Diagnosis, treatment and prevention of tuberculosis in children

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Abstract: In Australia, tuberculosis notification rates have plateaued at a low level and disease is highly concentrated in immigrant communities where children may be affected. Many clinicians regard tuberculosis as an adult disease, hence it is rarely considered in the differential diagnosis of sick children. This paper provides a brief overview of the natural history of the disease in children to demonstrate the importance of taking a careful tuberculosis exposure history. It also provides guidance regarding the diagnosis, treatment and prevention of tuberculosis in children. The management of paediatric cases is not difficult if important differences with adult disease are carefully considered; these differences are discussed in detail.

Tuberculosis (TB) remains a major, but often unrecognised, cause of disease and death among women and children in TB endemic areas.[1] Cases are highly concentrated in areas affected by poverty, social disruption, human immunodeficiency virus (HIV) infection and drug-resistant TB,[2,3] with increased international travel and immigration posing major challenges to the control of TB. In Australia, TB incidence rates are among the lowest in the world at 5–6 per 100 000 population per year.[4] However, rates are highly variable and up to 10 times higher in certain sub-groups of the population. More than 85% of cases occur in immigrant populations and represent imported infection, with the top five countries of origin being India, Viet Nam, the Philippines, China and Indonesia, where high rates of drug-resistant TB have been recorded.[2,4] Evidence of local transmission is limited and restricted to particular disease clusters.[5] New South Wales (NSW) reports the highest absolute number of TB cases within Australia.[4,6] In 2008, children aged under 15 years constituted less than 5% of the disease burden (18/498),[6] similar to other developed countries with minimal internal transmission and routine provision of post-exposure prophylaxis to young and vulnerable children.[7,8] Despite low numbers of children with TB, Australian clinicians need to consider TB as part of the differential diagnosis, as cases are observed at regular intervals.[9–13] This brief overview focuses on recent advances in diagnosis and on issues related to the clinical care of children with TB.

Natural history of disease

The pre-chemotherapy literature provides detailed natural history of disease descriptions which guide risk assessment and management.[14,15] An observation is that most children (>90%) who progress to TB disease do so within the first 12 months after primary infection; this is referred to as the 'window of risk'. Another observation is the pronounced bi-modal risk profile: very young children (aged less than 2 years) experience the greatest risk; a nadir occurs at around 5–10 years of age and then an increase is seen 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 due to immature T-cell responses and poor disease containment. The sudden switch to adult-type TB that occurs around puberty, first in girls and then in boys, remains an enigma, but may shed light on key variables underlying individual vulnerability.[16] It is important to remember that adolescent children with adult-type disease are highly infectious.[17] Table 1 summarises some important differences between TB in adults and children.

Diagnosis

Children are usually evaluated for TB as a result of immigrant screening, contact investigation or following presentation with symptoms or signs suggestive of TB disease. It is important to distinguish these different entry points since they influence the diagnostic work-up and interpretation of results (Figure 1). *Mycobacterium tuberculosis* infection detected during immigrant screening probably reflects remote past infection with reduced risk of disease progression, unless it is a young child or immunocompromised individual. *M. tuberculosis* infection detected during contact investigation is likely to be recent, implying a higher risk of disease progression, although this remains highly age-dependent. In this population, isolated radiographic findings in asymptomatic

Table 1. Tuberculosis (TB): differences between adults and children

Aspect	Adults[a]	Children[a]
Epidemiology/ 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 national TB control programs (NTPs)	Rarely recognised as a priority by NTPs
Pathogenesis of lung lesions	Usually adult-type lung disease (previously referred to as post-primary TB)	Usually intra-thoracic lymph node disease (previously referred to as primary TB)
Bacterial load/ transmission/ infection control	Multibacillary	Paucibacillary
	High infection risk after close contact	Low infection risk, but may be infectious if extensive lung involvement with/without cavities; epidemiologic marker of transmission
Drug resistance	Difficult to differentiate acquired from transmitted (primary) drug resistance	Nearly always transmitted (primary) drug resistance indicating recent transmission
Exposure history	Important, but often neglected[b]	Essential
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 (aged <5 years) and/or immunocompromised children
Imaging studies	Chest X-rays (CXRs) not routinely required, unless sputum negative	CXRs (with both frontal and lateral views, of good quality, and competently read) are the most informative study
Disease classification	Pulmonary vs extrapulmonary distinction	Intra-thoracic lymph node disease best classified as pulmonary TB
	Post-primary TB is a confusing concept[c]	Diverse spectrum of pathology that requires accurate classification
Microbiological studies	Easy to collect adequate respiratory specimen and confirm presence of mycobacteria	Difficult to collect adequate respiratory specimens (young children cannot expectorate); smear microscopy has very low yield; cultures and nucleic acid amplication tests have low-to-moderate yield depending on disease severity
Treatment	With at least four drugs	With three or four drugs depending on likely organism load and severity of disease
Prognosis	Excellent outcomes achievable with timely and appropriate treatment	Excellent outcomes achievable with timely and appropriate treatment; potentially grave outcome with delayed diagnosis

