Artigo revisão

Update on Childhood Tuberculosis

Atualização em Tuberculose na Infância

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ABSTRACT

The burden of childhood tuberculosis remains poorly known in the world. The diagnosis is challenging because tuberculosis in children is generally bacteriologically negative.

Recent studies have described diagnostic techniques involving molecular biology, advances in the standard treatment and new antituberculosis drugs, however, the diagnosis continues to be based on current clinical data, radiological imaging studies and epidemiological investigation.

Over the last decade, the treatment of childhood tuberculosis has improved because of scientific advances and international standardization of practices.

Keywords: Tuberculosis/diagnosis; Tuberculosis/therapy; Tuberculosis/epidemiology.

RESUMO

A situação mundial da tuberculose na infância é pouco conhecida. O diagnóstico é um desafio porque a tuberculose na infância é geralmente negativa bacteriologicamente.

Estudos recentes descrevem técnicas de diagnóstico por biologia molecular, avanços no tratamento padronizado e novos fármacos; entretanto, o diagnóstico tradicional ainda se baseia em dados clínicos atuais e em estudos radiológicos e epidemiológicos.

A tuberculose na infância incorporou avanços científicos e condutas padronizadas internacionalmente na ultima década.

Descritores: Tuberculose/diagnóstico; Tuberculose/terapia; Tuberculose/epidemiologia.

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INTRODUCTION

Tuberculosis continues to be a major, often unrecognized, cause of disease and death among women and children in areas where it is endemic (1). Cases are highly concentrated in areas affected by poverty, social disruption, HIV infection and drug-resistant tuberculosis (2,3). Although an emphasis on sputum smear-positive disease has excluded most children from care, this is slowly changing because of increased awareness about disease risks and manifestations in children, as well as because better diagnostic tools have become available.

Descriptions of the natural history of tuberculosis from the pre-chemotherapy literature provide detailed risk and disease descriptions that can guide the management of childhood tuberculosis (4,5). Important observations include the fact that most (> 90%) of children who progress to active tuberculosis do so within the first 12 months of primary infection, which is referred to as the "window of risk". Another striking observation is the pronounced bi-modal risk profile; the risk is greatest when children are very young (below 2 years of age), reaches a nadir between 5 and 10 years of age and increases again with the onset of puberty. This coincides with a radical shift in the disease spectrum. In young children, lymph node disease (with or without airway compression) predominates, due to exuberant lymph node responses and small, pliable airways. Disseminated disease is also more common because of immature T-cell responses and poor disease containment. The sudden switch to adult-type tuberculosis that occurs during puberty, first in girls and then in boys, remains an enigma but may shed light on key variables underlying individual vulnerability (6). It is important to remember that adolescent children with adult-type disease are highly infectious (7). Chart 1 summarizes some important differences between adults and children.

Chart 1 - Tuberculosis: differences between adults and children*

Aspect	Adults[1]	Children[1]
Epidemiology and awareness	Massive global disease burden that is well quantified; excellent awareness	Massive global disease burden that is poorly quantified; minimal awareness
Health policy	Main focus of NTPs	Rarely recognized as a priority by NTPs
Pathogenesis of lung lesions	Usually adult-type lung disease (previously referred to as post-primary TB)	Usually intrathoracic lymph node disease (previously referred to as primary TB)
Bacterial load, transmission and infection control	Multibacillary	Paucibacillary
	High infection risk after close contact	Low infection risk but can be infectious if there is extensive lung involvement (with or without cavities); epidemiologic marker of transmission
Drug resistance	Difficult to differentiate between acquired and transmitted (primary) drug resistance	Nearly always transmitted (primary) drug resistance indicating recent transmission
Exposure history	Important, but often neglected[2]	Absolutely essential part of work-up
Risk of progression to disease	Relatively low risk of progression to disease following TB exposure/infection	Highly variable risk of progression to disease following TB exposure/infection - greatest in the very young and/or immunocompromised
Preventive therapy	Limited value, except in immunocompromised adults	Definite value in young children (< 5 years of age) and immunocompromised children
Imaging studies	CXRs not routinely required, unless sputum negative	CXRs (with PA and lateral views, of good quality and competently read) are the most informative studies
Disease classification	Pulmonary vs. extrapulmonary	Intrathoracic lymph node disease best classified as pulmonary TB
	Post-primary TB is a confusing concept[3]	Diverse spectrum of pathology that requires accurate classification
Microbiological studies	Easy to collect adequate respiratory specimens and confirm the presence of mycobacteria	Difficult to collect adequate respiratory specimens (young children cannot expectorate); smear microscopy has very low yield; cultures and NAATs have low-to-moderate yield depending on disease severity
Treatment	With at least 4 drugs	With 3 or 4 drugs depending on estimated bacterial load and severity of disease
Prognosis	Excellent outcomes achievable with timely and appropriate treatment	Excellent outcomes achievable with timely and appropriate treatment. Delayed diagnosis resulting in potentially severe outcomes.

