

7. Key recommendations

Recommendation 1

Given the risk of drug-induced hepatotoxicity, WHO recommends the following dosages of antituberculosis medicines for the treatment of tuberculosis in children:

isoniazid (H) – 10 mg/kg (range 10–15 mg/kg); maximum dose 300 mg/day
rifampicin (R) – 15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day
pyrazinamide (Z) – 35 mg/kg (30–40 mg/kg)
ethambutol (E) – 20 mg/kg (15–25 mg/kg)

(Strong recommendation, moderate-quality evidence)

Remarks

The panel noted the absence of high-quality evidence available to directly assess the risk of drug-induced hepatotoxicity using the new recommended dosages of antituberculosis medicines in children. However, the panel took account of:

- the long duration of clinical experience with these medicines for the treatment of tuberculosis in adults and children;
- a relatively large quantity of low-quality observational studies carried out in a variety of settings and paediatric populations that show no evidence of increased toxicity with dosages of these medicines;
- the potential risk of inefficacy of treatment if lower dosages are used;
- the risk of developing isoniazid resistance if lower dosages are used;
- the relationship between mean inhibitory concentration of the medicines in adults and efficacy outcomes;
- the development of metabolic pathways that increase the metabolism in young children;
- the high likelihood of reporting bias that would over-report the occurrence of hepatotoxicity.

Recommendation 2

Children living in settings where the prevalence of the HIV is high¹ or where resistance to isoniazid is high, or both, with suspected or confirmed pulmonary tuberculosis or peripheral lymphadenitis; or children with extensive pulmonary disease living in settings of low HIV prevalence or low isoniazid resistance, should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months at the following dosages:

isoniazid (H) – 10 mg/kg (range 10–15 mg/kg); maximum dose 300 mg/day
rifampicin (R) – 15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day
pyrazinamide (Z) – 35 mg/kg (30–40 mg/kg)
ethambutol (E) – 20 mg/kg (15–25 mg/kg)

(Strong recommendation, moderate-quality evidence)

¹ Defined as countries, subnational administrative units, or selected facilities, where the HIV prevalence among adult pregnant women is $\geq 1\%$ or among TB patients is $\geq 5\%$.

Recommendation 3

Children with suspected or confirmed pulmonary tuberculosis or tuberculous peripheral lymphadenitis who live in settings with low HIV prevalence or low resistance to isoniazid and children who are HIV-negative can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug (HR) regimen for 4 months at the following dosages:

isoniazid (H) – 10 mg/kg (range 10–15 mg/kg); maximum dose 300 mg/day
rifampicin (R) – 15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day
pyrazinamide (Z) – 35 mg/kg (30–40 mg/kg)

(Strong recommendation, moderate-quality evidence)

Recommendation 4

Children with suspected or confirmed pulmonary tuberculosis or tuberculous peripheral lymphadenitis living in settings with high HIV prevalence (or with confirmed HIV infection) should not be treated with intermittent regimens (that is, twice-weekly or thrice-weekly doses).

(Strong recommendation, low-to-moderate-quality evidence against the use of intermittent treatment in children)

Remarks

The panel noted that in the systematic review comparing intermittent dosing of medicines with the daily treatment regimens, there were no high-quality studies of intermittent (thrice-weekly) treatment regimens in children. There is some evidence that twice-weekly intermittent regimens are inferior to daily regimens in children. The metabolism of these medicines in children makes it more likely that intermittent regimens may result in inadequate exposure to the medicines, therefore increasing the risk of inefficacy. This evidence is supported by evidence from adult studies where adult patients using intermittent therapy have a higher risk of treatment failure and developing multidrug-resistant tuberculosis.

Recommendation 5

During the continuation phase of treatment, thrice-weekly regimens can be considered for children known to be HIV-uninfected living in settings with well-established directly-observed therapy (DOT).

(Weak recommendation, very low-quality evidence for use of intermittent treatment in children in specific settings)

Remark

The panel noted that, in some regions and countries, there is considerable clinical evidence of success using thrice-weekly intermittent regimens. Recommending changing the well-established practice may result in excluding children from DOT. However, this should only be considered in settings with a low HIV prevalence and a well-established DOT programme.