Adjusted by the authors from their previous work.[14]
[a]Typical characteristics in the absence of HIV-infection and/or severely compromised immunity.
[b]Taking a careful contact history is often neglected for adults, but has particular relevance for the identification of drug-resistant TB suspects.
[c]The old distinction between primary and post-primary TB obscures the fact that adult-type (post-primary; secondary) TB frequently results from recent re-infection and may also occur within months of documented primary infection (particularly in adolescents).

children are problematic, since transient elements of the Ghon/primary complex are frequently visualised and not necessarily indicative of active disease. Observational studies and current World Health Organization guidance suggest that symptom-based screening is adequate, at least in older children, and the complete absence of current symptoms is sufficient to rule out TB disease in this group.[18,19] Table 2 provides an overview of investigations to establish a diagnosis of TB in children.

Clinical evaluation

Children rarely present with near pathognomonic signs of TB such as a TB gibbus; most clinical manifestations are non-specific. In fact, one of the remarkable features of intra-thoracic TB is the frequent absence of physical signs despite the presence of persistent non-remitting symptoms. Furthermore, despite minimal clinical findings, the clinician may be surprised by the radiographic extent of disease. The pathophysiological explanation for this discrepancy is not clear but may reflect the fact that TB often causes a vasculitis (as observed with TB meningitis) in addition to parenchymal involvement. This implies that both oxygen exchange and blood supply are reduced in affected parts of the lung, limiting the resultant ventilation:perfusion mismatch which may explain the frequent absence of acute respiratory distress despite extensive lung involvement.

A detailed history should explore the likelihood of recent (during the past 12 months) TB exposure and allow accurate symptom characterisation. This is important

