Childhood tuberculosis – risk assessment and diagnosis

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There is increased awareness of the severe tuberculosis (TB)-related morbidity and mortality suffered by children in TB-endemic countries. Access to accurate diagnosis and effective treatment in TB-endemic countries has been facilitated by recent landmark developments. The World Health Organization (WHO) published guidelines for national TB programmes on the management of TB in children,[1] and the Global Drug Facility (GDF) made child-friendly drug formulations available for the first time. However, establishing an accurate TB diagnosis in children, particularly in TB-endemic settings that carry the brunt of the TB disease burden, remains a tenacious problem.

Robert Koch proved that TB was a transmissible disease caused by *Mycobacterium tuberculosis*. However, it was soon recognised that only a small minority of people infected with *M. tuberculosis* ever progress to active disease. This explains why the diagnostic challenge is more pronounced in TB-endemic countries where TB infection is exceedingly common, which increases the need to differentiate between latent TB infection (LTBI) and active disease.

Risk assessment

Accurate risk assessment is essential, as it provides the rationale behind current diagnostic approaches. The most important variables that determine a child's risk to progress from: (*i*) exposure to infection; and (*ii*) infection to active disease, have been identified in the pre-chemotherapy literature that describes the natural history of childhood TB.[2]

Exposure to infection

TB is spread via tiny aerosol droplets. The risk of infection after exposure to an infectious source case is determined by the infectiousness of the source case, as well as the proximity and duration of contact. In TB-endemic areas the majority of TB transmission occurs outside the household, but this does not reduce the importance of household exposure when it is reported. Documented household exposure presents an important opportunity for health education and for the provision of preventive chemotherapy.

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Infection to disease

Table I summarises the age-dependent risk to progress to active TB following primary infection with *M. tuberculosis*.[2] Recent observations indicate that immune-compromised (e.g. HIV-infected) children experience a similar risk to that described in very young (< 2 - 3 years) immune-immature children. It is important to identify these variables before defining priority groups for preventive therapy intervention.

Diagnosis

Screening for latent TB infection and active disease

Current WHO guidelines advise that all children < 5 years of age in close contact with a sputum smear-positive index case should be actively traced, screened for TB and provided with preventive chemotherapy once active TB has been excluded[1] (Fig. 1). It recognises the fact that symptom-based screening may have considerable value to improve the access of children to preventive therapy, especially in settings where chest radiography and tuberculin skin testing are not readily available. The new guidelines indicate that any 'close contact' with a sputum smear-positive index case is important, even if this occurs outside the household. However, a poorly defined history of TB contact is insufficient to ascribe risk and it is important to carefully consider the proximity and duration of contact during the period when the index case would have been infectious, when deciding if preventive therapy is warranted. The new guidelines also acknowledge that HIV-infected (immune-compromised) children should be regarded as high-risk contacts, irrespective of their age.

Diagnosing active disease

Establishing a definitive diagnosis of childhood TB remains a challenge. Sputum-smear microscopy is positive in less than 10 - 15% of children with TB, and culture yields are generally low (30 - 40%), although the yield seems considerably higher in children with advanced disease.[3] In low-burden countries the triad of: (*i*) known contact with an infectious source case; (*ii*) a positive tuberculin skin test (TST); and (*iii*) a suggestive chest radiograph (CXR) is frequently used to establish a diagnosis of childhood TB, and it performs quite well in these settings.[3] However, this approach has reduced value in endemic areas where exposure to, and/or infection with, *M. tuberculosis* is common and often undocumented.[3] The diagnosis of TB is further complicated by the great diversity of disease manifestations seen in children. Table II reflects the disease diversity recorded among children diagnosed with TB in a community-based study from Cape Town. HIV-

Table I. Age-specific risk to progress to disease following primary infection with *M. tuberculosis* in immune-competent children*

Age at primary infection	Risk to progress to disease	
< 1 year	No disease	50%
	Pulmonary disease	30 - 40%
	Disseminated (miliary) disease or TBM	10 - 20%
1 - 2 years	No disease	75 - 80%
	Pulmonary disease	10 - 20%
	Disseminated (miliary) disease or TBM	2 - 5%
2 - 5 years	No disease	95%
	Pulmonary disease	5%
	Disseminated (miliary) disease or TBM	0.5%
5 - 10 years	No disease	98%
	Pulmonary disease	2%
	Disseminated (miliary) disease or TBM	< 0.5%
> 10 years	No disease	80 - 90%
	Pulmonary disease	10 - 20%
	Disseminated (miliary) disease or TBM	< 0.5%

*Adapted from Marais *et al*.[2]
TBM = tuberculous meningitis.

