

Guidance for National Tuberculosis Programmes on the  
management of tuberculosis in children  
CHAPTER 2 IN THE SERIES

## Chapter 2: Anti-tuberculosis treatment in children

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### SUMMARY

The management of children with TB should be in line with the Stop TB Strategy, taking into consideration the particular epidemiology and clinical presentation of TB in children. Obtaining good treatment outcomes depends on the application of standardised treatment regimens according to the relevant diagnostic category, with support for the child and carer that maximises adherence to treatment. A recent development in treatment recommen-

dations is that, following a comprehensive literature review, ethambutol is now considered safe in children at a dose of 20 mg/kg (range 15–25 mg/kg) daily. Critical areas for further research include the optimal formulations and dosing of first- and second-line TB drugs and new drug development.

**KEY WORDS:** children; tuberculosis; management; anti-tuberculosis drugs

THE MAIN OBJECTIVES in TB treatment are:

- 1 to cure the patient of TB (by rapidly eliminating most of the bacilli);
- 2 to prevent death from active TB or its late effects;
- 3 to prevent relapse of TB (by eliminating the dormant bacilli);
- 4 to prevent the development of drug resistance (by using a combination of drugs);
- 5 to reduce transmission of TB to others.

Children usually have paucibacillary disease, as cavitating disease is relatively rare (about 6% or less) in children <13 years of age and the majority of the organisms in adult-type disease are found in cavities. On the other hand, children develop extra-pulmonary TB (EPTB) more often than do adults. Severe and disseminated TB (e.g., TB meningitis and miliary TB) occur especially in young children (<3 years old). Both the bacillary load and the type of disease may influence the effectiveness of treatment regimens. Treatment outcomes in children are generally good, even in young and immune-compromised children who are at higher risk of disease progression and disseminated disease,

provided that treatment starts promptly. There is a low risk of adverse events associated with use of the recommended standardised treatment regimens.

### ANTI-TUBERCULOSIS TREATMENT

#### *Anti-tuberculosis drugs*

Anti-tuberculosis treatment is divided into two phases: an intensive (initial) 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. The intensive phase uses more drugs. The purpose of the continuation phase is to eradicate the dormant organisms. Fewer drugs are generally used in the continuation phase because the risk of acquiring drug resistance is low, as most of the organisms have already been eliminated. Either phase can be given daily or three times weekly. Table 1 shows the essential anti-tuberculosis drugs and their recommended doses.<sup>1</sup>

The need for better data on anti-tuberculosis drug pharmacokinetics in children is highlighted by the variations in national recommendations for drug doses in children, particularly for isoniazid (INH) (some guidelines, such as those of the American Thoracic Society, recommend a dose of INH of 10–15 mg/kg). Thiacetazone is no longer recommended as part of a first-line regimen to treat TB, as it has been associated with severe reactions (Stevens-Johnson Syndrome) in adults and children with TB who are coinfecting with the human immunodeficiency virus (HIV).

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**Table 1** Doses of first-line anti-tuberculosis drugs in adults and children

Essential drug	Recommended dose in mg/kg body weight (range)	
	Daily	Three times weekly
Isoniazid (H)	5 (4–6) max. 300 mg daily	10 (8–12)
Rifampicin (R)	10 (8–12) max. 600 mg daily	10 (8–12) max. 600 mg daily
Pyrazinamide (Z)	25 (20–30)	35 (30–40)
Ethambutol (E)	Children 20 (15–25)* Adults 15 (15–20)	30 (25–35)
Streptomycin (S) <sup>†</sup>	15 (12–18)	15 (12–18)

\* The recommended daily dose of E is higher in children (20 mg/kg) than in adults (15 mg/kg), because the pharmacokinetics are different (peak serum E concentrations are lower in children than in adults receiving the same mg/kg dose). Although E was frequently omitted from treatment regimens for children in the past, due in part to concerns about the difficulty of monitoring for toxicity (particularly for optic neuritis) in young children, a literature review indicates that it is safe in children at a dose of 20 mg/kg (range 15–25 mg/kg) daily.<sup>2</sup>

<sup>†</sup> Should be avoided when possible in children because the injections are painful and irreversible auditory nerve damage may occur. The use of S in children is mainly reserved for the first 2 months of treatment of TB meningitis.

