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ADRESSING TUBERCULOSIS IN CHILDREN

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Abstract: Tuberculosis (TB) in children remains a challenge for medicine due to the increased risk of its progression from infection to disease, the possibility of developing into more severe forms, and the existence of diagnostic problems, since microbiological samples and confirmation of the disease are increasingly difficult to obtain.
It is necessary to create a protocol for managing these cases for improved prevention and control of TB in the community.

Keywords: TB exposure, tuberculosis infection, pulmonary TB

ABORDAJE DE LA TUBERCULOSIS INFANTIL

Resumen. La tuberculosis (TB) en la edad pediátrica sigue siendo un reto para la medicina dado el mayor riesgo de progresión de infección a enfermedad, la posibilidad de desarrollar formas más graves y los problemas diagnósticos, dado que es más difícil la obtención de muestras microbiológicas y la confirmación de la enfermedad.
Es necesario protocolizar el manejo de estos casos para una mejor prevención y control de la TB en la comunidad.

Palabras clave: exposición a TB, infección tuberculosa, TB pulmonar.

ABORDAGEM DA TUBERCULOSE INFANTIL

Resumo: A tuberculose (TB) na idade pediátrica continua a ser um desafio para a medicina, dado o aumento do risco de progressão da infeção para a doença, a possibilidade de desenvolver formas mais graves e os problemas de diagnóstico, uma vez que é mais difícil obter amostras microbiológicas e a confirmação da doença.
É necessário protocolizar a gestão destes casos para uma melhor prevenção e controlo da TB na comunidade.

Palavras-chave: exposição à TB, infeção tuberculosa, tuberculose pulmonar

INTRODUCTION

According to the World Health Organization (WHO), by 2017, 10% of tuberculosis (TB) cases were diagnosed in children under 15 years of age (52% of them being under 5 years old). In addition, an estimated 7.5 million children become infected each year. As a result, a comprehensive approach will make a substantial contribution to global TB control (World Health Organization, 2018c)(World Health Organization, 2018a).

Children under 5 years of age are at greater risk of developing severe forms of this disease (disseminated TB or tuberculous meningitis) with a higher risk of death (especially those under 2 years of age). The diagnosis is more challenging due to the non-specific clinical symptoms of TB and the difficulty in obtaining biological samples for bacteriological confirmation (World Health Organization, 2018a).

However, in adolescents (in 10-19 year-olds), this disease can typically manifest as in adults, with the same level of transmission risk involved, as these are groups with multiple contacts in different environments.

For these reasons, diagnosing TB in children requires age-specific strategies and approaches. Accordingly, this bulletin focuses on the management of uncomplicated pulmonary TB in children, which is the most common form of presentation.

MANAGEMENT OF TUBERCULOSIS IN CHILDREN

When attending to a child with suspected TB, their family members and close contacts should always be included in the study at an early stage in order to disrupt the epidemiological chain of events.

All children who have been in contact with the TB bacillus should be studied and classified as exposed, infected, or diseased.

1. Children exposed to TB

A child is considered to be exposed when the following conditions are met:

1. Recent and close contact, during the past 3 months, with a confirmed/suspected bacilliferous TB patient (pulmonary, laryngeal, tracheal, or endobronchial).
2. Tuberculin test (TT) results are negative (< 5mm) and/or Interferon Gamma Release Assay (IGRA) results are negative.
3. Absence of symptoms and clinical signs consistent with TB.

In cases where, due to a clinical judgment or referral, there are diagnostic doubts in immunosuppressed patients or in patients under 2 years of age, a chest X-ray (frontal and lateral) is performed. This chest X-ray must be normal in order to classify the child as exposed.

The TT should be performed by trained personnel to avoid errors in both performance and readings, and may be performed on children aged 6 months and older.

