12. Tuberculosis in Children and Adolescents

12.1 Introduction

The WHO Global TB Report in 2016 estimated that children represented around 10% of the total burden of tuberculosis (TB) globally in 2015 with around 1 million TB cases and 210,000 TB-related deaths in children (WHO Global TB Report 2016). It is difficult to estimate the true burden of tuberculosis (TB) in children due to difficulties with confirming diagnosis, especially in young children in TB endemic settings, and due to the widespread problem of under-reporting of child TB cases by TB control programmes in those settings. In Australia, as in similar low incidence settings, around 4-5% of all TB cases are in children and the incidence rate is highest in overseas-born children compared to Australian-born (indigenous or non-indigenous) children, and in young children (< 5 years) (Teo et al. 2015). In Victoria 12 cases of active TB disease in children (0-15 years-old) were reported in 2016.

The clinical presentation of TB in children differs to that in adults. Following infection with Mycobacterium tuberculosis, there is an immune response that involves the regional lymph nodes. A positive tuberculin skin test (TST) or interferon gamma release assay (IGRA) is considered an immunological marker of response to infection. The primary complex comprising the site of infection and the involved regional lymph nodes may heal, or complications may develop from enlargement or rupture of the regional lymph nodes or the spread of tubercle bacilli into the bloodstream, giving rise to disseminated disease. Most children contain the infection resulting in what is commonly referred to as ‘latent TB infection’ (LTBI), but the risk of developing disease remains lifelong. Some children progress to develop disease, i.e. ‘active TB’, following infection. Progression to TB disease occurs more commonly in children than in adults and the risk of is greatest in the first 24 months following infection. Children are at particular risk of disseminated TB and TB meningitis, which are associated with a poorer outcome than localised disease. The increased likelihood of dissemination also explains why the presentation of extra-pulmonary TB is more common in children than adults. At all ages, however, pulmonary TB is the most common presentation. Adolescents also have greater risk of TB than adults, however the presentation of TB in adolescents is more similar to that of TB in adults.

12.2 Risk of Disease Following Primary Infection

In general, for children who have a normal CXR at the time a positive TST is first detected, the lifetime risk of developing active TB disease is between 2 and 10 per cent. However, the risk is much higher in young children, children who have been exposed very recently, and children who have malnutrition, immunodeficiency, or poor general health.

Recent data from Victoria found that the 4-year disease risk for children aged <5 years, 5 to 14 years, and ≥15 years was 56.0%, 27.6%, and 4.7% respectively (Table). For children under the age of 15 years, virtually all risk accrued in the first 5 months after exposure.

These results underline the importance of early referral and investigation of young children who have been exposed to TB, and prompt initiation of prophylactic therapy for young children with latent TB infection (to reduce the risk of disease).

<table>
<thead>
<tr>
<th>Age at primary infection</th>
<th>Risk of active TB disease in immunocompetent children</th>
<th>Highest risk period</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 years</td>
<td>56.0%</td>
<td>Almost all risk accrued in the first 5 months</td>
</tr>
<tr>
<td>5-15 years</td>
<td>27.6%</td>
<td>Approximately half the risk accrued in the first 8 months</td>
</tr>
<tr>
<td>≥15 years</td>
<td>4.7%</td>
<td></td>
</tr>
</tbody>
</table>
12.3 Infectivity

Childhood TB is rarely contagious because:

- Children with active TB usually have a low bacterial load
- Children are less able to generate the tussive forces needed to aerosolise bacilli
- Young children with pulmonary TB rarely have cavitating disease.
- Young children swallow rather than expectorate sputum

Older children (> 10 years) and adolescents may present with cavitatory TB and are commonly infectious.