Recommendation 6

Infants (aged 0–3 months) with suspected or confirmed pulmonary tuberculosis or tuberculous peripheral lymphadenitis should be promptly treated with the standard treatment regimens, as described above.

(Strong recommendation, low-quality evidence)

Remarks

Treatment may require adjustment of dosages to reconcile the effect of age and possible toxicity in young infants. The decision to adjust dosages should be taken by a clinician experienced in managing paediatric tuberculosis.

The panel noted the very limited systematic clinical data describing treatment and outcomes of the treatment of tuberculosis in this age group. The panel took account of:

- the importance of treating tuberculosis in infants as a serious infectious disease with a high morbidity and mortality in this age group;
- the importance of commencing treatment with an effective treatment regimen as soon as the diagnosis of tuberculosis is suspected;
- the need for simplified treatment instructions for programmes dealing with these children.

Recommendation 7

Streptomycin should not be used as part of first-line treatment regimens for children with pulmonary tuberculosis or tuberculous peripheral lymphadenitis.

(Strong recommendation, moderate-quality evidence)

Remarks

The panel noted the low-to-moderate-quality evidence of the efficacy of streptomycin in children and took into account the risk of toxicity associated with the use of streptomycin. Also considered were problems with injection-based treatment regimens and the availability of safer, more effective and oral alternatives.

Streptomycin should be reserved for the treatment of multi-drug resistant tuberculosis in children with known drug susceptibility to this medicine.

Recommendation 8

Children with suspected or confirmed tuberculous meningitis should be treated with a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months; the total duration of treatment being 12 months. The dosages recommended for the treatment of tuberculous meningitis are the same as those described for pulmonary tuberculosis.

(Strong recommendation, low-quality evidence)

Remarks

The panel noted the following:

- there are many observational studies of the treatment of tuberculous meningitis in children, but these are of very low quality;
- the existence of a number of treatment guidelines recommending longer durations of treatment (between 9 months and 2 years);
- high mortality and morbidity associated with tuberculous meningitis (in particular grade 2 and grade 3 tuberculous meningitis);
- that 30% of children with a miliary picture on chest radiography have central nervous system involvement and should be treated with a 12-month regimen.

The panel recommended that the upper end of the recommended dosage range should be considered, given the uncertain penetration of antituberculosis medicines into the central nervous system.

Recommendation 9

Children with suspected or confirmed osteoarticular tuberculosis should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 10 months; the total duration of treatment being 12 months. The doses recommended for the treatment of osteoarticular tuberculosis are the same as those described for pulmonary tuberculosis.

(Strong recommendation, low-quality evidence)

Remarks

The panel noted that although the evidence is of low quality, the treatment regimens used in children were generally given for at least 12 months duration; the studies reported “no relapse” as the main outcome, although the duration of follow-up was often poorly reported. The panel took into account the pharmacological arguments to support the longer duration of treatment for infections of bones and joints and the lack of evidence to indicate an increased risk of toxicity associated with increased duration of treatment and the difficulty of determining cure in patients treated for osteoarticular tuberculosis.

Recommendation 10

Children with proven or suspected pulmonary tuberculosis or tuberculous meningitis caused by multiple drug-resistant bacilli can be treated with a fluoroquinolone in the context of a well-functioning MDR-TB control programme and within an appropriate MDR-TB regimen. The decision to treat should be taken by a clinician experienced in managing paediatric tuberculosis.

(Strong recommendation, very low-quality evidence)

Remarks

The panel noted the lack of long-term safety data for the use of fluoroquinolones in children and the paucity of evidence for their use in the treatment of tuberculosis in children. The panel considered indirect evidence from the treatment of cystic fibrosis and osteomyelitis, which indicated that longer-term use was not associated with an increased risk of joint abnormalities in children. Where arthralgia has been described in studies, it has been completely reversible. The panel took into account the

pharmacological arguments for the use of fluoroquinolones, such as their good penetration of tissue and oral bioavailability and predictable pharmacokinetics in children. The panel reached a consensus that in the context of multi-drug resistant tuberculosis, the benefits of treatment outweighed the risks.