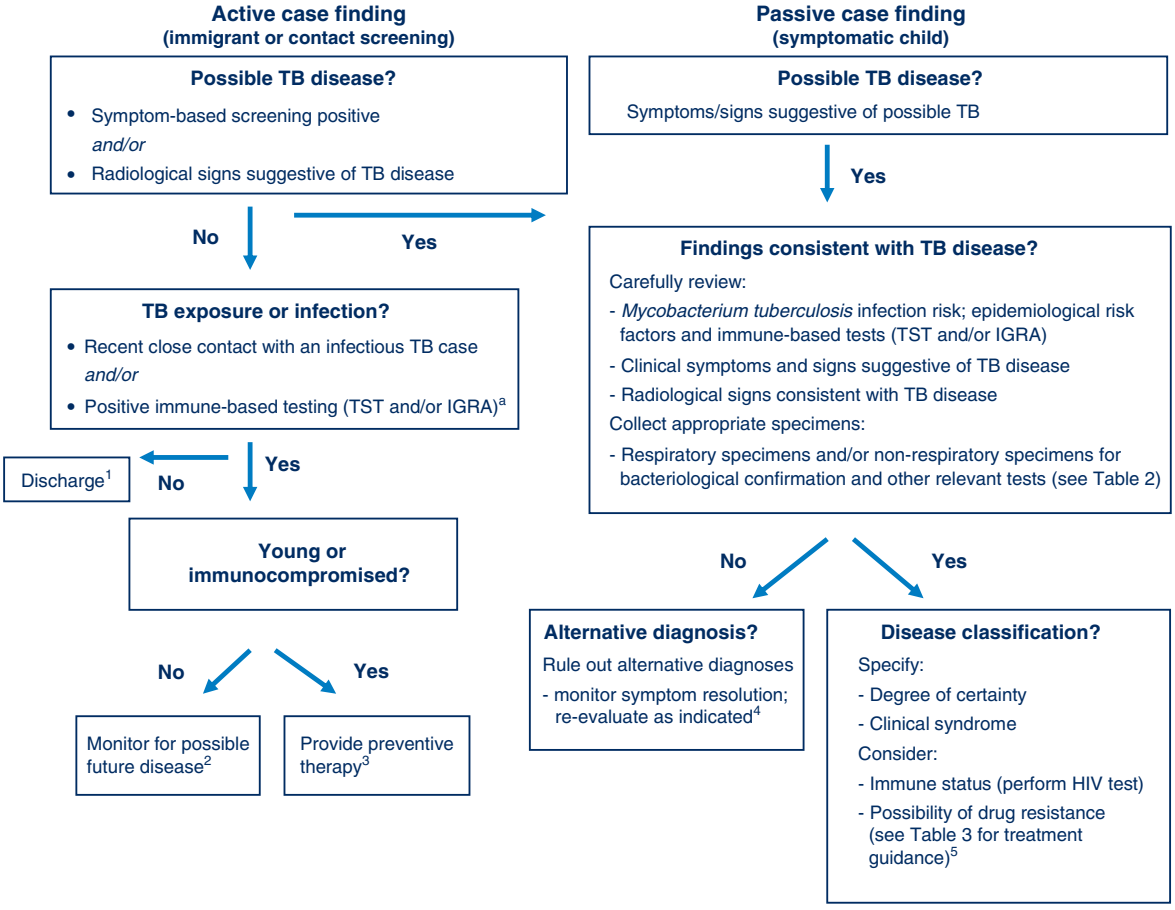

Figure 1. Algorithm for diagnosis and classification of tuberculosis (TB) in children.
Adjusted by the authors from their previous work.[14]

HIV: human immunodeficiency virus; TST: tuberculin skin test; IGRA: interferon-gamma release assay.
[a]Neither of the immune-based tests (TST/IGRA) can 'rule out' TB disease with confidence and conversion may be delayed for 2–3 months after documented exposure. All children aged <5 years and any child with current symptoms should receive a chest X-ray.
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.

because poorly-defined symptoms have poor discriminatory power.[20] Common constitutional symptoms include decreased appetite (recent crossing of weight centiles is most informative), fatigue or reduced playfulness, and fever. Despite TB being an infectious disease, fever is often absent, low-grade or intermittent. With lung involvement, children usually present with a persistent non-remitting cough that is unresponsive to standard first-line treatment. Airway compression may manifest as loud (large airway) wheezing that does not respond to bronchodilators. Clinical follow-up is a useful diagnostic tool in children with mild disease manifestations for whom the diagnosis cannot be made with certainty.[20]

Imaging studies

Chest radiography is generally the most informative investigation and should include both frontal and lateral views. Lateral views are important as they improve assessment of the mediastinum and hilar areas. Childhood intra-thoracic TB has a wide range of appearances associated with different disease entities, which justifies careful classification.[21,22] Visible hilar adenopathy with or without airway compression is highly suggestive of TB disease. High-resolution chest computed tomography (CT) provides the most accurate visualisation of intra-thoracic structures,[23] but due to the high cost and associated radiation exposure its use should be limited to complicated cases. CT and/or magnetic resonance imaging (MRI) is the best way to visualise extrapulmonary lesions, especially intra-cranial pathology. MRI is more sensitive for detecting brainstem lesions or early perfusion defects (infarcts) and also provides better evaluation of the spine and soft tissues.[24]

Laboratory studies

Immune-based tests are severely limited by their inability to differentiate *M. tuberculosis* infection from active disease,

Table 2. Summary of investigations to diagnose tuberculosis (TB) in children

Investigation	Uses	Strengths (S) and limitations (L)
Microbiological studies (detection of *Mycobacterium tuberculosis*)		
Microscopy	Diagnosis of TB	**S:** Specificity high; useful in all specimen types; rapid (<1 hour) detection; low cost (fluorescence microscopy most cost effective). **L:** Sensitivity very low, especially in young children; highly operator-dependent; labour intensive; unable to speciate or distinguish viable and dead bacilli.
Growth on special media	– Diagnosis of TB – Species identification	**S:** Specificity high. **L:** Sensitivity low in young children; slow turnaround time.
DNA detection	Drug susceptibility testing	**S:** Specificity high; fully automated platforms; rapid turnaround. **L:** Sensitivity low in young children; cannot distinguish viable from dead bacilli; quality control essential.
Histopathological studies		
Stained tissue samples	Diagnosis of TB	**S:** Allows exclusion of other diagnoses (such as malignancy).
Immune-based studies		
TST IGRAs	Identification of *M. tuberculosis* infection	**L:** Neither test can differentiate *M. tuberculosis* infection from active disease. **L:** TST: affected by BCG vaccination; requires a second visit after 48–72 hours. **S:** IGRAs: unaffected by BCG vaccination; requires a single visit. **L:** Low sensitivity in very young and/or immunocompromised children; indeterminate results problematic.
Imaging		
Radiography CT and MRI Ultrasonography	Diagnosis of TB	Chest radiography (frontal and lateral views) most helpful; CT or MRI useful in uncertain or complicated cases; ultrasonography useful to identify intra-abdominal/retro-peritoneal lymphadenopathy or pleural/pericardial effusions. **L:** Ultrasonography highly operator-dependent.