### Treatment regimens

The recommended treatment regimens for each TB diagnostic category are generally the same for children as for adults. New cases fall under Category I (new smear-positive pulmonary TB; new smear-negative pulmonary TB with extensive parenchymal involvement; severe forms of EPTB; severe concomitant HIV dis-

ease) or Category III (new smear-negative pulmonary TB—other than in Category I; less severe forms of EPTB). Most children with TB have uncomplicated (smear-negative) pulmonary/intrathoracic TB or non-severe forms of EPTB, and therefore fall under diagnostic Category III. Those children with smear-positive pulmonary TB, extensive pulmonary involvement, or severe forms of EPTB (e.g., abdominal or bone/joint TB) fall under diagnostic Category I. Children with TB meningitis and miliary TB deserve special consideration (see below). Previously treated cases fall under diagnostic Category II (previously treated smear-positive pulmonary TB) or IV (chronic and multidrug resistant [MDR] TB). Table 2 shows the recommended treatment regimens for each treatment category, based on the best available evidence.

There is a standard code for TB treatment regimens, which uses an abbreviation for each anti-tuberculosis drug. A regimen consists of two phases. The number in front of each phase represents the duration of that phase in months. A subscript number (e.g., <sub>3</sub>) following a letter (drug abbreviation) is the number of doses per week of that drug. If there is no subscript number following a letter, treatment with that drug is daily. An alternative drug (or drugs) appears as a letter (or letters) in parentheses.

*Example: 2HRZ/4H<sub>3</sub>R<sub>3</sub>*

The *initial phase* is 2HRZ. The duration of the initial phase is 2 months. Drug treatment is daily (no sub-

**Table 2** Recommended treatment regimens for each diagnostic category

TB diagnostic category	TB cases	Regimen (daily or 3 times weekly)*	
		Intensive phase	Continuation phase
III	New smear-negative pulmonary TB (other than in category I) Less severe forms of EPTB	2HRZ <sup>†</sup>	4HR or 6HE
I	New smear-positive pulmonary TB New smear-negative pulmonary TB with extensive parenchymal involvement Severe forms of EPTB (other than TB meningitis—see below) Severe concomitant HIV disease	2HRZE	4HR or 6HE <sup>‡</sup>
I	TB meningitis	2RHZS <sup>§</sup>	4RH
II	Previously treated smear-positive pulmonary TB: —relapse —treatment after interruption —treatment failure	2HRZES/1HRZE	5HRE
IV	Chronic and MDR-TB	Specially designed standardised or individualised regimens (see treatment guidelines for MDR-TB <sup>3</sup> )	

\* Direct observation of drug administration is recommended during the initial phase of treatment and whenever the continuation phase contains R.

<sup>†</sup> In comparison with the treatment regimen for patients in diagnostic category I, E may be omitted during the initial phase of treatment for patients with non-cavitary, smear-negative pulmonary TB who are known to be HIV-negative, patients known to be infected with fully drug-susceptible bacilli and young children with primary TB.

<sup>‡</sup> This regimen (2HRZE/6HE) may be associated with a higher rate of treatment failure and relapse compared with the 6-month regimen with R in the continuation phase.

<sup>§</sup> In comparison with the treatment regimen for patients in diagnostic category I, S replaces E in the treatment of TB meningitis.

TB = tuberculosis; H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol; EPTB = extra-pulmonary TB; HIV = human immunodeficiency virus; S = streptomycin; MDR-TB = multidrug resistant TB.

script numbers after the letters) with INH (H), rifampicin (R, RMP) and pyrazinamide (Z, PZA).

The *continuation phase* is 4H<sub>3</sub>R<sub>3</sub>. The duration of the continuation phase is 4 months, with H and R given three times weekly (number in subscript after the letters).

#### *Adjunctive treatment with corticosteroids*

Corticosteroids may be used for the management of some complicated forms of TB, e.g., tuberculous meningitis (TBM), the complications of airway obstruction by TB lymph glands, and TB pericarditis. In advanced TBM cases, corticosteroids have been shown to improve survival and reduce morbidity, and are thus recommended in all cases of TBM. The drug most frequently used is prednisone, in a dosage of 2 mg/kg/day (maximum dosage 60 mg/day) for 4 weeks. The dose should then be slowly reduced (tapered off) over 1–2 weeks before stopping.

## **TREATMENT ADMINISTRATION AND ADHERENCE**

Children, their parents and other family members and other care givers should be educated about TB and the importance of completing treatment. The support of the child's parents and immediate family is vital to ensure a satisfactory outcome of treatment. Preferably someone other than the child's parent or immediate family should observe or administer treatment. All children should receive treatment free of charge, whether or not the child is smear-positive at diagnosis. Fixed-dose combinations (FDCs) should be used whenever possible to improve simplicity and adherence. Patient treatment cards are recommended for documenting treatment adherence.

