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ORIGINAL ARTICLE

Treatment regimens for tuberculosis in children and related adverse effects

Emanuela da Rocha Carvalho[1], Andrea Maciel de Oliveira Rossoni[2,3], Tony Tannous Tahan[2,4], Marssoni Deconto Rossoni[3,5], Cristina de Oliveira Rodrigues[4]

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Abstract

The World Health Organization (WHO) recommends an initial treatment regimen for tuberculosis in children that is comparable to that for adults, with directly monitored multiple-drug therapy for 6 months. Early initiation of treatment in younger children is essential due to the possibility of rapid dissemination of the disease, severe sequelae, and death. Children and adolescents usually tolerate antituberculosis drugs very well. This article aims to review the main therapeutic regimens, dosages, and adverse effects associated with first-line drugs used in treatment regimens for tuberculosis in children and to provide some practical recommendations for the follow-up of children and adolescents undergoing treatment. The article reviews current guidelines from the WHO and the Brazilian Ministry of Health as well as currently used therapeutic regimens and their main adverse effects. The reviewed literature states that at recommended doses, antituberculosis drugs are well tolerated by the pediatric population, and severe adverse effects are rare and mostly temporary. The frequency of toxic effects may be related to disease severity. Isoniazid is the most extensively studied drug and the most commonly used in children because it is also used in the treatment of latent tuberculosis. Liver toxicity is the primary described adverse effect. In most cases, when treatment is started adequately on time, it proceeds without severe adverse effects that require the therapy to be suspended. A high degree of suspicion is required to establish the diagnosis and consequently the adequate treatment, aiming for a long-term change in the course of the disease in children.

[1] Physician, Master's Candidate in the Graduate Program in Child and Adolescent Health of the Sector of Health Sciences of the Federal University of Paraná (UFPR), Curitiba, Brazil.
[2] Physician of the Service of Pediatric Infectology of the Clinics Hospital Complex of the Federal University of Paraná (CHC-UFPR), Curitiba, Brazil.
[3] Professor of the Department of Medicine - State University of Ponta Grossa, Brazil.
[4] Professor of Department of Pediatrics of the Federal University of Paraná (UFPR), Curitiba, Brazil.
[5] Professor of the Department of Clinical Medicine of the Federal University of Paraná (UFPR), Curitiba, Brazil.

Correspondence to:
Andrea Maciel de Oliveira Rossoni.
Universidade Estadual de Ponta Grossa. Praça Santos Andrade, nº 1, Ponta Grossa - Paraná. Brazil. CEP: 84.010-919. E-mail: dearossoni@gmail.com

INTRODUCTION

The World Health Organization (WHO) estimates that 950,000 children and adolescents of < 15 years developed tuberculosis (TB) in 2015, accounting for 10% of all cases. Approximately 210,000 of them died as a result of the disease[1]. With regard to the global prevalence of TB in children, it is generally agreed that there are a large number of undiagnosed and consequently untreated children[2-4]. This is probably because, for many years, TB control programs focused only on adults with bacilliferous pulmonary disease and also because of the difficulties in confirming TB diagnosis in childhood.

TB is a disease with worldwide distribution and caused by *Mycobacterium tuberculosis*. It has variable characteristics in different regions because of socioeconomic factors, local drug-resistance profile, interaction with other epidemics such as HIV/AIDS, and the prevalence of the disease[1].

Children of < 5 years exposed to and infected by *M. tuberculosis* have a greater risk of progressing to active disease than older children (5-14 years old)[5,6]. They also have a greater probability of developing severe forms of the disease, such as tuberculous meningitis, and have a higher mortality rate than do older children[6-8].

The WHO recommends an initial treatment regimen for tuberculosis in children that is comparable to that for adults, with directly monitored multiple-drug therapy for 6 months[9]. It is essential to start the treatment early in younger children because of the possibility of rapid disease dissemination, severe sequelae, and death[10].

Children and adolescents usually tolerate antituberculosis drugs very well if taken at the currently recommended doses. Mild symptoms, such as nausea and vomiting, are uncommon, and severe adverse effects are rare. HIV infection and malnutrition may increase the frequency of adverse effects in antituberculosis therapy.