Given the risk of developing tuberculosis disease, all children under 5 years of age should follow a chemoprophylaxis regimen. Immunosuppressed individuals of any age, whether their immunosuppression is caused by HIV infection, drugs, or has a different aetiology, should similarly follow a chemoprophylaxis regimen, again due to increased risk of developing tuberculosis disease in these individuals. It is strongly recommended that preventative therapy be expanded to include children over 5 years of age because of its benefits in TB control (Grupo de trabajo Plan Prevención y Control de la Tuberculosis. Comisión de Salud Pública del Consejo Interterritorial del Sistema Nacional de Salud. Ministerio de Sanidad Consumo y Bienestar Social, 2019)

A new TT will be performed 8-12 weeks after the last risk contact, regardless of whether or not prophylaxis was carried out. If prophylaxis had indeed been carried out, it will be discontinued if the TT continues to be negative. If TT conversion is reported, the child will be considered to be infected.

The usual chemoprophylaxis regimen consists of the administration of 10 mg/kg/day (maximum 300 mg/day) of isoniazid for 8-12 weeks.

2. Children infected with TB

Asymptomatic contact with positive TT and/or positive IGRA and normal chest X-ray.

The risk of progression to TB disease in children is closely related to the age of infection and their immunological status. Children aged between 5-10 years old who are immunocompetent are less likely to become diseased, while children under 2 years of age represent a high-risk group.

Once tuberculous disease has been ruled out, treatment of tuberculous infection should be recommended, usually by ordering a 6-9 month treatment with isoniazid. Alternative regimens exist (Early identification and effective treatment of TB infection cases will reduce TB load in children.

Table 1. Recommendations for treating tuberculosis infection in children) and should be assessed individually.

In children, the risk of hepatotoxicity is low. However, transaminase levels should be studied if clinical symptoms appear, if there is an underlying liver disease, or if the child is receiving other hepatotoxic medications. In the case of immigrants from countries with widespread viral hepatitis or HIV infection, these conditions should be ruled out before starting treatment (Mellado Peña et al., 2018)

Early identification and effective treatment of TB infection cases will reduce TB load in children.

Table 1. Recommendations for treating tuberculosis infection in children

Regimen	Dosage per Kg per day	Maximum daily dosage
Daily with H	10 mg (range 7-15)	300 mg

for 6 to 9 months		
Daily with R	15 mg (range 10-20)	600 mg
for 3 to 4 months		
Daily with H + R	H: 10 mg (7-15)	H: 300 mg
for 3 to 4 months	R: 15 mg (range 10-20)	R: 600 mg
Weekly with H + Rifapentine	H:	H: 900 mg
for 3 months (12 doses)	2-11 years old 25 mg	Rifapentine: 900 mg
	≥ 12 years old 15 mg	
	Rifapentine:	
	10-14 kg: 300 mg	
	14,1-25 kg: 450 mg	
	25,1-32 kg: 600 mg	
	32,1-50 kg: 750 mg	
	> 50 kg: 900 mg	

H: isoniazida; R: rifampicina

Source: (World Health Organization, 2018b)

3. Children diseased with TB

TB in children is considered to be a "sentinel event" for a recent *Mycobacterium tuberculosis* transmission in the community. Therefore, even if it there is no evidence of it, there must be an adult with the bacilliferous disease nearby.

Inhalation of the bacillus may cause the apparition of what is known as a Ghon's complex (primary focus of infection and enlarged lymph nodes). The disease may appear between 2-12 months after infection, with the pulmonary form being the most common (in 60-80% of cases). The most frequent extrapulmonary sites are the following: lymph nodes, central nervous system, pleura, miliary and disseminated, and bones.

Clinical manifestations in children are unspecific and a high degree of suspicion is required for diagnosis. Clinical symptoms will depend on the inoculum size and its virulence, on the immune and nutritional status of the host, and on the existence of other conditions.

In the child population, complete clinical records (including history of contact with TB and symptoms consistent with TB), careful and thorough assessments of clinical examinations (including growth assessment), and all the radiological, microbiological, and immunological tests available should be conducted (World Health Organization, 2014a).

3.1. Clinical symptoms

Most children infected with *Mycobacterium tuberculosis* do not show symptoms or have painless symptoms, including the following:

- persistent cough
- low-grade fever, prolonged fever, and/or night sweats
- anorexia
- unexplained weight loss (> 5% weight loss compared to the highest weight recorded in the past 3 months) and deviation from the previous growth rate
- fatigue

- lack of motivation and will to play

Additional symptoms will show depending on the site of the disease.