NTPs: national tuberculosis (control) programs; TB: tuberculosis; CXRs: chest X-rays; NAATs: nucleic acid amplification tests.
*Adapted from on-line supplementary material (4).
[1]Typical characteristics in the absence of HIV infection or severe immunosuppression.
[2]Taking a careful contact history is often neglected in adults but has particular relevance for identifying individuals in whom drug resistant tuberculosis should be suspected.
[3]The old distinction between primary and post-primary tuberculosis obscures the fact that adult-type tuberculosis (post-primary; secondary) frequently results from recent re-infection and can also occur within months of documented primary infection, especially in adolescents (30).

DIAGNOSIS

Children are usually screened for tuberculosis after contact with a tuberculosis patient or when presenting with symptoms or signs suggestive of active tuberculosis. It is important to distinguish among these different entry points, because they influence the diagnostic work-up and interpretation of the findings (Figure 1). *Mycobacterium tuberculosis* infection detected during a contact investigation is likely to be recent, implying a higher, albeit highly age-dependent, risk of disease progression. Following documented tuberculosis exposure, the interpretation of isolated radiographic findings in asymptomatic children are problematic, because transient elements of the so-called primary complex, or Ghon complex, are frequently seen and are not necessarily indicative of active disease. The current World Health Organization guidelines suggest that symptom-based screening is adequate, at least in older children, and the complete absence of suggestive symptoms is sufficient to rule out active tuberculosis in that group. Chart 2 provides a comprehensive overview of investigations used in order to establish a diagnosis of tuberculosis in children.

