Pulmonol. 2018;24(2):106–114

PULMONOLOGY

www.journalpulmonology.org

REVIEW

Managing latent tuberculosis infection and tuberculosis in children

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Received 16 October 2017; accepted 27 October 2017
Available online 2 March 2018

KEYWORDS
Tuberculosis;
Pediatric;
Childhood;
Latent tuberculosis infection

Abstract Tuberculosis (TB) is a major cause of childhood morbidity and mortality worldwide. The aim of this review is to describe the management of the child with TB and latent tuberculosis infection (LTBI).

To develop this article, a working group reviewed relevant epidemiological and other scientific studies and established practices in conducting LBTI and TB in children. The article describes how to manage the child with LTBI, considering transmission and infectiousness of tuberculosis, contact screening and prioritization of contacts and recommendations on treatment of children with LTBI and how to manage the child with TB considering the susceptibility of children to developing tuberculosis, epidemiology and classification of tuberculosis in children, diagnosis and treatment.

Introduction

Tuberculosis (TB) is a major cause of childhood morbidity and mortality worldwide.[1] Childhood TB represents *Mycobacterium tuberculosis* (*Mt*) recent transmission and the failure of disease control in community. In this age group,

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https://doi.org/10.1016/j.rppnen.2017.10.007

pulmonary TB is the most frequent presentation. Infants and young children are more likely to develop severe forms of TB (disseminated and meningitis) due to immature immunological response.[2,3]

Investigation of children suspected of having TB is difficult. In clinical practice, the diagnosis requires a systematic approach that comprises 3 fundamental steps: (1) clinical history and detailed physical examination; (2) imaging evaluation and (3) identification of the pathogen. The disease has variable clinical presentations, and symptoms are often non-specific. For most children the TB is not confirmed bacteriologically, due to the paucibacillary nature of TB in these cases. Therefore, the diagnosis is often presumed rather than confirmed.[4–6]

Treatment of TB in children is challenging. Lack of pediatric formulations, drugs toxicity, and adherence to treatment are some of the concerns in the treatment of a child with TB.[4,5] Co infection with TB and multidrug-resistant TB further complicates the treatment, and are associated with higher rates of treatment failure and mortality.[1]

Investigation of contacts of persons with TB, with special efforts with children aged <5 years and immunocompromised people and treating all contacts with latent TB infection (LTBI), becomes essential to reduce TB incidence in childhood.[7]

The aim of this review is to describe the management of the child with TB and LTBI.

Methodology

To develop this review, a working group reviewed relevant studies and established practices in conducting LBTI and TB in children. The article focuses on identification and management of the child with LTBI, including – (1) management of TB exposure: definition of close contact considering transmission and infectiousness of tuberculosis; decision to initiate a contact screening and prioritization of contacts; screening methodology[2] management of LTBI: clinical approach; immunological tests; when to consider LTBI and recommendations on LTBI treatment. The review will also focus on managing the child with TB considering the following issues: susceptibility of children to developing tuberculosis; common and severe forms in childhood; epidemiology and classification of tuberculosis in children; managing tuberculosis suspicion; importance of history; clinical signs and symptoms; diagnostic tools including recent molecular and phenotypic methods improvements; treatment decisions and recommended drugs, doses and regimens.

Discussion

Managing the child with LTBI

How to manage a child exposed to a person with tuberculosis?

Definition of close contact considering transmission and infectiousness of tuberculosis. TB transmission directly relates to the intensity of exposure[8–14] of the child to the source of TB infection, the clinical severity and infectiousness of disease in the index case, nutritional status, presence of a Bacillus Calmette-Guérin (BCG) scar, physical long term proximity to the individual with TB, household size and duration of cough in the index case as well as magnitude of TST response. Determining which children with LTBI are at the greatest risk of progressing to active TB would allow the identification and treatment of at-risk individuals and reduce the number of active TB cases. This would be a major step forward for TB control programs. Not every child exposed to a contact becomes infected and the probability depends on several factors namely: contagiousness of the source, bacteriological status smears positive, virulence of the bacilli, environmental risks such as: infection control measures, air circulation, exposure to sunlight, proximity of the infected person.

