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Consensus statement on the use of a four-month treatment regimen for drug susceptible tuberculosis in children (< 10 years of age) with uncomplicated disease

Endorsed by the Australian and New Zealand Paediatric Infectious Diseases (ANZPID) interest group of the Australasian Society of Infectious Diseases (ASID) and the National Tuberculosis Advisory Committee (NTAC) on behalf of the Communicable Diseases Network of Australia (CDNA)

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Background

The recommended minimum duration for the treatment of drug-susceptible tuberculosis (TB) used to be six months. The standard six-month regimen for children includes a two-month intensive phase using isoniazid (H), rifampicin (R) and pyrazinamide (Z), with ethambutol (E) added if the patient has pulmonary TB with a high bacillary load (lung cavities) or in the presence of significant immune compromise, and a four-month continuation phase using HR. However, the standard six-month (so-called 'short course') treatment regimen (2HRZ(E)/4HR) is long and disruptive and finding a shorter treatment course with similar or improved efficacy has been the 'holy grail' of TB treatment research. Recent randomised controlled trials (RCTs) that assessed shorter four-month treatment regimens, in patients with drug-susceptible (DS) TB, have had promising results and require urgent consideration.

The first study assessed a regimen consisting of a two-month intensive phase using H, rifapentine (P), Z and moxifloxacin (M), followed by a two-month continuation phase using HPM in adolescents (≥ 12 years) and adults.[1] This regimen (2HPZM/2HPM) was found to be non-inferior to the traditional six-month regimen (2HRZE/4HR) using a 6% non-inferiority margin. However, primary and secondary outcomes were consistently less favourable than the standard 6-month regimen, without crossing the 6% non-inferiority margin. Given Food and Drug Administration (FDA) registration and ready availability of rifapentine in the United States of America (USA), this regimen is now endorsed by the Centres for Disease Control and Prevention (CDC)[2] as a first-line TB treatment option in people 12 years of age and older with drug-susceptible pulmonary TB, given that it is as effective as the standard six-month regimen, but more convenient and faster.

The second study (the SHINE trial) included children aged 3 months to 16 years. The SHINE trial assessed a regimen consisting of a standard two-month intensive phase followed by a two-month (rather than the traditional four-month) continuation phase using the same drugs as the standard six-month regimen (2HRZ(E)/2HR).[3] Only children with non-severe TB were included. Non-severe TB was defined as peripheral lymph node disease (in isolation) or pulmonary TB confined to less than one lobe of the lung with no cavities, intra-thoracic lymph node involvement without radiologically visible or clinically significant airway obstruction, no signs of disseminated (miliary) TB and no complex pleural effusion. The shorter four-month regimen demonstrated non-inferior outcomes (using a similar 6% non-inferiority margin) compared to the traditional six-month regimen, but in this instance all primary and secondary outcomes showed equivalent or more favourable outcomes than the standard six-month regimen.

Table 1: Guide for regimen selection for drug-susceptible tuberculosis (TB)[a]

<table>
<tr><th rowspan="2">Regimen[b]</th><th colspan="5">Age[c]</th></tr>
<tr><th>0–3 months</th><th>3 months – 10 years</th><th>10–12 years</th><th>12–16 years</th><th>> 16 years</th></tr>
<tr><td>2HRZ(E)/4HR</td><td colspan="2">Ethambutol should be added in settings with a high background prevalence of isoniazid resistance or HIV infection or in CLHIV</td><td colspan="3">Independent of disease severity or HIV status</td></tr>
<tr><td>2HRZ(E)/2HR</td><td></td><td colspan="2">Non-severe TB, > 3 kg, add ethambutol in settings with a high background prevalence of isoniazid resistance or HIV infection or in CALHIV</td><td></td></tr>
<tr><td>2HPMZ/2HPM</td><td colspan="3"></td><td colspan="2">Independent of disease severity or HIV status</td></tr>
<tr><td rowspan="3">Additional factors to be considered if several regimens are possible</td><td></td><td colspan="2">Disease severity</td><td></td></tr>
<tr><td colspan="5">Patient or family preference</td></tr>
<tr><td colspan="5">Access and cost of regimen component drugs</td></tr>
</table>

a Reproduced from reference 4, under a CC-BY-NC-SA 3.0 IGO licence (https://creativecommons.org/licenses/by-nc-sa/3.0/igo/deed.en).

b Note: all the regimens envisage daily dosing of all medicines.

c CALHIV: Children and adolescents living with HIV; CLHIV: Children living with HIV; HIV: Human immunodeficiency virus; TB: tuberculosis.

In recognition of these two studies the most recently updated World Health Organization (WHO) guidelines include the following new recommendations:[4,5]

1. Patients aged 12 years or older with pulmonary DS-TB may receive a four-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide (2HPMZ/2HPM). (Conditional recommendation, moderate certainty of evidence); and

2. In children and adolescents aged between 3 months and 16 years with non-severe TB (without suspicion or evidence of multi-drug- or rifampicin-resistant TB [MDR/RR-TB]), a four-month treatment regimen (2HRZ(E)/2HR) should be used. (Strong recommendation, moderate certainty of evidence).