12.4 Diagnosis

In the assessment of a child with possible infection or disease due to TB, a thorough history of TB contact should be sought as well as a history of recent travel to a TB endemic country. In a low incidence setting, a source case with TB is commonly identifiable. This may be a known contact already diagnosed with and treated for TB or a contact with TB-related symptoms who requires further investigation. Important information of the possible TB source (or index) case includes TB type, whether bacteriologically confirmed, drug susceptibility test results, as well as whether the index case is receiving treatment for TB, when the treatment was commenced, what treatment regimen, and adherence and response to that regimen.

Infection with *M. tuberculosis*

TB infection is most commonly diagnosed by a positive tuberculin skin test (TST) or interferon gamma release assay (IGRA). **TST and IGRA are both imperfect tests that can yield false positive and false negative results. Their interpretation and subsequent clinical management depends on the prior probability of the test being positive and on the clinical and epidemiological circumstances of the individual.**

A missed diagnosis of TB infection has greater implications for children than adults (due to the higher risk of disease, particularly severe disease). As such, interpretation and response to TB testing depends on age, TB contact history (including the infectiousness of the source case and the timing, closeness and duration of contact), and the clinical situation.

*Tuberculin skin test (TST)*

The TST has been the standard indicator of infection with *M. tuberculosis* since the 1930s, and remains the preferred diagnostic tool for children (particularly children <5 years of age), where available. The interpretation of a positive test may be modified by the risk of infection which is influenced by the contact history, medical history and age of the child – see Table 2.1. Criteria for Tuberculin Positivity, by Risk Group (adapted from ATS/CDC, 2000)

*Interferon-gamma release assays (IGRA)*

IGRA, like TST, can be used as an indicator of infection with *M. tuberculosis*. Most studies show that IGRA and TST have similar sensitivity for the detection of latent TB infection in adults - although the results for the two tests are not always concordant. Studies suggest that IGRA are less sensitive than the TST in children. As such, the TST remains the test of choice for asymptomatic children, particularly children <5 years of age.

Limited data suggest that IGRA may be useful in situations where the value of TST is greatly reduced, e.g. the immunocompromised. In Australia, Medicare funding for IGRA is available for individuals with exposure to active TB, or for conditions where risk of reactivation occurs (including HIV and planned immunosuppressive therapy).

Other specific situations where IGRA might be indicated are:

- A child who has been vaccinated with BCG and the TST is borderline.
- If TST testing is considered likely to result in a blistering or a large painful response.
(e.g. where active TB is strongly suspected).
• The child is unable or unlikely to return at 48-72 hours for reading of the TST.

Interpretation of TST and IGRA results in children

Positive TST or IGRA (eg QuantiFERON-TB Gold)
A positive TST or IGRA indicates infection with TB but does not distinguish individuals with LTBI from those with active TB disease.
Interpretation of the test is made in the context of contact history, symptoms, signs and radiology according to established guidelines. Recent conversion of either a TST or IGRA from negative to positive is likely to indicate a greater likelihood of progression to active disease.

Negative TST or IGRA
Although a positive TST or IGRA confirms infection with *M. tuberculosis* (due to its high specificity), a negative test does not rule out either LTBI or active TB disease due to the imperfect sensitivity of these tests in children, especially in children <5 years of age.

Discordant IGRA and TST result
In some children the IGRA and TST results are contradictory; i.e. TST + / IGRA – (more commonly) or TST – / IGRA +. It is safest to assume that a negative IGRA or TST in this situation does not exclude TB infection. Also there remains controversy about whether an IGRA is necessarily more specific than a TST in BCG-immunised children. Most experts therefore recommend that a discordant result is regarded as a positive result when making treatment decisions.

Indeterminate IGRA result
Indeterminate IGRA results are more common in children, especially in infants and young children under 5 years of age. If the result is indeterminate no interpretation can be made and the test should either be repeated or excluded from the process of evaluating the diagnosis.

History of BCG
BCG vaccination can cause false positive TST results – however the risk of this is lower than previously thought, especially if BCG was administered in infancy. Given the implications of missing TB infection in children, guidelines on the interpretation of TST results no longer account for prior BCG. It is safest to assume that a positive test is truly positive, regardless of BCG status.