Recently, the possibility that a short occasional contact with an infectious adult (15–20 min) is sufficient to generate TB infection and disease has been demonstrated.[15]

Decision to initiate a contact screening and prioritization of contacts. Infected children represent a large proportion of the pool from which TB cases will arise, knowledge of the factors that influence TB infection in children allows intervention in community tuberculosis transmission and adapting TB control activities. One of the global indicators is the proportion of children, among those eligible, under 5 years of age and household contacts of TB cases, started on LTBI treatment.

To avoid the administration of LTBI treatment to those without the infection,[12–14] thus potentially increasing costs and adverse events, it is crucial to improve tools to maximize the predictive value of existing tests. This is of particular importance in high incidence HIV co-infection countries because both currently available tests, TST and IGRA, have reduced sensitivity in immune compromised patients so have a low predictive value for progression to active TB. For these reasons, LTBI screening should be reserved for those children who are at a sufficiently high risk of progressing to disease. Such high-risk children may be identifiable using multivariable risk prediction models, which incorporate test results with traditional risk factors, and using serial testing to resolve underlying phenotypes.

Screening methodology – clinical approach, immunological tests. A latent infection is defined by a positive score to an immune-based assay, either the tuberculin skin test (TST) or the interferon-γ release assays (IGRA), which are based on the recognition of mycobacterial antigens[16] in a healthy person without lesions of active TB in the chest radiological images. TST is quantified by measuring the transverse diameter of skin induration resulting from intradermal injection of purified protein derivative, a crude mixture of antigens, many of which are shared by *Mt* and other *Mycobacteria*, in particular Bacillus Calmette–Guérin (BCG). IGRA, including QuantiFERON TB Plus (QFT-Plus; Qiagen, Hilden, Germany) and T-SPOT.TB (Oxford Immunotec, Abingdon, UK), are blood assays measuring in vitro IFN-γ production to specific antigen of *Mt*, not shared with BCG.[16–21] Based on the characteristics of the assays, TST is less specific for latent tuberculosis identification in those that are BCG-vaccinated, compared to IGRA. However, IGRA may be less sensitive, in younger aged children. In spite of increasing evidence of potential utility of IGRA, advisory boards recommend the use of TST in children younger than 5 years of age.[7,22–24]

When to consider LTBI?

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by *Mt* antigens without evidence of clinically manifested active TB.[16] Children under 5 years old and children in household contact with an index-case have a relatively high risk of active disease and latent infection, given these considerations it is important to detect LTBI cases and treat them early regarding adherence and compliance to therapy hence this group may also benefit from additional interventions. The fact that prevalence of TB decreases with more remote exposure in children lends support to implement contact screening in concentric circles starting with household contacts and progressing through other close contacts to more remote contacts and isolation to the index case as soon as possible.

Recommendations on treatment of LTBI. Systematic review and meta-analysis report the prevalence of active TB in all contacts to be 3.1% (95% CI 2.2–4.4%, $I^2 = 99.4\%$), 1.2% (95% CI 0.9–1.8%, $I^2 = 95.9\%$) in microbiologically confirmed TB with latent TB infection at 51.5% (95% CI 47.1–55.8%, $I^2 = 98.9\%$). Similar findings are replicated looking only at MDR-TB exposure. Incidence was greatest in the first year after exposure year and remains above background incidence for at least 5 years after exposure to a patient with TB.[2,3]

Considering that children under 5 years old and people living with HIV contacts of TB patients are a high-risk group for developing TB, particularly within the first year, it is mandatory to screen HIV TB co-infection on those groups. Children under 5 years old diagnosed with LTBI need to get preventive treatment or 2 years of radiological follow-up, depending on their probability of developing TB, contra-indications for preventive treatment and willingness to start preventive treatment for 4 months of rifampicin (RIF) only or 3 months of rifampicin/isoniazid. The appropriate regimen is based on the following: Drug-susceptibility results of the presumed source case (if known), coexisting medical illness and potential for drug-drug interactions. In all cases, children need to go on directly observed therapy (DOT) for LTBI Treatment.