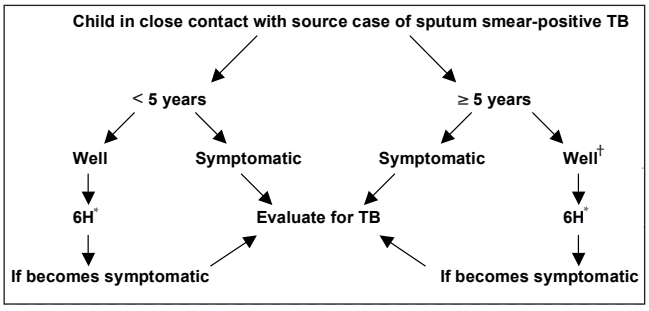

*Fig. 1. Suggested approach (WHO, 20061) to contact management when chest X-ray and tuberculin skin testing are not readily available (*isoniazid 5 mg/kg daily for 6 months; †unless the child is HIV-infected, in which case isoniazid 5 mg/kg daily for 6 months is indicated).*

infected children seemed to experience a similar risk and developed similar disease manifestations as very young (immune-immature) children,[4] demonstrating the importance of establishing a child's HIV status to facilitate optimal management and care.

Symptom-based approaches

Because of the diagnostic limitations and the difficulty of obtaining a CXR in TB-endemic areas with limited resources, a variety of clinical scoring systems have been developed to diagnose active TB. These are all severely limited by the absence of standard symptom definitions and inadequate validation. Accurate symptom definition is important, as poorly defined symptoms (such as a cough of > 3 weeks' duration) have poor discriminatory power. In a cross-sectional observational study well-defined symptoms with a persistent, non-remitting character offered far better diagnostic promise. The most helpful symptoms identified were: (*i*) persistent, non-remittent coughing or wheezing; (*ii*) documented failure to thrive despite deworming and food supplementation (if food security is a concern); and (*iii*) fatigue or reduced playfulness.[5] In a subsequent prospective, community-based study conducted in Cape Town, the presence of a persistent, non-remitting cough, together with documented failure to thrive in the preceding 3 months and fatigue, provided excellent diagnostic accuracy in HIV-uninfected children ≥ 3 years of age (sensitivity 82.3%, specificity 90.2%, positive predictive value 82.3%). However, these criteria performed less well in diagnosing the younger children (sensitivity 51.8%, specificity 92.5%, positive predictive value 90.1%), in whom the use of a positive TST as the third variable instead of fatigue increased the sensitivity to 67.3% and retained a high specificity (93.8%).[6] In uncertain cases, where all the diagnostic criteria were not met at presentation, simple clinical follow-up provided important additional diagnostic information, by documenting natural symptom resolution in the vast majority of uncertain cases without TB. In HIV-infected children the same symptoms provided far less favourable results (sensitivity 56.2%, specificity 61.8%, positive predictive value 61.9%); in addition, owing to the poor sensitivity of the TST in these children, documented household contact with a TB index case provided more diagnostic value than a positive TST result.[6]

Radiology-based approaches

Despite its many limitations the CXR remains the most valuable special investigation to perform in children whose symptoms lead one to suspect TB. If evaluated by an

Table II. Disease spectrum documented in a prospective community-based survey of all children < 13 years of age, treated for TB in a highly endemic area*

TB manifestation	Total (%) *N* = 439
Not TB	**85 (19.4)**
Intrathoracic TB	**307 (69.9)**
Ghon focus	
Uncomplicated (with/without hilar adenopathy)	16/307 (5.2)
Complicated	3/307 (1.0)
Lymph node disease	
Uncomplicated	147/307 (47.9)
Complicated	
Compression	25/307 (8.1)
Consolidation	62/307 (20.6)
Pleurisy	24/307 (7.8)
Pericarditis	1/307 (0.3)
Disseminated (miliary) disease	15/307 (4.9)
Adult-type disease	14/307 (4.6)
Extrathoracic TB	**72 (16.4)**
Peripheral lymphadenitis	
Cervical	35/72 (48.6)
Other	1/72 (1.4)
Central nervous system TB	
Meningitis	14/72 (19.4)
Tuberculoma	2/72 (2.8)
Abdominal TB	1/72 (1.4)
Osteo-articular TB	
Vertebral spondylitis	4/72 (5.6)
Other	7/72 (9.7)
Skin	8/72 (11.1)
[Intra- + extrathoracic TB]	**[25 (5.7)]**

