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ORIGINAL ARTICLE

Updated WHO MDR-TB treatment guidelines and the use of new drugs in children

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Abstract

Little data is available on the occurrence of MDR-TB in children due to difficulty of bacteriological confirmation of drug resistance in this age group. However, the World Health Organization (WHO) recognizes the growing problem of MDR-TB in children and for the first time included child-specific recommendations for treatment of MDR-TB in the 2016 update of the Treatment guidelines for drug resistant tuberculosis. Preliminary reports are also becoming available on the use of delamanid in children. More research is needed to provide evidence for the use of new drugs in this age group.

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In the latest Global Tuberculosis Report, published in October 2016, the World Health Organization (WHO) estimates that in 2015, there were 10.4 million new (incident) TB cases worldwide, of which 5.9 million (56%) were among men, 3.5 million (34%) among women and 1.0 million (10%) among children. In 2015, there were an estimated 480 000 new cases of multidrug-resistant TB (MDR-TB[1]) and an additional 100 000 people with rifampicin-resistant TB (RR-TB) who were also newly eligible for MDR-TB treatment.

Little data is available on the occurrence of MDR-TB in children which reflects the fact that bacteriological confirmation of drug-resistant TB is more difficult in children than in adults and children are more likely to have a paucibacillary disease. In a recently published mathematic modelling study, Dodd et al estimate that in 2014, 58,000 children developed an isoniazid-monoresistant TB, 25,000 had MDR-TB and 1200 had XDR-TB[2].

In addition, the authors estimate that 67 million children are infected with *M. tuberculosis*, 5 million with isoniazid monoresistance, 2 million with MDR and 100,000 with XDR-TB[3]).

MDR-TB in children is mainly the result of transmission of a strain of *M. tuberculosis* that is MDR from an adult source case, and therefore often not suspected unless a history of contact with an adult pulmonary MDR-TB case is known[4].

When drug-resistant TB or MDR-TB is suspected in a child, every effort should be made to confirm the diagnosis by obtaining specimens for culture and DST. Rapid DST or rifampicin and isoniazid or Rifampicin alone is recommended over the conventional testing, results of which may take a long time to obtain. In all cases of confirmed MDR-TB, second-line DST should be performed to exclude XDR-TB[5].

In 2016, WHO published updated guidelines for treatment of drug resistant tuberculosis[6]. One of the key changes in this document from the previous edition is that specific recommendations are made on the treatment of children with rifampicin-resistant or MDR-TB. These treatment regimen recommendations are based on a first-ever meta-analysis of individual-level paediatric patient data for treatment outcomes. Where data on children were unavailable, evidence from adults was extrapolated to children, as there was no plausible biological reason to believe that these regimens are less effective in children than in adults.

Two types of regimens are now recommended by WHO for treatment of MDR- TB or RR-TB in children:

1. In patients with MDR/RR-TB who were not previously treated with second line-drugs and in whom resistance to fluoroquinolones and second-line injectable agents was excluded or is considered highly unlikely, a shorter MDR-TB regimen of 9 - 12 months may be used instead of the longer regimens (*conditional recommendation, very low certainty in the evidence).*

This shorter regimen is standardised with a possibility for limited modifications and consists of 4-6 months of the intensive phase of treatment with Moxifloxacin (or Gatifloxacin), Kanamycin, Prothionamide, Clofazimine, Pyrazinamide, high-dose Isoniazid and Ethambutol followed by 5 months of the continuation phase with Moxifloxacin (or Gatifloxacin), Clofazimine, Pyrazinamide and Ethambutol.

4-6 Km-Mfx-Pto-Cfz-Z-Hhigh-dose-E/5 Mfx-Cfz-Z-E

All data used to assess the shorter MDR-TB treatment regimen were derived from observational studies including a total number of 1205 observations. The analysis performed for the evidence assessment showed that patients who met specific inclusion criteria for receiving the shorter MDR-TB treatment regimen had a statistically –significant higher likelihood of treatment success than those who received longer, conventional regimens (89,9% *vs*. 78,3% respectively).

Patients who receive a shorter MDR-TB treatment regimen need to be monitored during treatment and after completion using schedules of relevant clinical and laboratory testing which have been successfully applied in the studies under field conditions[7]. The WHO framework for adctive TB drug-safety monitoring and management (aDSM) needs to be applied to ensure appropriate action to monitor and respond promptly to adverse events[8].