Isoniazid (INH) Regimen – There are 2 options[9–11] for treatment with INH: 9 or 6 month regimen. The 9-month regimen is preferred because it is more effective. Treatment for LTBI for 6 months rather than 9 months may be more cost-effective and result in greater adherence by patients; therefore, health care providers may prefer to implement the 6-month regimen rather than the 9-month regimen. Every effort should be made to ensure that patients adhere to LTBI treatment for at least 6 months. The preferred regimen for children aged 2–11 years is 9 months of daily INH.

12-Dose (Isoniazid and Rifapentine [RPT]) Regimen – The directly observed 12-dose once-weekly regimen of INH and RPT is recommended as an option equal to the standard INH 9-month daily regimen for treating LTBI in otherwise healthy people, 12 years of age and older, who were recently in contact with infectious TB, or who had TST or IGRA test or blood test for TB infection conversions, or those with radiologic findings consistent with healed pulmonary TB. The 12-dose regimen can be considered for other groups on a case by case basis when it offers practical advantages, such as completion within a limited timeframe. The regimen may be used in otherwise healthy HIV-infected persons, 12 years of age and older, who are not on antiretroviral medications. It may also be considered for children aged 2–11 years if completion of 9 months of INH is unlikely and hazard of TB disease is great. The 12-dose regimen is NOT recommended for the following individuals: (1) children younger than 2 years of age; (2) children HIV/AIDS who are taking antiretroviral therapy (ART); (3) people presumed to be infected with INH or rifampin-resistant *M. tuberculosis*.

A 4-month regimen of RIF can be considered for children who cannot tolerate INH or who have been exposed to INH-resistant TB. It should not be used to treat HIV-infected persons taking some combinations of ART.

The choice between the 12-dose regimen and other recommended LTBI treatment regimens depends on several factors, including: feasibility of DOT, resources for drug procurement and children monitoring, considerations of medical and social circumstances that could affect patient adherence, preferences of the patient and prescribing health care provider.

Managing the child with TB

Susceptibility of children to develop tuberculosis. Common and severe forms of disease

Household exposure to a sputum smear-positive source case poses the greatest risk for children to become infected and to develop subsequent disease. Children could be infected even by household contacts with smear-negative TB disease. Infection in children under 5 years of age indicates a probable household source case. Therefore, TB in children under age five suggests recent and/or ongoing transmission in the community.[2]

There is a bimodal pattern risk of TB among children: children under five and adolescents were the groups at highest risk for disease development and death following primary infection. Children infected at 5–10 years of age are presumably infected in the community, and had the lowest risk of disease development and death.[2]

Pulmonary disease and intrathoracic adenopathy are the most common forms of pediatric TB and account for 60–80% of all cases.[25] The severe forms of pediatric TB (disseminated TB and TB meningitis) are more common in infants and young children than older children.[26,27]

Age related inadequate or inappropriate immune responses may lead to progression of pulmonary disease and possible dissemination to extrapulmonary sites.[2,28] In young children, TB frequently progresses rapidly from latent infection to disease, and its most severe forms, such as miliary TB and meningitis, are more common.[2] Among children under 1 year of age, approximately 30–40% will progress from primary infection to active disease. For children aged between 1 and 5 years old, this risk is approximately 24%. The risk of progression declines slowly beyond 5 years and increases again around 10 years of age.[3,29,30] Risk factors for progression from primary infection to disease include duration and burden of exposure, the virulence of the mycobacterial strain, HIV infection or other clinical conditions that impair the immune system, malnutrition, and exposure to tobacco smoke.[31–37]

Epidemiology and classification of tuberculosis in children

The estimation of the global burden of TB in children is challenging, especially due to difficulties in recognizing and confirming the disease. In addition, the lack of standard case definition and the occurrence of extrapulmonary disease further complicate the achievement of accurate statistics on pediatric TB.[38]