*Adapted from Marais *et al*.[4]
TB = tuberculosis; Not TB = chest radiograph not suggestive of TB (confirmed by two independent child TB experts), no bacteriological or histological proof and no extrathoracic TB recorded; [Intra+extra thoracic TB] = children with intra- and extrathoracic TB were included in both groups, and therefore this number should be deducted to add up to a total of 439 or 100%.

experienced clinician it provides a fairly accurate diagnosis in the vast majority of TB cases, at least in HIV-uninfected children. High-resolution computed tomography (HRCT) has a role to play in complicated problem cases, but caution is required when interpreting the clinical relevance of this sensitive test, as a limited degree of hilar adenopathy is not uncommon in asymptomatic children following recent primary infection. The International Union Against Tuberculosis and Lung Disease (IUATLD) recently published a radiographic atlas of childhood TB, which serves as an excellent reference and training resource.[7]

Other approaches

A positive culture provides a definitive diagnosis of TB in a symptomatic child. However, traditional culture methods are limited by suboptimal sensitivity, slow turnaround times, excessive cost and low bacteriological yields. It is important to point out that adolescent children (>10 years of age) frequently develop sputum smear-positive disease that may be diagnosed using traditional sputum microscopy.[4]

Collecting an adequate sample presents a challenge in small children who cannot produce a good sputum specimen. In children with suspected TB lymphadenitis, the most common extrathoracic manifestation of childhood TB, fine-needle aspiration (FNA) is a robust and simple technique that provides a rapid and definitive diagnosis; the use of a small 23-gauge needle is associated with minimal side-effects.[8] Immune-based diagnosis is complicated by the wide spectrum of disease and other factors such as BCG vaccination, exposure to environmental mycobacteria and HIV co-infection, all of which are particularly prevalent in TB-endemic areas. A more comprehensive overview of novel diagnostic tests and sample collection methods is provided in Zar's article in this issue.[9]

HIV infection

The diagnostic challenge is most pronounced in HIV-infected children:[5,10]

1. HIV-infected children who live with HIV-infected adults are more likely to be exposed to a sputum smear-negative index case at home. Although they are less infectious (20 -