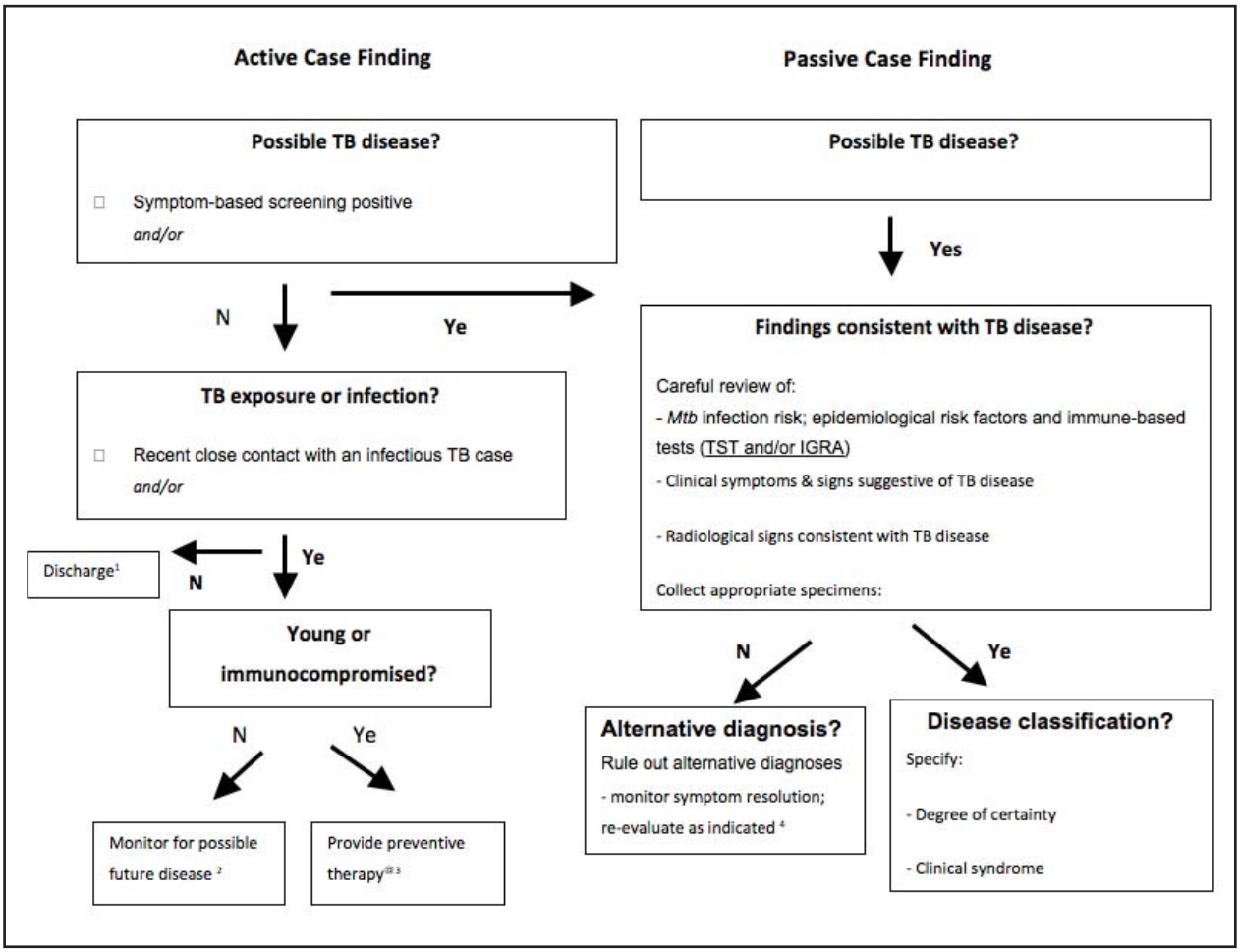

Figure 1 - Algorithm for diagnosis and classification of tuberculosis in children*

*Adjusted from (4)

HIV – human immunodeficiency virus; TST - tuberculin skin test; IGRA - interferon gamma release assay; *Mtb – Mycobacterium tuberculosis*

#None of the immune-based tests can"rule-out"TB disease with confidence. All children <5yrs of age and any child with current symptoms should receive a chest radiograph.

@Preventive therapy should be provided to all child TB contacts less than 5 years of age, once TB disease has been excluded.It should be considered that conversion of immune-based tests (TST/IGRA) may delayed for 2-3 months after documented exposure.

Preventive therapy may be offered to older children, but their risk of disease progression is substantially less. Preventive therapy would eliminate the remote risk of future reactivation disease and also reduce the "pool of latent infection" within the community, but the benefit:risk ratio in older children has not been established.

Diagnostic labels

[1] No TB exposure or infection

[2] TB exposure/infection with low risk of progression to disease

[3] TB exposure/infection with high risk of progression to disease

[4]Not TB disease

[5] TB disease (specify degree of certainty)

Chart 2 - Summary of first-line tuberculosis drugs and dosage recommendations in children*

First-line drug	Mode - mechanism of action	Main toxicities[1]	Daily dose (range)
	Characteristics		**[maximum daily dose][2]**
INH	Bactericidal - inhibits cell wall synthesis	Hepatitis; peripheral neuropathy	10 mg/kg (10-15 mg/kg)
	- most potent early bactericidal activity offering the best protection to companion drugs		
	- contributes mainly by rapidly killing actively metabolizing extracellular bacilli, contributes to sterilization if given for a prolonged period		[300 mg]
RMP	Bactericidal and sterilizing - inhibits RNA synthesis	Hepatitis; orange discoloration of secretions; drug-drug interactions	15 mg/kg (10-20 mg/kg)
	- contributes by killing extracellular and slower growing intracellular bacilli, important contribution to sterilization		[600 mg]
PZA	Sterilizing - disrupts energy metabolism	Hepatitis; arthralgia	35 mg/kg (30-40 mg/kg)
	- contributes by specifically killing bacilli that persist within the acidic centers of caseating granulomas		[2000 mg]
EMB	Bacteriostatic - inhibits cell wall synthesis	Visual disturbance (acuity, color vision)	20 mg/kg (15-25 mg/kg)
	- contributes mainly by offering additional protection against drug-resistant mutants		[1200 mg]
SM	Bacteriostatic - inhibits protein synthesis	Ototoxic and nephrotoxic	15 mg/kg (12-18 mg/kg)
	- contributes very little to treatment of drug-susceptible tuberculosis. Use not advised in children		[1000 mg]

Disease category[3]	**Suggested treatment regimens**	
	Treatment regimen	**Rationale**
Uncomplicated intrathoracic disease	INH+RMP+PZA (2 month intensive phase)	Bacterial load low, drug penetration good
	INH+RMP (4/12 - continuation phase)	
Extensive lung infiltrates or cavities	Add EMB during 2-month intensive phase	Bacterial load high, drug penetration good
Tuberculous meningitis	Add 4th drug - at least during 2-month intensive phase	Bacterial load low, drug penetration variable, risk of severe immune mediated sequelae
	Add steroids for 1 month[4]	
Severe airway compression	3 or 4 drug regimen depending on extent of lung infiltration/cavities	Bacterial load and drug penetration variable[5]; inflammation may worsen airway compression
	Consider adding steroids for 1 month	
Recent exposure or infection	Preventive therapy	Bacterial load very low, drug penetration good
No active disease	INH (6-9 months)	
	INH+RMP (3 months)	

INH: isoniazid; RMP: rifampin; PZA: pyrazinamide; EMB: ethambutol; SM: streptomycin.