In 2015, there were an estimated 10.4 million new (incident) TB cases worldwide, of which one million (10%) were among children. The highest burden of TB cases in pediatric patients is in sub-Saharan Africa and Southeast Asia. Among children with TB, 210,000 died in 2015 from disease complications, 24% of whom were coinfected with human immunodeficiency virus (HIV). Infants and young children have a high risk of disseminated disease and meningitis; consequently, this age group carries the highest risk of mortality from TB.[1]

Pulmonary TB and extrapulmonary TB account for up 60–80% and 20–30%, respectively, of the total caseload of TB in children. The gender distribution in pediatric TB is about 1:1. Approximately 50% of cases of pediatric TB occur in children less than 5 years old. Children between 5 and 14 years old have the lowest rates of TB disease.[1] Perinatal TB (congenital and neonatal) can be a life-threatening condition, with about 50% of mortality. Congenital TB is rare and is associated with tuberculous endometritis or disseminated TB in the mother.[39,40] Neonatal TB is secondary to the exposure of an infant to the mother's respiratory secretions, and is far more common.[9]

The clinical classification of intrathoracic TB based on immunopathogenesis considers TB as a continuum of states and not a dichotomy of infection or disease. The classifications includes: TB exposure, latent TB infection, subclinical intrathoracic TB, non-severe intrathoracic TB, and severe intrathoracic TB. A child with subclinical TB has incipient disease, with replicating bacteria, metabolically active, but the infection is contained. This child will not have clinical manifestations or mycobacterial detection. Radiologically, they could have uncomplicated hilar/mediastinal lymphadenopathy, non-calcified nodules, and uncomplicated pleural effusion. Children with non-severe TB will have mild-to moderate clinical manifestations, once infection is only partially contained. Also, cultures will be positive in 10–30% of cases. In severe TB cases, the infection is not contained, there is more clinical complication, and cultures are positive in 30–70% of cases.[6,10]

How to manage the child suspected of TB disease

Importance of clinical signs and symptoms. Childhood tuberculosis is characterized by a nonspecific symptomatology. Therefore it is very important to know the history of contacts of the child with pulmonary or laryngeal TB patients that are usually close family members. In fact a child with active TB represents a sentinel event, typically reflecting ongoing transmission in the community.

M. tuberculosis may infect nearly any organ; however, the most common clinical manifestations of disease are found within the thoracic cavity and peripheral lymph nodes. The intrathoracic manifestations are mediastinal or hilar lymphadenopathy and pulmonary parenchymal lesions. More rarely, the pleura or pericardium are additional sites. Isolated intrathoracic lymphadenopathy may be detected early after infection and is often not associated with symptoms. Later, this inflammatory process increases, leading to an enlargement of lymph nodes with complications characterized by an obstruction or compression of the small airways which may be associated with cough, wheezing, or dyspnea; the caseous necrosis of the lymph nodes that may erupt into the airway, leading to bronchopneumonia and manifesting with cough, dyspnea, malaise, and fever; hypersensitivity reactions may also occur, including pleural effusions, which may provoke symptoms of chest pain, fever, and weakness. This nonspecific symptomatology can easily be confused with bacterial or viral causes of pneumonia. Chronic cough may apply, but young children may rapidly progress to disease after exposure, especially if immune depressed and/or very young.[41,42]