Active TB disease
The care of a child suspected of having TB should involve a physician experienced in the management of childhood TB. Diagnosis of active TB disease is based on clinical symptoms and signs, chest x-rays or other investigations, smear microscopy, culture and molecular tests of infected body samples. Lateral chest x-rays increase the yield for detecting lymphadenopathy as do CT scans. However, the latter requires a volumetric scanning protocol and should not be performed routinely because of the associated radiation dose.

Even though the yield from culture is low (around 50%) in children, microbiological confirmation of TB should be sought whenever possible as well as drug susceptibility test results. Treatment should be started as soon as samples have been obtained, and choice of treatment regimen may be guided by the drug susceptibility profile of the index case (if known).

12.5 Collection of specimens for demonstration of tubercle bacilli

Pulmonary:
In younger children when it is not possible to obtain sputum, gastric aspirates should be collected on three consecutive days. About 50 mL of gastric contents should be aspirated via a nasogastric tube early in the morning after the child has fasted for 8 to 10 hours, preferably while the child is still in bed. This is best performed in hospital but can be undertaken through some hospital in the home programmes.
Smear microscopy, culture and PCR should be performed on the aspirate. If there is radiological evidence of focal disease such as lobar, segmental or subsegmental collapse or clinical evidence of bronchial obstruction a flexible fiberoptic bronchoscopy with broncho-alveolar lavage may be indicated in addition to gastric aspiration. Otherwise, there is no advantage of bronchoscopy over gastric aspiration.

Inhalation of nebulised sterile hypertonic saline (3 to 6%) via an ultrasonic nebuliser can be used to induce sputum in those unable to expectorate sputum. However, the cough produced by this technique may be of sufficient force to aerosolize tubercle bacilli and infect health care workers. Thus, induced sputum should only be performed in areas with high-efficiency particulate air filters and qualified personnel should wear appropriate respiratory protection. For this reason, it is not the procedure of choice for obtaining respiratory samples in children.

### Extra-pulmonary:

<table>
<thead>
<tr>
<th>Site</th>
<th>Imaging</th>
<th>Biopsy</th>
<th>Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node</td>
<td>Plain X-ray and computed tomography (CT)</td>
<td>Node</td>
<td>Node or aspirate</td>
</tr>
<tr>
<td>Bone/joint</td>
<td>Magnetic resonance imaging (MRI)</td>
<td>Site of disease</td>
<td>Biopsy or paraspinal abscess Site or joint fluid</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Ultrasound CT abdomen</td>
<td>Omentum</td>
<td>Biopsy</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Intravenous urography Ultrasound</td>
<td>Site of disease</td>
<td>Early morning urine Site of disease</td>
</tr>
<tr>
<td>Disseminated</td>
<td>CXR High-resolution CT thorax Ultrasound abdomen CT brain</td>
<td>Lung Liver Bone marrow Blood Bronchial wash Liver Bone marrow</td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td>CT brain MRI</td>
<td>Tuberculoma</td>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>Skin</td>
<td>Site of disease</td>
<td>Site of disease</td>
<td>Site of disease</td>
</tr>
<tr>
<td>Pericardium</td>
<td>Echocardiogram</td>
<td>Pericardium</td>
<td>Pericardial fluid</td>
</tr>
<tr>
<td>Cold/liver abscess</td>
<td>Ultrasound</td>
<td>Site of disease</td>
<td>Site of disease</td>
</tr>
</tbody>
</table>

### 12.6 Latent Tuberculosis Infection (LTBI)

Treatment of children with LTBI and no evidence of active disease is indicated for two reasons:
- Firstly, to reduce the risk of developing disease in the years immediately after acquiring the infection, particularly in children under the age of five.
- Secondly, there is a lifelong risk of developing disease and this can be reduced substantially by the use of isoniazid or other preventative therapy, which in children and adolescents has few side effects.
Therefore preventative therapy is recommended for otherwise healthy children and adolescents who have a positive TST or IGRA as defined above and no evidence of TB disease (i.e. asymptomatic with a normal CXR), and is strongly recommended in the following risk groups:

- HIV-infected children.
- Children in whom corticosteroid or immunosuppressive therapy (including DMARS) is contemplated.
- Those with diabetes or other chronic diseases associated with malnutrition (for example, coeliac disease).
- Children under age five who have been in close contact with a case of bacteriologically confirmed TB, who are TST negative on initial screening, pending further review of their tuberculin status at three months from break of contact. (If break of contact TST is negative, isoniazid may be ceased)

For preventative therapy, a minimum of six months of isoniazid 10 mg/kg (up to max of 300 mg) once daily is recommended. An alternative regime is a minimum of three months of isoniazid and rifampicin.

Isoniazid-related liver toxicity is rare in children routine monitoring of liver function is not recommended if the baseline liver function tests are normal.

Isoniazid-related peripheral neuropathy is rare in children, and prophylactic pyridoxine is not normally recommended with isoniazid in children.

Isoniazid is not recommended as preventive therapy for children who are contacts of drug-resistant TB cases. The use of preventive therapy and choice of preventive therapy regimen in child contacts of drug-resistant TB cases who do not have active TB should be considered on an individual basis against perceived risks and benefits, and informed by the drug susceptibility profile of the index case.

12.7 Treatment of Pulmonary TB Disease

Children with active TB disease are usually treated with daily therapy with four drugs, isoniazid, rifampicin, pyrazinamide and ethambutol for two months, and then generally two drugs, isoniazid and rifampicin, for a further four months. Normally these drugs are given daily, but supervised therapy given on three days a week is sometimes necessary when treatment adherence with daily therapy is considered likely to be poor. In those in whom culture sensitivity from an index case is unknown, or when the child has migrated from a country where there is a low prevalence of drug-resistant TB, ethambutol can be omitted and a three-drug regimen used for the first two months of treatment in those less than 12 years old. As optic neuritis is extremely rare in children receiving recommended doses of ethambutol, an ophthalmology review is not necessary before or during treatment.

Short course therapy (six months) has been shown to be effective in children with primary drug-susceptible TB and complicated primary TB limited to the respiratory tract, but there are insufficient data to recommend it for CNS, bone or joint TB infections. The WHO currently recommends 8 months continuation phase (10 months total treatment duration) in these cases (WHO 2014). Management of these require multi-disciplinary specialist input.

12.8 Treatment of Extra-pulmonary TB Disease

Meningeal: Minimum 12 months treatment using a four drug regime for initial 2 months and 2 drugs for the rest of the course. Corticosteroids are indicated (1-2 mg/kg prednisolone, maximum 40 mg with gradual withdrawal starting within 2-3 weeks of initiation).

Peripheral lymph node: Minimum 6 months standard treatment even in those who have had an affected gland surgically removed.
**Bone and joint:** Minimum 6 months standard treatment. If there is spinal cord involvement management should be as for those with meningeal TB.

**Pericardial:** Minimum 6 months standard treatment. Corticosteroids are indicated (1-2 mg/kg prednisolone, maximum 40 mg with gradual withdrawal starting within 2-3 weeks of initiation).

**Miliary:** Minimum 6 months standard treatment. Brain scan (CT or MRI) and lumbar puncture are indicated to assess for central nervous system involvement. If CNS involvement is detected, treat as for meningeal TB.

**Genitourinary:** Minimum 6 months standard treatment.

**12.9 Strategies to Improve Adherence**
- Strategies to enhance adherence to treatment (see DOT chapter) are generally relevant to treatment in children.
- Wherever possible, liquid preparations should be used.
- Easy access to follow-up.
- Involve the Victorian Tuberculosis Program clinical nurse consultant.

**References**

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