*Adjusted from on-line supplementary material (4).

[1]Hypersensitivity reactions and drug rashes may occur with any drug.

[2]Most recent (2010) World Health Organization (WHO) dosage recommendations (42).

[3]Only the most common disease entities are discussed.

[4]Recommendations regarding the 4th drug and duration of therapy vary; the WHO recommends INH+RMP+PZA+EMB for 2 months followed by 10 months of INH+RMP.

[5]Drug penetration into large cold abscesses may be limited, and surgical drainage can be required.

Clinical evaluation

Although children with tuberculosis may present with pathognomonic signs, such as the formation of a gibbus, most clinical manifestations are non-specific. In fact, one of the remarkable features of intrathoracic tuberculosis is the frequent absence of physical signs despite the presence of persistent symptoms. In addition, because the clinical findings can be minimal, clinicians may be surprised by the extent of disease seen in radiographic imaging. Although the pathophysiological reason for this discrepancy has not been fully elucidated, it might involve the fact that tuberculosis often causes vasculitis, as observed in tuberculous meningitis (TBM), as well as the fact that there is parenchymal involvement. This implies that oxygen exchange and blood supply are both reduced in affected parts of

the lung, limiting the resulting ventilation-perfusion mismatch, which could explain the frequent absence of acute respiratory distress despite extensive lung involvement.

A detailed history should be taken, and clinicians should explore the likelihood of recent exposure to tuberculosis (during the last 12 months) and should characterize symptoms accurately. This is important, because poorly-defined symptoms have poor discriminatory power (8). Common constitutional symptoms include decreased appetite (recent weight percentile crossing is most informative), fever, fatigue or reduced playfulness. Although tuberculosis is an infectious disease, fever is often absent, low-grade or intermittent. Children with lung involvement mostly present with a persistent cough that is unresponsive to standard first line treatment. Airway compression can manifest as loud (upper airway) wheezing refractory to bronchodilators. Clinical follow-up is a useful diagnostic tool in children with mild disease manifestations in whom the diagnosis cannot be made or ruled out with certainty (8).

Imaging studies

Chest radiography is generally the most informative investigation and should include both posteroanterior, anteroposterior and lateral views. Lateral views are important because they facilitate the assessment of the mediastinum and hilar areas. Childhood intrathoracic tuberculosis has a wide range of appearances associated with different disease entities, which justifies careful classification (9,10). Visible hilar adenopathy with or without airway compression is highly suggestive of active tuberculosis. Using HRCT of the chest provides the most accurate visualization of intrathoracic structures (11). However, due to the high cost of HRCT and the risks associated with radiation exposure, its use should be limited to complicated cases. Extrapulmonary lesions, especially intracranial pathologies, are best visualized with CT or magnetic resonance imaging (MRI), the latter being more sensitive for detecting brainstem lesions or early perfusion defects (infarcts) and allowing better evaluation of the spine and soft tissues (12).

Laboratory studies

Immunological tests are limited by the inability to differentiate between latent *M. tuberculosis* infection and active disease, and neither the PPD tuberculin skin test (TST) nor interferon-gamma release assays (IGRAs) offer a simple solution (13). Due to suboptimal sensitivity, IGRAs, like TSTs, cannot be used as a rule-out test for tuberculosis. Confirmation of *M. tuberculosis* infection can provide important ancillary information for case identification and the management of latent infection, and, in certain clinical situations, complimentary tests can increase the sensitivity or specificity of the diagnosis (13).

Smear microscopy has poor sensitivity in young children, most of whom are paucibacillary and unable to expectorate. It has been largely superseded by culture and nucleic acid amplification tests (NAATs). In general, culture yields in children are lower than in adults, depending on the severity of disease as well as the quality, quantity and types of specimens collected (14). Two studies have evaluated the performance of the rapid NAAT-based Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) in children, demonstrating a performance similar to that seen in adults, with excellent specificity and the ability to detect approximately 70% of culture-positive cases (15,16).