Extrathoracic manifestations make up approximately 20–40% of TB cases, although concomitant overlap with pulmonary disease can occur. Extra-pulmonary symptoms depend on the TB localization and therefore they may greatly vary. *M. tuberculosis* can reach the central nervous system causing meningitis and tuberculoma; the eye causing uveitis and phlyctenular conjunctivitisa; the ear causing optic or nasopharyngeal chronic suppurative otitis media, mastoiditis, tonsillitis, laryngitis; the heart causing cardiac pericardial effusion; the gastrointestinal apparatus causing abdominal peritonitis, enteritis, involvement of lymph nodes, visceral involvement; the genitourinary involvement causing interstitial nephritis and glomerulonephritis; the bone causing osteoarticular and vertebral osteomyelitis; the lymphatic adenopathy (cervical localization is the most common); the skin causing different manifestations such as chancres, warts, lupus vulgaris like lesion, pustulonodular lesions, erythema induratum. The most commonly involved extrathoracic sites are the peripheral lymph nodes or the central nervous system. Lymphadenitis often manifests in the cervical regions with enlarged, painless lymph nodes. A solitary elastic node without erythema or warmth is a common manifestation of the disease. Contiguous nodes may enlarge and become palpable and the lesion then grows tangled and immovable; fistulas may also form. The most worrying complication of TB is when it is localized in the central nervous system because it leads to a significant morbidity or mortality occurring in approximately 50% of cases.[43,44] The start is subacute and the symptoms nonspecific during the early stages, such as irritability, fever, and anorexia, and possible focal respiratory or gastrointestinal symptoms. As disease progresses, findings of meningitis become apparent, including vomiting, altered consciousness, convulsions, meningismus, cranial nerve palsies, or signs of raised intracranial pressure. It is crucial to obtain an early diagnosis which is the only tool to improve the clinical outcomes.

Diagnostic tools available to confirm TB. Imaging studies play an important role in the diagnosis of intrathoracic TB. Chest radiographs, although commonly used, are relatively nonspecific per TB diagnosis.[45,46] Indicative findings consist of: thoracic lymphadenopathy; air-space disease, which may be indistinguishable from other causes of pneumonia; miliary nodules or cavitation. Computer-aided detection for pulmonary TB has not yet been validated among children.

Depending on the extra-pulmonary TB localization, ultrasonography, computer-aided detection, magnetic resonance can be used.

The diagnosis of TB in children is challenging due to the paucibacillary nature of disease and the subtle or nonspecific radiographic findings.[47] Up to the present time, an accurate diagnostic test for pediatric TB is not available. Therefore, it is crucial for clinicians to suspect of the possibility of active TB and to look for all the clinical symptoms that may be the basis for a diagnosis. Indeed, given the poor sensitivity of the current diagnostic tools, TB diagnosis is often based on clinical means.

TB diagnosis can be ''confirmatory'' if based on the direct detection of the pathogen; alternative approaches include the evaluation of the histopathological lesions or the detection of the host immune response to the pathogen.

Direct pathogen-based tests include *Mt* smear microscopy, culture, nucleic acid amplification tests (NAATs). The mycobacterial culture is the gold-standard test for TB. The sensitivity is low (7–40%) due to the paucibacillary nature of disease.[48,49] It takes up to 6 weeks for positive growth. When *Mt* is isolated, it is important to perform drug-sensitivity testing against first-line TB drugs to start with, and against second-line TB drugs if needed. The smear microscopy has a lower sensitivity compared to culture and therefore its accuracy is limited in pediatric TB cases. The newer GeneXpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) assay is a NAAT that detects M tuberculosis DNA and concomitant resistance to rifampicin.[50] The GeneXpert MTB RIF assay requires less training and infrastructure to perform and interpret than other commercially available molecular assays, produces results in about 2 h which has contributed to its wide spread implementation throughout high-TB burden settings.[51] GeneXpert only has a pooled sensitivity of approximately 66% compared with TB culture in pediatric populations. Repeated sampling offers incremental yield.[52–54]

For pulmonary TB, the collection of sputum may be very difficult, especially for children younger than 7 years. Semi-invasive techniques, such as gastric aspiration and lavage, or sputum induction with or without nasopharyngeal aspiration, may be required. The use of the string test in which a gelatin capsule containing a nylon string is swallowed and later retrieved for TB culture[49] is an alternative method of obtaining respiratory specimens.[55]

In extrapulmonary TB, site-specific specimens for TB culture are often collected, such as cerebrospinal fluid, lymph node aspirates, and other tissue specimens. Mycobacterial blood cultures have a lower accuracy in children compared with adults.[49,56] Histopathological diagnosis is used, but the accuracy is not well characterized.