TB infection should be suspected if symptoms persist for more than 2 weeks and if other conditions causing these symptoms are ruled out.

The manifestations of primary pulmonary TB tend to vary according to age. Infants and adolescents tend to be more clinically expressive than school-aged children among which the disease is often asymptomatic.

3.2. Diagnostic tests

3.2.1. Chest X-rays

Upon clinical suspicion, chest X-ray remains to be the primary test, although radiological expression in children is less florid than in adolescents or adults, and there are no pathognomonic TB lesions.

Posteroanterior and lateral projections must be obtained, since the latter provides a better visualisation of hilar, mediastinal, or subcarinal lymphadenopathies, which are characteristic in children, as well as little or no parenchymal involvement.

A CT scan or MRI may be considered on an individual basis in children in contact with a bacilliferous patient, with a positive TT, and with clinical symptoms and a normal chest X-ray; as well as in children in contact with a bacilliferous patient, a positive TT without symptoms, and a questionable chest X-ray. However, these methods are not necessary for routine diagnosis (American Academy of Pediatrics, 2015).

3.2.2. TT

In the event of epidemiological, clinical, or radiological suspicion, TT continues to be crucial.

It is the induration, not the erythema, which should be assessed (measured in millimetres) from the transverse diameter to the major axis of the forearm. An induration of ≥ 5 mm is considered to be positive in children with close contact with an index or suspected case, in children with clinical or radiological suspicion of disease, and in cases of immunosuppression, including immunosuppression caused by HIV infection.

False positives may occur in children vaccinated with BCG. As a result, it is recommended to perform an IGRA, which has a similar degree of sensitivity to TT, but greater specificity, and makes it easier to distinguish between indurations secondary to atypical mycobacterial infections and BCG-induced indurations.

3.2.3. Laboratory tests

If TB is suspected, microbiological confirmation should be attempted by isolating *Mycobacterium tuberculosis* from a biological sample.

In young children, obtaining sputum samples is more complicated, so induction of sputum or gastric aspiration will be considered depending on age and safety. Obtaining other samples will be considered according to the suspected site.

Bacilloscopy, culture, and, if positive, an antibiogram must be performed on all of the samples obtained.

PCR should also be performed. PCR does not only increase sensitivity to staining, but also facilitates the detection of resistance to rifampicin (Gene-Xpert). This test is of paramount importance in countries with high prevalence rates of TB (and in patients from these countries) for the early detection of different types of resistance, as it is considered to be a marker for multidrug-resistant TB (Lewinsohn et al., 2017).

HIV testing should be offered routinely to all patients, including children diagnosed with TB (OMS, 2012).

3.3. Treatment

In the initial treatment of pulmonary tuberculosis disease without widespread resistance, associated risk factors, or complications, the same guidelines are recommended for children and adults (the appropriate dosages are based on weight, not age).

TB treatment has two phases: a first induction or bactericidal phase, lasting 2 months, and a second continuation or sterilising phase that usually lasts 4 months.

The therapeutic regimen and its duration are determined by the clinical form and prevalence of isoniazid resistance in the community. When this prevalence is greater than 4%, it is recommended to start with four drugs (isoniazid + rifampicin + pyrazinamide + ethambutol (2 HRZE)) until the patient antibiogram or the index case antibiogram is obtained. After this initial phase of 2 months, treatment continues with 4 more months with isoniazid + rifampicin (4 HR).

2 HRZE + 4 HR

Table 2. Recommended dosages for the most commonly used first-line antituberculosis drugs in children, shows the recommended dosages of each drug. As children approach a body weight of 25 kg, adult doses may be used.