This article aims to review the main therapeutic regimens, dosages, and adverse effects associated with first-line drugs in the treatment of TB in children. It also provides some practical recommendations for the follow-up of children and adolescents under treatment.

Current guidelines from the WHO and the Brazilian Ministry of Health have been reviewed as well as studies on the therapeutic regimens used and the most important adverse effects caused by first-line drugs.

Treatment regimen for tuberculosis in children

The best treatment regimen for TB should meet the following recommendations: early bactericidal activity, capable of preventing the appearance of drug-resistant bacilli, and sterilizing activity[11]. For treating children of <10 years with drug-sensitive pulmonary or extrapulmonary TB (except tuberculous meningoencephalitis), the Brazilian Ministry of Health recommends a 2-month loading phase with rifampicin, isoniazid, and pyrazinamide, followed by a 4-month maintenance phase with rifampicin and isoniazid. In children of ≥ 10 years, ethambutol is added to the loading phase[11]. Tables 1 and 2 present the dosage according to age range and weight.

Table 1. Basic treatment regimen for children of < 10 years (all forms of tuberculosis, except meningeal and osteal forms).

Treatment phase	Drugs	Patient weight			
		≤ 20 kg	21-35 kg	36-45 kg	> 45kg
		mg/kg/day	mg/day	mg/day	mg/day
First phase (2 months)	R	15 (10-20)	300-500	600	600
	I	10 (7-15)	200-300	300	300
	P	35 (30-40)	750-1000	1500	2000
Second phase (4 months)	R	15 (10-20)	300-500	600	600
	I	10 (7-15)	200-300	300	300
R - rifampicin		I - isoniazid		P - pyrazinamide	

SOURCE: Adapted from the WHO: *Guidance for national tuberculosis programmes on the management of tuberculosis in children*, 2014.

When treating tuberculous meningoencephalitis and osteal TB, the WHO advises the maintenance phase to be extended to 10 months; the total length of the treatment will therefore be 12 months (Table 3). For tuberculous meningitis, corticosteroids should be added to the regimen to improve survival and reduce mortality. Prednisone or prednisolone (1-2 mg/kg/day) is most frequently used; in more severe cases, up to 4 mg/kg/day may be prescribed, with a maximum dose of 60 mg/day for 4 weeks. In very severe cases, intravenous corticosteroids, such as dexamethasone at 0.3-0.4 mg/kg/day may be used for 4-8 weeks. The dose must be gradually reduced in the last 2 weeks until complete suspension. In such cases, early initiation of physical rehabilitation treatment with motor therapy is of paramount importance to reduce morbidity[11].

First-line antituberculosis drugs Isoniazid

Isoniazid has great bactericidal power and acts on all sensitive bacillus populations, whether they are intracavitary, in granulomas, or intracellular. It is highly soluble in water

Table 2. Basic treatment regimen for children of ≥ 10 years (all forms of tuberculosis, except meningeal and osteal forms).

Treatment phase	Patient weight			
	Drugs	20 a 35 kg	36 a 50 kg	> 50kg
First phase (2 months)	RHZE (150/75/400/275)	2 tablets	3 tablets	4 tablets
Second phase (4 months)	RH (150/75)	2 tablets	3 tablets	4 tablets
R - rifampicin	I - isoniazid		P - pyrazinamide	E - ethambutol

SOURCE: Table from the *Manual of Recommendations for Tuberculosis Control in Brazil*, 2011.

Table 3. Basic treatment regimen for children of < 10 years (meningeal and osteal tuberculosis).

Treatment phase	Drugs	Patient weight			
		≤ 20kg	21-35 kg	36-45 kg	> 45kg
		mg/kg/day	mg/day	mg/day	mg/day
First phase (2 months)	R	15 (10-20)	300-500	600	600
	I	10 (7-15)	200-300	300	300
	P	35 (30-40)	750-1000	1500	2000
Second phase (4 months)	R	15 (10-20)	300-500	600	600
	I	10 (7-15)	200-300	300	300
R - rifampicin		I - isoniazid		P - pyrazinamide	

SOURCE: Adapted from the WHO: *Guidance for national tuberculosis programmes on the management of tuberculosis in children*, 2014.

and most stable at pH 6.6. It is distributed to all body fluids and tissues, including the central nervous system[12]. The most important adverse effects described in the literature are neurological and hepatic, both of which are rare in children. Serum levels of isoniazid, both in children and adults, depend on the acetylation rate (fast, intermediate, or slow), determined by the N-acetyltransferase 2 genotype, which differs between ethnic groups[13]. Children are considered fast acetylators. In slow-acetylating patients, greater incidence of adverse effects has been observed.