Improved diagnostic tools are urgently needed for children.[57] New approaches have been evaluated in pediatric studies using nonrespiratory specimens, such as blood-based assays, such as the T-cell activation marker which use host immune responses as a diagnostic biomarker[58] and transcriptomic studies, which hold promise as a diagnostic and prognostic marker.[18,59–61] Other biomarkers that have shown promise in adult populations, such as the antibodies in lymphocyte supernatant assay and the urinary lipoarabinomannan assay or IP-10, have not shown consistent results in pediatric populations.[62–67] Urine is an interesting diagnostic specimen, especially for children because easy to obtain and safe to handle for health care personnel. These characteristics would provide an extraordinary advantage as a point-of-care diagnostic test, and further work in this area is needed.

Decision to treat, recommended regimens and drugs doses recommended

The decision to initiate treatment on a child with suspected tuberculosis, especially in children younger than 5 years old, is challenging. Children commonly develop tuberculosis as a complication of the initial infection with *Mt*.[5] Confirmation of a TB diagnosis by identification of the infectious agent can be difficult, given that microbiological confirmation occurs only in 15–50% of pediatric cases.[68–70] Treatment failure, relapse, and development of secondary resistance are less common among children when standard treatment regimens are initiated.[71]

Empiric treatment is started as soon as possible specially in children under 4 years old, given the risk of disseminated disease. Choosing appropriate treatment drugs requires specimen culture: gastric aspirations, sputum induction, bonchoalveolar lavage and relies on drug susceptibility tests from the person presumed to be the source of the child's infection.[72–74] When drug resistance is suspected or no source-case isolate is available, attempts to isolate organisms are required.

The criteria found to be related to the decision to treat children less than 6 years of age without diagnostic confirmation, were the following: epidemiological context of tuberculosis, radiological abnormalities, clinical history and positivity in immunological tests. Factors associated with epidemiological context found included history of exposure to tuberculosis, immunodeficiency and country of origin with a high prevalence of TB. Radiological criteria included finding on chest radiography, followed by computerized axial tomography. The most relevant clinical findings were sustained fever and respiratory symptoms.[75]

Tuberculosis treatment requires multiple drugs be given for several months. Involvement of the child and his/her parents is crucial, with explanation of the decision to initiate treatment, the chosen drugs, prevention of side effects and importance of DOT. When assessing several outcomes of interest, including mortality, treatment completion and relapse, DOT was significantly associated with improvement in the final number of patients cured and patients completing treatment.[76] Parents should not supervise DOT for their children.[77] Tolerance to medication should be closely monitored even when on daily DOT[78] and good child growth, clinical and imaging improvement predict a positive outcome of treatment.

In order to achieve appropriate concentrations of medications in young children and considering pharmacokinetic evidence, the recommended dosages of these first-line anti-TB medications were revised in 2010. Children metabolize the drugs more rapidly than adults resulting in a lower serum concentration. WHO recommends the following dosages of antituberculosis drugs for the treatment of tuberculosis in children: isoniazid (H) – 10 mg/kg (range 10–15 mg/kg); maximum dose 300 mg/day; rifampicin (R) – 15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day;

pyrazinamide (Z) – 35 mg/kg (30–40 mg/kg); ethambutol (E) – 20 mg/kg (15–25 mg/kg).[72,79–81]

WHO recommend selection of a 3-drug or 4-drug regimen based on the location of tuberculosis, risk of isoniazid resistance and prevalence of HIV.[79,82] According to WHO, children with suspected or confirmed pulmonary tuberculosis or tuberculous peripheral lymphadenitis who live in settings with low HIV prevalence or low resistance to isoniazid and children who are HIV-negative can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug (HR) regimen for 4 months. Children living in settings where the prevalence of HIV is high or where resistance to isoniazid is high, or both, with suspected or confirmed pulmonary tuberculosis or peripheral lymphadenitis; or children with extensive pulmonary disease living in settings of low HIV prevalence or low isoniazid resistance, should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months. As the prevalence of and risk for drug-resistant tuberculosis can be difficult to ascertain, the AAP and most experts include ethambutol (EMB) as part of the intensive phase regimen for children with tuberculosis. AAP recommends the 4-drug regimen (HRZE) for 2 months followed by a 2-drug (HR) regimen for 4 months for suspected or confirmed pulmonary tuberculosis.[78,79,82,83]