Children with severe forms of TB should be hospitalised for intensive management where possible. Conditions that merit hospitalisation include: 1) TB meningitis and miliary TB, preferably for the first 2 months, 2) any child with respiratory distress, 3) spinal TB and 4) severe adverse events, such as clinical signs of hepatotoxicity (e.g., jaundice). If it is not possible to ensure good adherence and treatment outcome as an out-patient, some children may require hospitalisation for social or logistical reasons.

## **FOLLOW-UP**

Ideally, each child should be assessed by the National Tuberculosis Programme (NTP) (or those designated by the NTP to provide treatment) at least at the following intervals: 2 weeks after treatment initiation, at the end of the intensive phase, and every 2 months until treatment completion. The assessment should include, at a minimum, a symptom assessment, an assessment of adherence, enquiry about any adverse events, and weight measurement. Medication dosages should be adjusted to account for any weight gain. Adherence should be

assessed by reviewing the treatment card. A follow-up sputum smear for microscopy at 2 months should be obtained for any child who was smear-positive at diagnosis. Follow-up chest radiographs are not routinely required in children, particularly as many children will have a slow radiological response to treatment. A child who is not responding to TB treatment should be referred for further assessment and management. These children may have drug-resistant TB, an unusual complication of pulmonary TB, other causes of lung disease, or problems with treatment adherence.

The NTP is responsible for organising treatment in line with the Stop TB Strategy, and ensuring the recording and reporting of cases and their outcomes. Good communication is necessary between the NTP and clinicians treating children with TB. Adverse events noted by clinicians should be reported to the NTP.

#### *Immune reconstitution*

Sometimes referred to as a paradoxical reaction, this temporary exacerbation of symptoms, signs or radiographic manifestations sometimes occurs after beginning anti-tuberculosis treatment. This can simulate worsening disease, with fever, and increased size of lymph nodes or tuberculomas. Immune reconstitution can be brought about by improved nutritional status or by the anti-tuberculosis treatment itself. Clinical deterioration due to immune reconstitution can occur after initiation of antiretroviral therapy (ART) in HIV-infected children with TB, and is known as the immune reconstitution inflammatory syndrome (IRIS). Anti-tuberculosis treatment should be continued, although in some cases the addition of corticosteroids might be useful. If in doubt, refer the child to the next level of care.

#### *Adverse events*

Adverse events caused by anti-tuberculosis drugs are much less common in children than in adults. The most important adverse event is the development of hepatotoxicity, which can be caused by INH, RMP, or PZA. Serum liver enzyme levels should not be monitored routinely, as asymptomatic mild elevation of serum liver enzymes (less than 5 times normal values) is not an indication to stop treatment. However, the occurrence of liver tenderness, hepatomegaly or jaundice should lead to investigation of serum liver enzyme levels and the immediate stopping of all potentially hepatotoxic drugs. Patients should be screened for other causes of hepatitis, and no attempt should be made to reintroduce these drugs until liver functions have normalised. An expert should be involved in the further management of such cases. If treatment for TB needs to be continued for severe forms of TB, non-hepatotoxic anti-tuberculosis drugs should be introduced (e.g., ethambutol [E, EMB], an aminoglycoside and a fluoroquinolone).

INH may cause symptomatic pyridoxine deficiency, particularly in severely malnourished children and HIV-infected children on highly active antiretroviral ther-

apy (HAART). Supplemental pyridoxine (5–10 mg/day) is recommended in 1) malnourished children, 2) HIV-infected children, 3) breastfeeding infants, and 4) pregnant adolescents.

## SPECIAL CASES

### *TB meningitis and miliary TB*

TB meningitis and miliary TB are more common in young children and are associated with high rates of death and disability, particularly if the diagnosis is delayed. It is therefore important to consider these diagnoses in young children as early as possible, especially in children who have a history of contact with an adult with infectious TB.

Miliary or haematogenously disseminated TB has a high risk (60–70%) of meningeal involvement and should therefore be managed similar to TB meningitis. For this reason, many experts recommend that all children with miliary TB (or suspected of having miliary TB) should undergo lumbar puncture to evaluate the presence of meningitis.

Table 3 summarises the commonly recommended regimens for the treatment of TB meningitis. Due to different degrees of drug penetration into the central nervous system (CNS), some experts recommend modifying the standard TB treatment regimen for children. In other forms of EPTB and in smear-positive pulmonary TB, EMB is recommended as the fourth drug. However, as EMB penetrates poorly into the CSF except in the presence of inflamed meninges, streptomycin (S, SM) should replace ethambutol in the initial phase of treatment of meningeal TB. Some experts recommend ethionamide (ETH) as the fourth drug, because ETH crosses both healthy and inflamed meninges. Furthermore, because RMP does not penetrate the uninfamed meninges well and PZA does, some experts recommend continuing PZA for the full 6 months of treatment. On the other hand, some experts recommend a longer duration of continuation phase treatment. Because penetration into the CSF is poor with some drugs, such as RMP and SM, treatment regimens for TB meningitis and miliary TB will most likely benefit from the upper end of the recommended dose ranges (see Table 1).