Isoniazid may induce hepatitis, which in turn may cause severe liver failure, but this is rare in children who take the usual 10 mg/kg/day doses[14]. During the first months of therapy, subclinical and asymptomatic increases in transaminases (5%-10%) are observed[15]. However, it is uncommon for severe symptomatic liver toxicity that leads to therapy discontinuation to occur in this age range.

Isoniazid competes with vitamin B6 (pyridoxine) as a cofactor in the synthesis of neurotransmitters. Neurological symptoms, such as peripheral neuropathy, ataxia, and paresthesia, may appear, depending on the dose taken.

Pediatric patients are less likely than adults to develop vitamin B6 deficiencies, even when taking isoniazid doses of 20 mg/kg/day. In studies with children from Zaire, now known as the Democratic Republic of Congo, and from South Africa who received isoniazid doses of 3-15 mg/kg/day, no cases of vitamin B6 deficiency were identified[16]. The WHO does not recommend routine supplementation with pyridoxine, except in children with severe nutritional deficit and in infants and children living with HIV/AIDS[9].

In Brazil, isoniazid is available as 100mg tablets or associated with other drugs, as described in Table 4. Some facilities use compounded isoniazid preparations for children, but in such cases, special attention must be given to the preparation's expiration date and guarantee of efficacy. In 2016, water-dispersible tablets for pediatric use were introduced, but they are not yet available in Brazil. This new preparation has several advantages, such as better taste, easier preparation by parents or guardians, and possible combination of formulations with other drugs, as in those used for adults. Table 4 presents the available formulations of antituberculosis drugs, including the new ones.

Rifampicin

Rifampicin has great bactericidal power and the greatest sterilizing power of all antituberculosis drugs. It is because of this drug that the duration of TB treatment course is 6 months; in special regimens without rifampicin, due to adverse effects or tolerability problems, the treatment must be extended to 1 year. Rifampicin is highly lipophilic and can enter the central nervous system in the presence of inflammation and consequently disrupt the blood-brain barrier. It is metabolized chiefly in the enterohepatic circulation[17].

Rifampicin is a potent inducer of several enzymes involved in drug metabolism. It also induces the P-glycoprotein

Table 4. Available presentations of first-line drugs for tuberculosis treatment.

DRUG	PRESENTATION
"4-in-1" RHZE tablets (Coxipe®)	Tablets with rifampicin (150 mg), isoniazid (75 mg), pyrazinamide (400 mg), and ethambutol (275 mg)
Rifampicin	300-mg tablets or 20-mg/mL suspension
Isoniazid	100-mg tablets
Rifampicin + isoniazid	Capsules with rifampicin (150 mg) and isoniazid (75 mg)
Pyrazinamide	500-mg tablets or 150-mg/5 mL suspension
Ethambutol	400-mg tablets
New formulations (not yet available in Brazil)	
Isoniazid	Water-dispersible 100-mg tablets
Rifampicin + isoniazid	Water-dispersible tablets with rifampicin (75 mg) + isoniazid (50 mg)
Rifampicin + isoniazid + pyrazinamide	Water-dispersible tablets with rifampicin (75 mg) + isoniazid (50 mg) + pyrazinamide (150 mg)
Ethambutol	Water-dispersible 100-mg tablets

SOURCE: Table from the Manual of Tuberculosis Control in Brazil, 2011.

drug efflux pump. This affects the serum level of several other drugs and interferes with their therapeutic efficacy. These drug interactions result from rifampicin's capability of stimulating cytochrome P450 CYP3A and glucuronidation, thereby speeding up drug excretion and increasing drug efflux, which contributes to decreased gastrointestinal absorption of drugs[17]. An example would be the reduction in serum levels of protease inhibitors when rifampicin and antiretroviral medication are taken simultaneously[18]. This makes treatment of co-infected HIV/AIDS patients more difficult.

