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REVIEW

Managing latent tuberculosis infection and tuberculosis in children

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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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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]

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