Corticosteroids (usually prednisone) are recom-

mended for all children with TB meningitis in a dosage of 2 mg/kg/day for 4 weeks. The dose should then be slowly reduced (tapered off) over 1–2 weeks before stopping. The dosage of prednisone can be increased to 4 mg/kg/day (maximum 60 mg/day) in the case of seriously ill children because RMP will reduce corticosteroid concentrations, but higher doses carry a risk of greater immune suppression.

All children with suspected or confirmed TB meningitis or miliary TB should be hospitalised initially until their clinical status has stabilised. Children with TB meningitis are at high risk of long-term disability, and will therefore benefit from specialist care where this is available.

### *Retreatment cases*

In childhood TB cases when anti-tuberculosis treatment has failed or a relapse occurs, every effort should be made to find the most likely cause for the failure of treatment or relapse. Cultures and drug susceptibility testing (DST) should be done in all retreatment cases where possible.

Children who fail Category I treatment should be managed in the same way as adults who fail, with either a Category II or a Category IV regimen, depending on what is known about the risk for MDR-TB in this group of patients. The standard Category II regimen is 2HRZES/1HRZE/5HRE. Category IV regimens are specially designed and may be standardised or individualised. If an adult source case with drug-resistant TB is identified, the child should be treated according to the DST pattern of the source case's strain if an isolate from the child is not available. Two or more new drugs should be added to any retreatment regimen in case of genuine failure of treatment, and the duration of treatment should be not less than 9 months.

### *Drug-resistant TB*

As far as monoresistance is concerned, resistance to INH and/or RMP is the most important, as these two drugs are the mainstay of current chemotherapy.<sup>3</sup> In cases where monoresistance to INH is known or suspected when treatment is initiated, the addition of EMB (to INH, RMP and PZA) as a fourth drug in the intensive phase will probably suffice. The addition of a fluoroquinolone and overall treatment for 9 months should be considered for patients with more extensive disease. Monoresistance to RMP should be treated with INH, EMB and a fluoroquinolone for at least 12–18 months, with the addition of PZA for at least the first 2 months.

MDR-TB is resistance to both INH and RMP, with or without resistance to other anti-tuberculosis drugs. MDR-TB in children is mainly the result of transmission of a MDR *M. tuberculosis* strain from an adult source case, and is therefore often not suspected unless a history of contact with an adult pulmonary MDR-TB case is known. As treatment is difficult, spe-

**Table 3** Selected regimens for treatment of TB meningitis in children

Intensive phase	Continuation phase	Reference
2HRZS	4HR	WHO (Treatment guidelines)
2HRZ(S or Eth)	7–10HR	American Academy of Pediatrics <sup>4</sup>
6HRZEth	None (regimen for 6 months total)	Donald, 1998 <sup>5</sup>

TB = tuberculosis; H = isoniazid; R = rifampicin; Z = pyrazinamide; S = streptomycin; Eth = ethionamide; WHO = World Health Organization.

cialist referral is advised. Some basic principles of treatment are the following:

- Do not add one drug to a failing regimen
- Treat the child according to the DST pattern (and using the treatment history) of the source case's strain if the child's isolate is not available
- Use at least four drugs that are certain to be effective
- Use daily treatment only, and directly observed treatment is essential
- Counsel the care giver at every visit for support, about adverse events, and the importance of adherence/completion of treatment
- Follow-up is essential—clinical, radiological and with cultures (for any child who had bacteriologically confirmed disease at diagnosis)
- Treatment duration depends on the extent of the disease, but for most cases it will be 12 months or more (or at least 12 months after the last positive culture)

Children with MDR-TB should be treated with the first-line drugs to which they (or their source case) are susceptible, including SM, EMB and PZA. EMB is bactericidal at higher doses, so doses of up to 25 mg/kg/day should be used in children being treated for MDR-TB. Table 4 summarises the reserve (or second-line) anti-tuberculosis drugs for treatment of MDR-TB in children.

With correct dosing, few long-term adverse events are seen with any of the more toxic second-line drugs in children, including ETH and the fluoroquinolones. Although fluoroquinolones are not approved for use in children in most countries, the benefit of treating children with MDR-TB with a fluoroquinolone may outweigh the risks in many instances.

