Control Programme[6] for HE in the continuation phase are the same as recommended by WHO[1] but this regimen may be associated with a higher rate of treatment failure and relapse as compared with the regimen with R in the continuation phase in TB diagnostic category III[1].

**Table-I. WHO Recommended treatment regimens for children**

| TB diagnostic category | TB cases | Regimen | |
|---|---|---|---|
| | | Intensive phase | Continuation phase |
| III | New smear-negative pulmonary TB (Other than in category I).<br>Less severe forms of extrapulmonary | 2HRZ | 4HR or 6HE |
| I | New smear-positive pulmonary TB.<br>New smear-positive pulmonary TB with extensive parenchymal involvement<br>Sever forms of extrapulmonary TB (Other than TBM).<br>Severe concomitant HIV disease. | 2HRZE | 4HR or 6HE |
| I | TB meningitis | 2RHZS | 4RH |
| II | Previously treated smear positive pulmonary TB:<br>Replace treatment after interruption treatment failure | 2HRZES/1HRZE | 5HRE |
| IV | Chronic and MDR-TB | Specially designed standardized or individualized regimens | |

**Table-II. Treatment regimens in TBM and disseminated tuberculosis (including miliary)**

| organization guidelines | Regimen | |
|---|---|---|
| | TBM | Disseminated (including military) |
| NICE guideline UK | 2HPRS/E 10HR | 2HPRE 4HR |
| IUATALD* | 2HPPS 7HR | 2HRPS 7HR |
| APP | 2HRZ aminoglycoside / ethionamide 7-10 HR | 2HRZ 4HR |
| WHO | 2RHZS 4HR | 2HRZE 4HR or 6HE |
| Pakistan National TB Control Programme** | 2HRZ E/S 7HR/10HR | 2HRZ E/S 7HR/10HR |

** IUATALD also recommends this regimen for spinal tuberculosis with neurological involvement*
***Pakistan National TB Control Programme also recommends this regimen for bone and joint tuberculosis.*

| Table-III. Recommended doses of first-line anti-TB drugs for children | | | | |
|---|---|---|---|---|
| Drug | Recommended doses | | | |
| | Daily | | Three times weekly | |
| | Dose and range (mg/kg body weight) | Maximum (mg) | Dose and range (mg/kg body weight) | Maximum (mg) |
| Isoniazid | 5 (4-6) | 300 | 10 (8-12) | - |
| Rifampicin | 10 (8-12) | 600 | 10 (8-12) | 600 |
| Pyrazinamide | 25 (20-30) | - | 35 (30-40) | - |
| Ethambutol | Children 20 (15-25)<br>Adults 15 (15-20) | - | 30 (25-35) | - |
| Streptomycin | 15 (12-18) | - | 15 (12-18) | - |

## DOSES OF ANTI-TUBERCULOSIS DRUGS

The recommended drug dosages by WHO is shown in table-III. The dosage recommended by Pakistan National TB Control Prgramme[6] are higher than those of WHO's[1] with the exception of E (15-20 mg/kg/day). The IUATALD dosage for anti tuberculosis drugs are the same[7].The exception is E 15 (15-20) mg/kg/day. The doses recommended by AAP[8] are higher as compared to recommendation from WHO, the most notable is H of 10–15 mg/kg. The exception is E which has the same dosage as in WHO protocol (Table-III).

The recommended daily dose of E is higher in children (20mg/kg) than in adults (15mg/kg); because the peak serum E concentrations are lower in children than in adults receiving the same mg/kg dose. Recent literature review indicates that E is safe in children at a dose of 20mg/kg (range15– 25mg/kg) daily[12]. It is better to avoid E in TBM as optic atrophy is a common feature of the disease process and may resemble optic atrophy due to E[12]. Moreover it penetrates poorly the blood brain barrier[1].

Streptomycin should be avoided whenever possible in children because the injections are painful and irreversible auditory nerve damage may occur. The use of streptomycin in children is mainly reserved for the first 2 months of treatment of TB meningitis[1].

AAP uses ethionamide as the fourth drug for TBM, because it crosses both healthy and inflamed meninges[8] but it is the most unpleasant drug to take and is associated with high incidence of gastrointestinal symptoms[13].

There is recommendations from WHO[13], IUATALD[7] and the NICE guidelines for high risk persons like refugees[9] that intermittent therapy can be used 3 times a week in the continuation phase of all types of tuberculosis if DOT is to be used except in TBM where daily dose is recommended. AAP[8] recommends 2-3 times a week therapy in continuation phase of all types of tuberculosis if DOT is to be used.

## FIXED DOSE COMBINATIONS

There is general consensus that fixed dose combinations can be used safely in children[1,7,8,9]. The bioavailability of R is negatively affected if combined with other drugs in the same formulation if manufacturing procedures are not strictly controlled. So bioavailability testing of the locally available fixed dose combination preparations should be certified by the WHO certified laboratory[14]. He dosage of fixed dose therapy is according to WHO recommendations.

## FOLLOW UP

According to WHO[1] each child should be assessed at

least at the intervals: 2 weeks after treatment initiation, at the end of the intensive phase and every 2 months until treatment completion. While IUATALD[7] recommend every 14 day for the first 2 month of treatment and then monthly. AAP recommends monthly assessment[8]. The assessment should include, as a minimum; symptom assessment, assessment of treatment adherence, enquiry about any adverse events and weight measurement. The gain in weight is one of the important criteria for successful treatment[1,7]. Medication dosages should be adjusted to account for any weight gain. Adherence should be assessed by reviewing the treatment card. A follow-up sputum sample for smear microscopy at 2 months after treatment initiation[1,7], at 4 and 6 month (in case of 6 month regimen) while 5 and 7 in case of 8 month regimen should be obtained for any child who was smear-positive at diagnosis[7] . Follow-up CXRs are not routinely required . AAP[8] recommends CXR at 2 month of treatment in spite of the fact many children will not have radiological response to treatment .Hilar lymphadenopathy may persist even after 2-3 years of successful treatment of tuberculosis[8]. Pakistan National TB Control Programme[6] also recommends follow up with CXRs.

There is a latest recommendation from WHO that E is safe in children and there is no need of routine visual and colour vision assessment in children on E[12] but other agencies including Pakistan National TB Control Programme are still cautious about E and recommend visual screening[6,8].

Routine liver transaminases monitoring is not recommended. AAP[8] recommends liver transaminase monitoring in children with severe form of tuberculosis (disseminated tuberculosis, TBM), children with liver disorders and children on hepatotoxic drugs.

A child who is not responding to anti-TB treatment should be re-evaluated and be referred for further assessment and management if necessary. These children may have drug-resistant TB, an unusual complication of pulmonary TB, other causes of lung disease or problems with treatment adherence[1].

## CONCLUSIONS

1. WHO regimens are appropriate for all types of tuberculosis except for the disseminated tuberculosis including military and TBM.
2. Rifampicin containing regimens are better than one without it.
3. Daily therapy is better than intermittent. If intermittent is to be used it must be directly observed and three times a week.
4. WHO drugs dosages are appropriate.
5. Regimens but not dosages used in Pakistan National Tuberculosis Control Programme are suitable for children.
6. Fixed dose combination preparations should be used if the bioavailability of rifampicin is certified by WHO reference laboratory
7. No need of CXR for follow up
8. A follow-up sputum sample for smear microscopy in cases of sputum positive cases.
9. No need to monitor optic toxicity in case of use of ethambutol.
10. Liver transaminase assessment is indicated only in selected cases.

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