Collecting adequate respiratory specimens in young children is problematic, but gastric aspirates, induced sputum (with or without laryngopharyngeal suction) and BAL (in select patients) offer feasible alternatives. A combination of specimens provides the best yield (17). Fine-needle aspiration biopsy has excellent utility in children with a peripheral lymph node mass (18). A slow clinical onset, cerebrospinal fluid pleocytosis (total cell count < 500) and elevated protein levels are highly suggestive of TBM (19). Despite the challenges, bacteriological confirmation should always be attempted, although it should not delay initiation of treatment in young and vulnerable children. Tuberculosis can be diagnosed with relative certainty on the basis of a combination of clinical data, radiological findings, laboratory test results and (when feasible) histopathological findings consistent with active tuberculosis, together with the identification of epidemiological factors or immunological evidence of *M. tuberculosis* infection.

TREATMENT

If a diagnosis of active tuberculosis is established, pragmatic classification of the disease guides management and facilitates case-case comparisons. From a treatment perspective, the bacillary load expected, anatomical location and possibility of drug resistance are the most important variables to consider. If high bacillary loads are anticipated, the use of multiple drugs during the intensive phase of treatment reduces the risk of acquired drug resistance. Consideration should also be given to the possible involvement of "sanctuary sites" such as the brain and cerebrospinal fluid, given that the degree of cerebrospinal fluid penetration varies among drugs (20). The high and rising rates of drug-resistant tuberculosis require that drug-resistant tuberculosis should be suspected, especially after close contact with a drug-resistant source case and in residents of countries with a high known prevalence of drug-resistant tuberculosis, as well as after contact with someone who died while under treatment for tuberculosis, was poorly adherent to treatment, or required more than one course of treatment.

The long-term goal of tuberculosis treatment is to achieve a cure without serious adverse effects for the individual patient. From a public health perspective, it is important to prevent transmission and the emergence of drug-resistance. Chart 2 summarizes the mode of action, main adverse effects and recommended dosages of first-line tuberculosis drugs, including dosage recommendations for children; suboptimal drug levels are achieved using adult doses adjusted for body weight (21).

In the absence of drug-resistance, the most likely cause of a poor treatment response is non-adherence. In children, tuberculosis recurrence more than 6 months after treatment completion and clinical cure most likely represents re-infection, and, in the absence of risk factors for drug-resistant disease, the most appropriate course of action is to administer the standard first-line treatment. There is no indication for using a aggressive retreatment regimen. When there is a poor response to therapy, careful re-evaluation of the original diagnosis and screening for drug resistance are warranted. At our facility, all positive cultures undergo drug susceptibility testing, which provides additional motivation to achieve bacteriological confirmation. In drug-resistant tuberculosis, the basic principles of management remain unchanged and excellent outcomes can be achieved (22,23). All children diagnosed with tuberculosis should be tested for HIV infection; the management of children co-infected with tuberculosis and HIV has been recently reviewed (24).

PREVENTION

Prevention strategies include vaccination; pre- and post-exposure prophylaxis; treatment of latent infection; and secondary prophylaxis after the completion of tuberculosis treatment (25).

Although BCG vaccination reduces the risk of disseminated (miliary) disease and TBM in very young children, the protection is incomplete and offers no consistent protection against adult-type tuberculosis (26). Due to limited tuberculosis exposure risk, BCG is not included in routine vaccination schedules in Australia. However, it should be considered when vulnerable children (e.g., those < 2 years of age) are exposed to a high-risk environment, such as by visiting a tuberculosis endemic country. Research is ongoing to develop novel vaccines with improved efficacy and safety.

Careful risk stratification identifies those at greatest need of preventive therapy following tuberculosis exposure. Although the target population for preventive therapy can vary depending on feasibility and available resources, all young children (< 5 years of age), as well as immunocompromised children, should receive preventive therapy following documented exposure or infection (27). With good adherence and no drug-resistance, isoniazid monotherapy for 6-9 months provides excellent protection. However, parents are often reluctant to provide "treatment" to an otherwise well child and ensuring good adherence is a major challenge. Providing directly observed preventive therapy to high-risk contacts may be feasible if the source case is treated at the same time. A 3-month course of isoniazid and rifampin has demonstrated equivalent efficacy and improved adherence in comparison with 9 months of isoniazid monotherapy, with no increase in adverse events (28). Twelve doses of weekly rifapentine and isoniazid proved efficacious in a recent study involving adults (29,30), although this regimen cannot be recommended for use in children below 12 years of age until more safety and efficacy data are available. In HIV-infected children on antiretroviral therapy, drug-drug interactions should be considered when any rifamycin-containing regimens are employed (24).

Among children in endemic countries from which Australia continues to receive immigrants, the burden of tuberculosis is huge but under-recognized. Multiple challenges remain, primarily to develop more effective vaccines, to improve diagnostic procedures and to shorten the duration of treatment regimens. However, it should be borne in mind that most children with tuberculosis would be well served by the sensible application of existing tools.

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