#### *HIV coinfection*

(See also later in the series, Chapter 3, Management of tuberculosis in the HIV-infected child—December issue).

Most current international guidelines recommend

that TB in HIV-infected children should be treated with a 6-month regimen, as in non-HIV-infected children. Where possible, HIV-infected children should be treated with RMP for the entire treatment duration, as higher relapse rates among HIV-infected adults have been found when EMB is used in the continuation phase. Most children with TB, including those who are HIV-infected, have a good response to the 6-month regimen. Possible causes of failure, such as non-adherence to treatment, poor drug absorption, drug resistance and alternative diagnoses, should be investigated in children who are not improving on anti-tuberculosis treatment.

All children with TB and HIV coinfection should be evaluated to determine whether ART is indicated during the course of treatment for TB. Appropriate arrangements for access to ART should be made for patients who meet indications for treatment. Given the complexity of co-administration of anti-tuberculosis treatment and ART, consultation with an expert in this area is recommended before initiation of concurrent treatment for TB and HIV infection, regardless of which disease appeared first. However, initiation of treatment for TB should not be delayed. Children with TB and HIV infection should also receive cotrimoxazole as prophylaxis for other infections.

In HIV-infected children with confirmed or presumptive TB disease, initiation of TB treatment is the priority. However, the optimal timing for initiation of ART during TB treatment is not known. The decision on when to start ART after starting TB treatment involves a balance between the child's age, pill burden, potential drug interactions, overlapping toxicities and possible immune reconstitution inflammatory syndrome versus the risk of further progression of immune suppression with its associated increase in mortality and morbidity. Many clinicians will start ART 2–8 weeks after starting anti-tuberculosis treatment.

**Table 4** Reserve or second-line anti-tuberculosis drugs

Reserve (second-line) drug	Mode of action	Common side effects	Recommended daily dose	
			Dose (mg/kg)	Maximum (mg)
Ethionamide or prothionamide	Bactericidal	Vomiting, gastrointestinal upset	15–20	1000
Fluoroquinolones		Arthropathy, arthritis		
Ofloxacin	Bactericidal		15–20	800
Levofloxacin	Bactericidal		7.5–10	
Moxifloxacin	Bactericidal		7.5–10	
Gatifloxacin	Bactericidal		7.5–10	
Ciprofloxacin	Bactericidal		20–30	1500
Aminoglycosides		Ototoxicity, renal toxicity		
Kanamycin	Bactericidal		15–30	1000
Amikacin	Bactericidal		15–22.5	1000
Capreomycin	Bactericidal		15–30	1000
Cycloserine or terizidone	Bacteriostatic	Psychiatric, neurologic	10–20	1000
Para-aminosalicylic acid (PAS)	Bacteriostatic	Vomiting, gastrointestinal upset	150	12 g

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## TB meningitis and miliary TB

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## R É S U M É

La prise en charge des enfants atteints de tuberculose (TB) devrait s'aligner sur la stratégie Stop TB qui prend en considération l'épidémiologie particulière et la présentation clinique de la TB chez les enfants. L'obtention de bons résultats du traitement dépend de l'application de régimes standardisés de traitement en fonction de la catégorie des diagnostics concernés, accompagnés par un soutien pour l'enfant et son soignant qui assure l'adhésion maximale au traitement. Une modification récente

des recommandations de traitement résulte du fait que, après une revue complète de la littérature, l'éthambutol est considéré comme sans risque pour les enfants à la dose de 20 mg/kg (extrêmes 15–25 mg/kg) et par jour. Les zones critiques pour la recherche à venir comportent les formulations et les dosages optimaux pour les médicaments antituberculeux de première et de deuxième ligne ainsi que le développement de nouveaux médicaments.

## R E S U M E N

El tratamiento de niños con tuberculosis (TB) debe acoplarse a la estrategia Alto a la TB y tener en cuenta las características epidemiológicas y la presentación clínica particulares de la TB en los niños. La obtención de buenos desenlaces terapéuticos depende de la aplicación de pautas de tratamiento estandarizadas, según la categoría diagnóstica pertinente y el suministro de apoyo para el niño y para el proveedor de atención, a fin de optimizar el cumplimiento terapéutico. Una novedad en las re-

comendaciones terapéuticas, producto de un análisis exhaustivo de los estudios publicados, es considerar que el etambutol es seguro en los niños en dosis diarias de 20 mg/kg (entre 15 y 25 mg/kg). Entre los aspectos primordiales de investigación futura se encuentran la optimización de las formulaciones y pautas terapéuticas de los medicamentos antituberculosos de primera y segunda línea y el desarrollo de nuevos principios activos.