Currently recommended doses of rifampicin are well tolerated by children, and allergic or hepatotoxic adverse effects are rare. On the other hand, adverse effects are widely reported in adults and more commonly seen when high and intermittent doses are taken. There can be reactions such as fever, skin rashes, flu-like syndrome, eosinophilia, and less frequently hemolytic anemia and acute kidney failure[19].

In Brazil, rifampicin is available as a solution (20 mg/mL) and in capsules (300 mg). There are also combined preparations, as described in Table 4.

Pyrazinamide

Pyrazinamide is produced as a crystalline powder with low water solubility, forming suspensions that sediment easily. The drug is active either in acid intracellular moieties or inside granulomas. It has good oral absorption and is distributed into several tissues, including the central nervous system[12]. Pyrazinamide is more commonly used in combination with other agents in the intensive phase of treatment for active TB.

The most frequently observed adverse effects during pyrazinamide use are gastrointestinal intolerance, hepatotoxicity, polyarthralgia, and gouty arthritis. Articular problems are more commonly described in adults and related to dosage and treatment length. There are few data on the tolerance and adverse effects of pyrazinamide alone in children. In 2005, Tortajada et al. evaluated pyrazinamide use in 86 children as part of combined chemoprophylaxis with rifampicin for 2 months, and no hepatotoxicity related to the therapy was observed[20]. Liver enzyme abnormalities were infrequent and temporary, and the drug was well tolerated, even when it was used in chemoprophylaxis regimens[15,20].

In Brazil, pyrazinamide is available as a solution (30 mg/mL), in capsules (500 mg), and in combination with other drugs, as described in Table 4.

Ethambutol

The last drug of those considered to be the first-line treatment for TB, ethambutol is bacteriostatic, and it is used in combined therapeutic regimens. Its concentration in the central nervous system is low[9]. Its use in association with more potent drugs is intended to prevent the emergence of drug-resistant bacilli. In Brazil, it is currently used in basic treatment regimens for children and adolescents of ≥ 10 years, and it is not part of the initial scheme for younger children. This is not because of possible toxic effects, as many believe, but rather because of the low risk for primary resistance in this population and because suitable ethambutol formulations for the pediatric age range are unavailable.

The most severe toxic effect of ethambutol is retrobulbar neuritis, which is reversible when detected early. This effect is related to dosage and treatment duration[9]. In a study of 3,811 children who received ethambutol doses of 15-30 mg/kg, only two (0.05%) had to discontinue the medication due to ocular toxicity[21]. Therefore, given the small incidence of reported adverse effects, the WHO considers ethambutol safe and supports its use in infants and children at a dose of 20 mg/kg/day[1].

In Brazil, ethambutol is available only in coated tablets at a dose of 400 mg and also in combination with other drugs, as described in Table 4.

Treatment for drug-resistant tuberculosis in children

Failed treatments, low adherence, and spontaneous mutations in *M. tuberculosis* strains have contributed to the appearance of new cases of drug-resistant TB[11]. TB is classified according to the drug-sensitivity profile of the bacillus. It is called monoresistant when the bacillus is resistant to only one drug and polyresistant when resistant to two or more drugs. The particular case of resistance to both rifampicin and isoniazid is called multidrug-resistant TB (MDR-TB), and when it occurs jointly with resistance to at least one fluoroquinolone and one injectable second-line drug (amikacin, kanamycin, or capreomycin), it is called extensively drug-resistant TB[11].

Drug-resistant TB is curable, just like drug-susceptible TB, but the treatment requires longer-lasting and more toxic regimens, with little availability of liquid preparations for children[22].

According to Kritski et al., drug-resistant TB is associated with a high mortality rate, particularly in children and patients living with HIV/AIDS[23]. It is estimated that in 2014, 25,000 children and adolescents developed drug-resistant TB worldwide, but most of them have not been adequately diagnosed and treated[24,25]. Therefore, additional effort is needed to improve the detection of drug-resistant TB in this population.