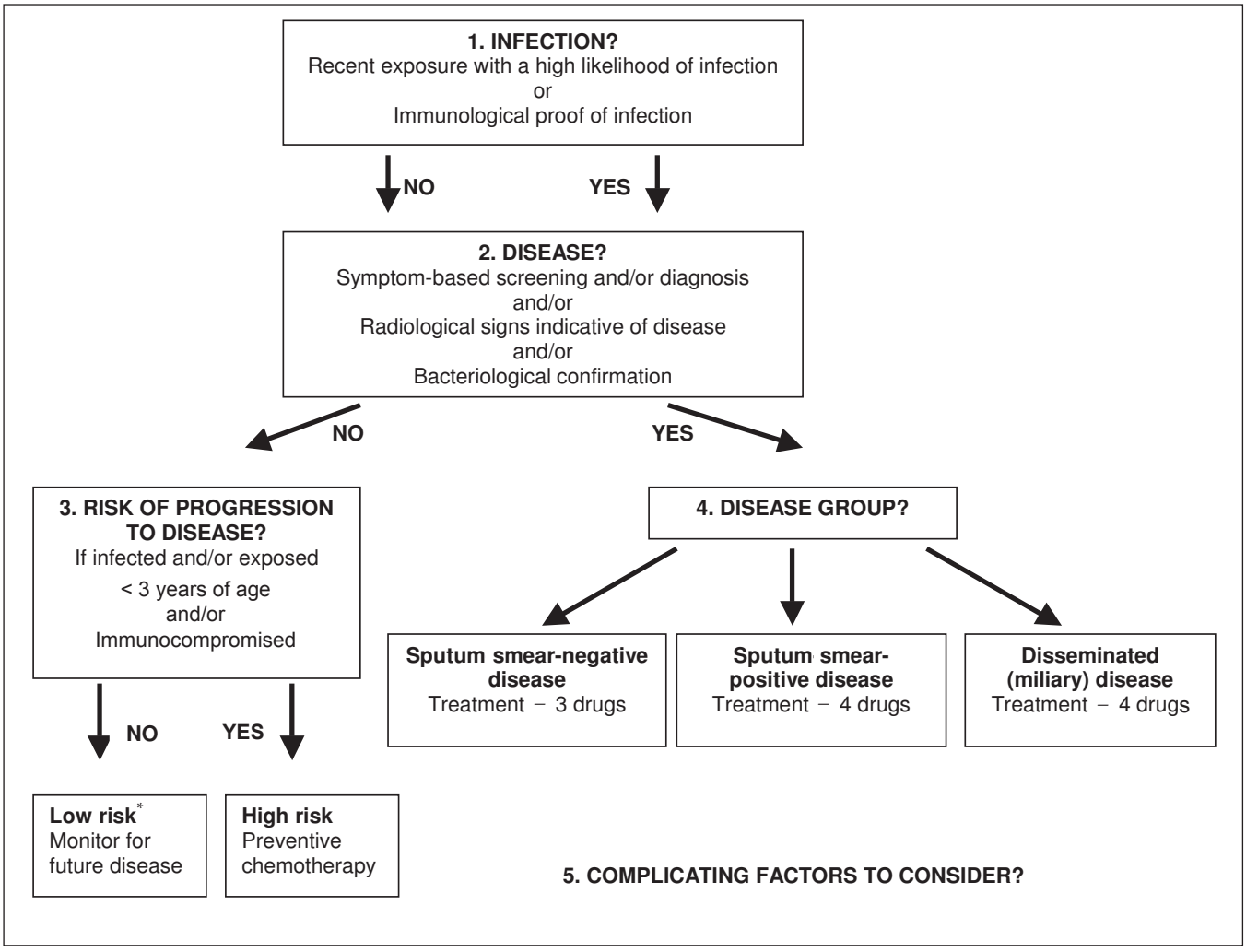

Fig. 2. Flow diagram to guide the diagnosis and management of children with suspected pulmonary tuberculosis (adapted from Marais et al.[3]*). (*In non-endemic areas where the risk of re-infection is low and where TB eradication is an achievable goal, it would be desirable to provide preventive treatment to all individuals with documented TB infection.)*

40% as infectious as a sputum smear-positive patient), sputum smear-negative index cases still pose a significant transmission risk, which is often enhanced by prolonged diagnostic delay and the fact that no preventive therapy is given to close contacts.

2. The TST has very low sensitivity in HIV-infected children, despite using a reduced induration size cut-off of ≥ 5 mm.[3]
3. Chronic pulmonary symptoms from other HIV-related conditions such as gastro-oesophageal reflux and bronchiectasis are not uncommon and failure to thrive is a typical feature of both TB and HIV, greatly reducing the specificity of symptom-based diagnostic approaches.[9]
4. CXR interpretation is complicated by HIV-related co-morbidity such as bacterial pneumonia, lymphocytic interstitial pneumonitis (LIP), bronchiectasis, pulmonary Kaposi's sarcoma (KS) and the atypical presentation of TB in immune-compromised children.[10]

Conclusion

In order to reduce the severe TB-related morbidity and mortality suffered by children in TB-endemic areas two groups of children require access to anti-TB therapy: (*i*) high-risk, exposed and/or infected children require access to preventive therapy; and (*ii*) all children with active disease require access to effective treatment. Fig. 2 presents a flow diagram to guide individual patient management, based on answers to five simple questions. The underlying principles remain consistent, irrespective of the resources available in any particular setting.[3]

1. Is the child exposed to or infected with *M. tuberculosis?*
2. Does the child have active TB?
3. If the child is exposed to or infected with *M. tuberculosis* and active TB has been excluded, is preventive chemotherapy indicated?
4. If the child has active TB, what is the disease manifestation and appropriate treatment regimen?

5. Are there any special circumstances to consider such as HIV infection or exposure to a drug-resistant index case?

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