Table 1 provides a concise overview of current WHO recommendations.[4]

Australian Therapeutic Guidelines (eTG) and jurisdictional guidance documents still indicate six months as the minimum TB treatment duration. Given the excellent outcomes achieved with the standard six-month regimen in Australia and no major issues with treatment adherence or completion, there is no perceived urgency to use the 2HPZM/2HPM regimen now. Although the defined non-inferiority margin was not breached, potential inferior outcomes remain a concern; this justifies further monitoring of outcomes in areas that do adopt the new guidance (like the USA). The new regimen also has altered requirements for routine laboratory drug susceptibility testing (DST), with a need to include moxifloxacin in routine first-line DST. In addition, the increased costs and complicated logistics of drug acquisition (especially rifapentine that is not Therapeutic Goods Administration [TGA]-registered) need to be considered. Given that higher rifamycin exposure, achieved by rifapentine's longer half-life compared to rifampicin, is likely the key factor allowing regimen shortening with this regimen, it also seems prudent to await the results of ongoing studies assessing the effect of increased rifampicin dosing. If equally effective, this will be simpler and cheaper to implement than the use of rifapentine. Current NTAC consensus is to await more study and operational data before

recommending the use of the 2HPZM/2HPM regimen, persisting with the standard six-month treatment regimen in adults and adolescents in the meantime.

However, paediatric data from the SHINE trial were highly encouraging and not associated with any major concerns or practical considerations. In general, children (< 10 years of age) develop pauci-bacillary TB without lung cavities, which implies greater potential for treatment shortening and a greatly reduced risk of both acquired drug resistance and TB transmission. Although the SHINE trial only enrolled children with non-severe TB (as defined) and without any suspicion of drug-resistant disease, this represents the vast majority of childhood TB cases in Australia. The excellent outcomes achieved are highly encouraging and country implementation is encouraged by the WHO.5 Paediatricians in Australia caring for children with TB are also keen to move to a four-month TB treatment regimen, where this is appropriate. One limitation to consider is that the study was not powered to assess differences in key sub-populations. Although initial sub-group analysis did not indicate any differences of concern, it seems prudent to await more study and operational data before recommending the four-month treatment approach in particular sub-populations. These include:

- children with extra-pulmonary TB other than uncomplicated peripheral lymph node disease (they were excluded from the trial);
- children living with human immunodeficiency virus (HIV) or with significant immune compromise (only 127 (11%) HIV-positive children were included in the trial); and
- adolescents (≥ 10 years of age) who are at greater risk of developing adult-type lung disease with cavities (which may initially be invisible on chest radiograph) and high bacillary loads (the median age of children included in the trial was 3.5 years; the number of adolescents (10 –< 16yrs) were not reported, but only 172 (14%) weighed 25 kg or more; there was also an over-representation of peripheral lymph node disease among adolescent children recruited).[i]

Despite these exclusions, most children diagnosed with TB in Australia (who generally have non-severe disease) would benefit from a shortened four-month treatment regimen. In general, it is important to limit unnecessary drug exposure in children, especially if they are unlikely to benefit from a longer treatment course. A shorter treatment course will also reduce family disruption, cost and complexity of care, and load on the health care system.

The WHO operational handbook encourages TB programmes to use the following age categories; child 0–9 years (generally less than 25 kg) and adolescent 10–19 years. Child-friendly water-dispersible fixed dose combination (FDC) tablets have been specifically developed for children < 25 kg. The child-friendly FDCs are available in parts of Australia, but are not on the Australian Therapeutic Goods Register and require a Special Access Scheme (SAS) pathway for administration. The child-friendly FDCs contain HRZ for the intensive phase and HR for the continuation phase of treatment, simplifying dosing of the new four-ethambutol (2HRZ/2HR) regimen. The addition of EMB is rarely required in children but should be considered as/when necessary. Adolescents (≥ 10 years of age) generally present with adult-type cavitary lung disease and high bacillary loads, which requires extra caution. Adolescents are old enough to provide an expectorated sputum specimen for microbiological diagnosis and to take adult tablets. They also display the same pharmacokinetics as adult patients. Therefore, although they require age-appropriate and individually tailored support,[6] adolescents with TB should generally be managed like an adult TB patient.

i Anneke Hesseling, personal communication.

Consensus statement (endorsed by NTAC and ANZPID)

In children aged between 3 months and < 10 years with non-severe TB (without immune compromise or suspicion of multidrug-, rifampicin, isoniazid, or pyrazinamide-resistant TB), a four-month treatment regimen (2HRZ(E)/2HR) should be used.

Non-severe TB is defined as peripheral lymph node disease (in isolation) or pulmonary TB confined to less than one lobe of the lung with no cavities, intra-thoracic lymph node involvement without radiologically visible or clinically significant airway obstruction, no signs of disseminated (miliary) TB and no complex pleural effusion. See the revised Diagnostic Atlas for Tuberculosis in Children for exemplars of radiological disease classification.[7]

The four-month treatment regimen can also be considered in children with minimal immune compromise or aged 10 –< 16 years, if non-severe TB is verified by an experienced clinician.

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