The management of drug-resistant TB in pediatrics is similar to that in adults, prioritizing shorter regimens. However, the use of second-line antituberculosis drugs in children is complicated by the absence of pediatric formulations of most drugs, which may lead to under or overdosage[1,10]. In some cases, personalized treatment regimens have been necessary for pediatric patients, and the results have been satisfactory, as described in a retrospective study of 149 children of < 15 years with documented or suspected drug-resistant TB in South Africa. Treatment regimens included four active drugs and one injectable agent for 66% of the patients, and they were administered for an average of 13 months; either confirmed or likely cure was obtained in 92% of the patients[26].

MDR-TB treatment duration is longer and requires the use of second-line drugs, with more adverse effects. However, there is little information in the literature about the safety and tolerability of these drugs in children[27]. Generally, MDR-TB treatment in pediatric patients has an 80% success rate compared with approximately 60% in adults[11,26,28]. Children and adolescents under special regimens for drug-resistant TB must be frequently re-evaluated for adherence, therapeutic response, and potential adverse effects.

What is necessary during treatment besides drugs?

The WHO recommends that children and adolescents be properly informed and stimulated to actively participate in the treatment. Adolescents should receive individualized care aimed at strengthening bonds and making them aware of the importance of adherence. Clinical evaluation should be performed monthly to adjust doses according to weight gain, explain about possible adverse effects, and observe the therapeutic response. In every consultation, health professionals have the important duty of evaluating risk factors that may contribute to treatment abandonment.

The WHO recommends the directly observed therapy (DOT) strategy to promote treatment adherence and completeness in children. One of the pillars of this strategy is the direct observation or administration of the medication by a health professional. Support from the caregivers is paramount to ensure adherence and consequently a satisfactory therapeutic response. It must be emphasized that when only the parents or guardians supervise the taking of medication, this is not considered DOT.

In cases of pulmonary TB in children and adolescents, treatment must be controlled not only clinically but also radiologically. The first radiological examination should be performed in the second month of treatment if the evolution is favorable, but an earlier examination should be considered for patients exhibiting no clinical response and for differential diagnosis purposes. When the treatment is finished, radiological control should be repeated[9].

Because children are paucibacillary, bacilloscopy rarely confirms the diagnosis. Therefore, patient improvement confirmed by clinical exam and radiology becomes the

criterion to determine a cure. In bacilliferous patients, usually adolescents, bacilloscopy should be repeated every month.

Routine liver function control tests are not necessary, except for patients who already have an underlying liver disease and for those who develop liver symptoms. It should be noted that liver enzyme levels may increase without symptoms and without any need to change the therapeutic regimen[11].

Final Remarks

It could be seen in the present review that the recommended doses of first-line antituberculosis drugs are well tolerated by the pediatric population, and severe adverse effects are rare and mostly transient. The frequency of toxic effects may be related to the severity of the disease. Isoniazid is the most extensively studied drug because it is also used to treat latent tuberculosis. Hepatotoxicity is the most important described event. The literature gives evidence that children tolerate antituberculosis drugs better than adults, perhaps because the latter have slower isoniazid acetylation, may have chronic liver disease, and may consume alcohol, which can influence the outcome[19].

More rigorous monitoring for the possibility of adverse effects is needed in children and adolescents living with HIV/AIDS who undergo treatment for TB and in patients who are under special therapeutic regimens. Adverse effects such as hepatotoxicity, skin rashes, gastrointestinal distress, leukopenia, anemia, and neuropathy may be caused by both the antiretroviral therapy and antituberculosis medication, and it is difficult to determine which drug is responsible for the adverse effect when both therapies are combined[29].

The WHO strategy for the elimination of TB targets a substantial reduction in the incidence of the disease and its mortality rates and provides opportunities to conduct pediatric TB treatment on a large scale[1].

Because TB is predominantly paucibacillary and presents nonspecific clinical forms in children, it becomes a challenge for health professionals. Therefore, a high degree of suspicion is needed to diagnose the disease and consequently treat it adequately, aiming for a long-term change of the disease course in pediatric patients. In the vast majority of cases, when treatment is adequately instituted, it proceeds without important adverse effects that would require it to be suspended.

During treatment, attention must be given to the prescription of adequate doses for the child's weight, adherence to treatment, presence of adverse effects, possibility of drug interactions, and clinical course of the patient, with the goal of obtaining a better therapeutic response.

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