Table 2. Recommended dosages for the most commonly used first-line antituberculosis drugs in children

Drug	Dosage per kg per day	Maximum daily dosage
Isoniazid (H)	10 mg (range 7-15)	300 mg
Rifampicin (R)	15 mg (range 10-20)	600 mg
Pyrazinamide (Z)	35 mg (range 30–40)	2.000 mg
Ethambutol (E)	20 mg (range 15-25)	2.500 mg

Source: Adapted from: World Health Organization (2014). Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children; Mellado (2018). Actualización del tratamiento de la tuberculosis en niños. (World Health Organization, 2014b)

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When receiving ethambutol, optical neuritis (loss of visual acuity and lack of red-green distinction) may occur and should be monitored. With young children who do not collaborate with the examination, visual evoked potentials may be conducted.

All drugs should be taken together while fasting, and, if possible, in fixed-dose drug combinations (rather than separately) and under direct supervision.

In case of drug-resistant TB, treatment should be directed by experts.

Clinical monitoring should be conducted monthly (or less frequently if required). A baseline analysis of the amount of pre-treatment transaminases should be conducted. Subsequently, the case should be assessed after 2-3 weeks or earlier if symptoms of hepatotoxicity are present. In cases with a positive progression and without extensive lung disease, a radiological control should be conducted at the end of the initial phase and at the end of the treatment (Mellado Peña et al., 2018).

Response to treatment, with resolution of symptoms and weight gain, is usually observed at the end of the intensive phase.

A poor response to TB treatment may suggest the following:

- Poor adherence to treatment
- Wrong diagnosis
- Drug-resistant TB
- Incorrect dosages
- Untreated comorbidities (e.g. HIV infection)

The categories of treatment completion for children (see Table 3. Categories of treatment completion for TB cases sensitive to anti-TB drugs) are the same for adults and it is important to report them to TB control programmes for monitoring and evaluation (World Health Organization, 2014b).

Table 3. Categories of treatment completion for TB cases sensitive to anti-TB drugs

Outcome	Definition
Cured*	The patient has completed the treatment and, in addition: If the diagnosis was culture-confirmed, the patient presents with a negative culture of a sample taken at the end of the treatment and, at least, of another sample taken on a previous occasion. If the diagnosis was made using bacilloscopy, the patient presents with a negative result of a sample taken at the end of the treatment and, at least, of another sample taken on a previous occasion, and provided that the culture is also negative.
Completed treatment	The patient has completed the treatment and does not meet the criteria to be classified either as a cure or as a therapeutic failure.
Therapeutic failure	The patient, five months after starting treatment and despite having followed it correctly, has not reached bacteriological conversion or, having reached it, presents with a bacteriological reversal and requires a new treatment. The following should be considered: a) bacteriological conversion has not been achieved when positive cultures persist;

	b) the conversion has been reversed when 2 consecutive positive cultures reoccur after having had 2 consecutive negative cultures. Treatment is also considered to have failed when there is a clinical decision to stop treatment due to adverse effects or lack of response.
Transfer	The patient has relocated and therefore has been transferred to another registration system. Therapeutic outcomes are unknown.
Dropout	The patient has discontinued treatment for two or more months against their doctor's orders; or the patient has been missing for two months or more during follow-up before the treatment is completed, except in the case of a transfer.
Death	The patient has died from any cause during the course of treatment. Individuals who have died of TB, who never started treatment or were diagnosed post mortem, should be reported and classified in this category of treatment completion and included in the denominator for the calculation of the percentages of the indicators for successful treatment and death. This category can be broken down into death from TB and death from other causes.
Other, not evaluated, or still in treatment	The patient is still under treatment 12 months after starting it and meets any of the following criteria: a) Prolonged treatment due to side effects/complications b) Initial treatment planned to last longer than 12 months (includes patients whose initial treatment had been modified because polyresistance (resistance to at least two first-line drugs) has been found in a sample taken at the start of the treatment) c) There is no information on why the patient is still under treatment
Unknown	The patient's treatment results are unknown and the patient is not known to have been transferred.

* In children, sputum bacilloscopy and cultures are often negative. TB is considered to be cured when the prescribed treatment has been completed, the clinical symptoms have been resolved, and radiological improvement has occurred. If the culture was positive at the time of the diagnosis, TB is considered to be cured when culture conversion is observed.

Source: (Centro Nacional de Epidemiología. Instituto de Salud Carlos III. Red Nacional de Vigilancia Epidemiológica, 2013)

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