EMB can be used routinely to treat tuberculosis disease in infants and children unless otherwise contraindicated. Children with ethambutol should have their visual acuity regularly monitored. When visual acuity cannot be monitored, such as in young children, the use of EMB requires evaluation of risks and benefits.[72,78,79,81,84]

Most forms of extrapulmonary tuberculosis in children can be treated with the same regimens as pulmonary disease. However, the duration of the continuation phase should be extended in children with confirmed or suspected tuberculous meningitis or osteoarticular tuberculosis caused by a drug-susceptible organism. For tuberculous meningitis, WHO recommends a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months for meningitis known or presumed to be caused by susceptible strains; the total duration of treatment being 12 months.[81,82] The AAP lists an initial 4-drug regimen of HRZ, and an aminoglycoside or ethionamide for 2 months in place of EMB, followed by 7–10 months of HR.[78]

Children with proven or suspected pulmonary tuberculosis or tuberculous meningitis caused by multiple drug-resistant bacilli can be treated with a fluoroquinolone in the context of a well-functioning MDR-TB control program and within an appropriate MDR-TB regimen. The decision to treat should be taken by a clinician experienced in managing pediatric tuberculosis. Despite the absence of long-term safety-data for the use of fluoroquinolones in children, it is recommended for use in children with cystic fibrosis and in the context of multi-drug resistant tuberculosis, the benefits of treatment outweigh the risks.[85]

Corticosteroids have significantly improved the survival rate and intellectual outcome of children with tuberculous meningitis and adjunctive corticosteroid therapy with dexamethasone or prednisolone over 6–8 weeks should be provided for patients with tuberculous meningitis.[86]

The use of corticosteroids was also previously recommended as adjunctive therapy for pericardial tuberculosis. The use of corticosteroids is recommended in patients with large pericardial effusions, high levels of inflammatory cells or markers in pericardial fluid, or those with early signs of constriction. The administration of prednisolone in pleural tuberculosis did not confer beneficial effect on residual pleural thickening or prevention of long term sequelae.[87–89]

WHO considers as a weak recommendation and very-low evidence a 3-weekly regimen in children. This regimen should only be considered during continuation phase in settings with a low HIV prevalence and a well-established DOT program. There is a strong recommendation that children with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis living in settings with a high HIV prevalence (or with confirmed HIV infection) should not be treated with intermittent regimens (that is, twice-weekly or thrice-weekly doses).[79,82]

The manufacture and distribution of child-friendly formulations is crucial for reducing barriers to antituberculosis treatment in children. The lack of child-friendly formulations leads to incorrect dosing and overloads TB outpatient centers workers.[90,91]

Conclusions

Tuberculosis remains the infectious disease with the highest global burden and humanistic impact, with high morbidity and mortality. Pediatric tuberculosis requires special attention. Consensus guidelines and recommendations for the management of pediatric TB contacts, latent infection and active TB disease are fundamental to improve outcomes in the quality of life and survival of children with tuberculosis. More appropriate diagnostic tools are lacking, though some new technical advances show promise.

Conflicts of interest

The authors have no conflicts of interest to declare.

Authorship

Isabel Carvalho: conceived and supervised the manuscript. Delia Goletti, Selene Manga, Denise Rossato, Davide Manissero: conceived the manuscript. Giovanni Migliori: revised and commented the text.

Acknowledgements

The paper is part of the ERS/ALAT (and the ERS/SBPT collaborative projects (ERS: European Respiratory Society; ALAT: Latino-American Society of Respiratory Medicine): SBPT: Brasilan Society of Pulmonology).

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