BCG: Bacille Calmette-Guérin; CT: computed tomography; IGRAs: interferon-gamma release assays; MRI: magnetic resonance imaging; TST: tuberculin skin test.

and neither the purified protein derivative tuberculin skin test (TST) or interferon-gamma release assays (IGRAs) (e.g. QuantiFERON-Gold In Tube®) offer a simple solution.[25] IGRAs do not replace TSTs for the detection of *M. tuberculosis* infection in children and, like TSTs, cannot be used to exclude TB. In certain clinical situations IGRAs may be used in addition to TSTs to improve sensitivity and specificity in the detection of TB infection.[25]

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. Two studies have evaluated the performance of the rapid NAAT-based Xpert® MTB/RIF assay in children, demonstrating similar performance characteristics to adult studies, with excellent specificity and detection of around 70% of culture-positive cases.[26,27]

Collecting adequate respiratory specimens in young children is problematic, but gastric aspirates, induced sputum (with or without laryngopharyngeal suction) and bronchoalveolar lavage (in select patients) offer feasible alternatives. A combination of specimens provides the best yield.[28] Fine-needle aspiration biopsy has excellent utility in children with a peripheral lymph node mass.[29] With tuberculous meningitis, slow clinical onset, cerebrospinal fluid pleocytosis (with total cell count <500) and elevated protein is highly suggestive.[30] Despite the challenges discussed, bacteriological confirmation should always be attempted, although it should not delay treatment initiation in young and vulnerable children. TB can be diagnosed with relative certainty based on a combination of clinical, radiological, laboratory and histopathological (when feasible) findings consistent with TB disease, in association with epidemiological factors and/or immunological evidence of *M. tuberculosis* infection.

Treatment

If a diagnosis of TB disease is established, pragmatic disease classification guides management and facilitates case comparison. From a treatment perspective, likely bacillary load, anatomical location and the 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

Table 3. Summary of first-line tuberculosis (TB) drugs and dosage recommendations for children

First-line drugs	Mode and mechanism of action	Main adverse effects[a]	Daily dose mg/kg (range)[b] [maximum dose][c]
Isoniazid	Bactericidal • Inhibits cell wall synthesis • Most potent early bactericidal activity offering the best protection to companion drugs • Contributes mainly by rapidly killing actively metabolising extracellular bacilli; contributes to sterilisation if given for a prolonged period	Hepatitis; peripheral neuropathy	10 (7–15)[d] [300 mg]
Rifampicin	Bactericidal and sterilising • Inhibits ribonucleic acid synthesis • Contributes by killing extracellular and slower growing intracellular bacilli; important contribution to sterilisation	Hepatitis; orange discolouration of secretions; drug-drug interactions	15 (10–20) [600 mg]
Pyrazinamide	Sterilising • Disrupts energy metabolism • Contributes by specifically killing bacilli that persist within the acidic centres of caseating granulomas	Hepatitis; arthralgia	35 (30–40) [2000 mg]
Ethambutol	Bacteriostatic • Inhibits cell wall synthesis • Contributes mainly by offering some additional protection against drug-resistant mutants	Visual disturbance (acuity, colour vision)	20 (15–25) [1200 mg]

Suggested treatment regimens

Disease category	Treatment regimen	Rationale
Uncomplicated intra-thoracic disease	Isoniazid, rifampicin and pyrazinamide (2-month intensive phase) Isoniazid and rifampicin (4/12 continuation phase)	Organism load low, drug penetration good
Extensive lung infiltrates and/or cavities	Add ethambutol during 2-month intensive phase	Organism load high, drug penetration good
Tuberculous meningitis	Add fourth drug, at least during 2-month intensive phase Add steroids for 1 month[e]	Organism load low, drug penetration variable, risk of severe immune-mediated sequelae
Severe airway compression	Three or four drug regimen depending on extent of lung infiltration/cavities Consider adding steroids for 1 month	Organism and drug penetration variable,[f] inflammation may worsen airway compression
Recent exposure/infection No active disease	Preventive therapy Isoniazid (6–9 months) Isoniazid, rifampicin (3 months)	Organism load very low, drug penetration good

Adjusted by the authors from their previous work.[14]
[a]Hypersensitivity reactions and drug rashes may occur with any drug.
[b]Most recent World Health Organization dosage recommendations for children,[37] except where indicated.
[c]Maximum doses from Australian Therapeutic Guidelines.[38]
[d]Range from additional reference.[39]
[e]Recommendations around fourth drug and duration of therapy vary; WHO advise isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months followed by 10 months isoniazid and rifampicin.
[f]Drug penetration into large cold abcesses may be limited, requiring surgical drainage.

should also be given to the possible involvement of 'sanctuary sites' such as the brain and cerebrospinal fluid (CSF), since drugs have highly variable CSF penetration.[31] High and/or rising rates of drug-resistant TB, documented in many countries within the Asia-Pacific region, Eastern Europe and sub-Saharan Africa,[2] make it necessary for clinicians to carefully scrutinise patients who resided in, or travelled through, these countries. The possibility of

drug-resistant TB should be suspected following close contact with a drug-resistant source case; in residents of countries known to have a high prevalence of drug-resistant TB; or following contact with someone who died on TB treatment, is poorly adherent to therapy, or required more than one treatment course.

TB treatment aims to ensure long-term cure without serious adverse effects for the patient. From a public health perspective it is important to terminate transmission and prevent the emergence of drug resistance. Table 3 summarises the mode of action, main adverse effects and recommended dosages of first-line TB drugs, including dosage recommendations for children; sub-optimal drug levels result from using weight-adjusted adult doses.

In the absence of drug resistance, the most likely cause of poor treatment response is non-adherence. If a child presents with a TB recurrence more than 6–12 months after treatment completion and clinical cure, it most likely represents re-infection. Standard first-line treatment would be appropriate (in the absence of risk factors for drug-resistant disease); there is no indication to use an escalated re-treatment regimen. With poor response to adherent therapy, careful re-evaluation of the original diagnosis and assessment for drug resistance is warranted. In NSW, all positive cultures undergo drug susceptibility testing, which provides additional motivation to achieve bacteriological confirmation. With drug-resistant TB, the basic principles of management are unchanged and excellent outcomes can be achieved.[32] All children diagnosed with TB should be tested for HIV infection; management of co-infected children has been recently reviewed.[33]

Prevention

Prevention strategies include vaccination, pre- and post-exposure prophylaxis, treatment of 'latent' infection, and secondary prophylaxis (provided after completion of TB treatment). Bacille Calmette-Guérin (BCG) vaccination reduces the risk of disseminated (miliary) disease and tuberculous meningitis in very young children but protection is incomplete and it offers no consistent protection against adult-type TB.[34] It is not included in routine vaccination schedules in Australia, however, it should be considered when vulnerable children (e.g. aged less than 2 years) are exposed to a high-risk environment, such as visiting a TB endemic country. Research to develop novel vaccines with improved efficacy and safety is ongoing.

Careful risk stratification identifies those at greatest need of preventive therapy following TB exposure. The target population for preventive therapy provision may vary in different settings depending on feasibility and available resources, but all young (aged less than 5 years) and/or immunocompromised children should receive preventive therapy following documented exposure/infection.[19] With good adherence and in the absence of drug resistance, isoniazid monotherapy provides excellent protection following documented exposure/infection. However, parents are often reluctant to provide 'treatment' to an otherwise well child and ensuring good adherence is challenging. Treatment with isoniazid and rifampicin for 3 months has demonstrated equivalent efficacy and improved adherence compared to 9 months of treatment with isoniazid alone, with no increase in adverse events.[35] Twelve doses of weekly rifapentine and isoniazid proved efficacious in a recent adult study,[36] but this regimen cannot yet be recommended in children aged less than 12 years until more safety and efficacy data are available. In HIV-infected children on antiretroviral therapy, drug-drug interactions should be considered with all rifamycin-containing regimens.[33]

Conclusion

Children suffer a huge but under-recognised TB disease burden in endemic countries from which Australia continues to receive immigrants. Multiple challenges remain: to develop more effective vaccines, better diagnostics and shorter treatment regimens. However, it is worth emphasising that most children would be served well by the sensible application of existing tools.

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