Continuous observational studies and clinical trials evaluating shorter MDR-TB treatment regimens are currently ongoing and are expected to provide higher quality of evidence as well as increased knowledge base for the effectiveness, efficacy and safety of these regimens, including new drugs.

2. In patients who are not eligible for a shorter MDR-TB regimen, a longer, conventional MDR-TB regimen for a total duration of 20 months[3] is prescribed as follows:

A regimen with at least 5 effective TB medicines during the intensive phase is recommended, including pyrazinamide and four core second-line TB medicines - one chosen from group A, one from group B, and at least two from group C[4] (*conditional recommendation, very low certainty in the evidence).*

The recommendations for children are mostly identical to those of adults. However, in children with mild forms of diseases, the harms associated with the group B medications (second-line injectable agents) outweigh potential benefits and therefore group B medications may be excluded in this group of children.

Figure 1 summarises the main factors to consider when deciding on the choice of the appropriate regimen in patients with MDR/RR-TB.

[1] MDR-TB - tuberculosis with strains resistant to Rifampicin and Isoniazid.
[2] XDR-TB - tuberculosis with strains resistant to Rifampicin and Isoniazid, a fluoroquinolone and one of the second-line injectable drugs.

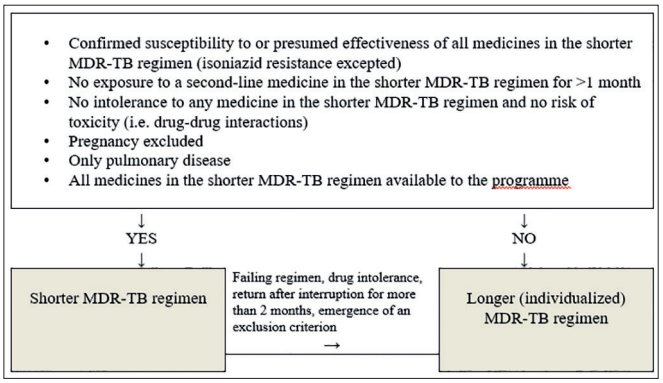

Figure 1. Factors to consider on the choice of the regimen in patients with MDR/RR-TB.

Use of new drugs in children

WHO issued two interim policy guidance on the use of new drugs in the treatment of patients with MDR-TB[9,10]. At the time of issuing these two interim policy guidance, treatment of children with new drugs was not recommended by WHO due to lack of evidence. However, the compassionate use programme of delamanid is available for children older than 6 years and reports have become available on treatment of children with delamanid with good safety and tolerability and with encouraging treatment response[11].

Recently, data describing safety, tolerability and pharmacokinetics (PK) of delamanid in children with MDR-TB aged 6 - 17 years became available in the middle of 2016. WHO reviewed this evidence and issued an interim policy guidance on the use of Delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents[12].

The clinicians treating children with MDR-TB may use delamanid following this recommendation: **WHO recommends that delamanid may be added to the WHO-recommended longer regimen in children and adolescents (6 - 17 years) with multidrug- or rifampicin-resistant TB (MDR/RR-TB) who are not available for the shorter MDR-TB regimen under specific conditions (*conditional recommendation, very low confidence in estimates of effect).***

The recommended dose of delamanid in children (aged 6 - 11 years) is 50 mg BID for 6 months, and in adolescents (12 - 17 years) it is 100 mg BID for 6 months. Patients who may benefit from delamanid are those of higher risk for poor outcomes (e.g. drug intolerance or contraindication, extensive or advanced disease); patients with additional resistance to fluoroquinolones or injectable second-line agents; or patients with confirmed XDR-TB.

[3] The duration may be modified according to patient's response to therapy.
[4] Group A - Levofloxacin, Moxifloxacin, Gatifloxacin; Group B - Amikacin, Capreomycin, Kanamycin (Streptomycin); Group C - Ethionamide or Prothionamide, Cycloserine or Teridizone, Linezolid, Clofazimine.

Because delamanid is shown to cause prolongation of the QT interval, children and adolescents with a QTcF > 500 msec should not receive the drug[12]. Studies are underway, however, currently there are no data on the effect of delamanid in children younger than 6 years of age and weighting under 20 kg. Bedaquiline is not recommended for the use of patients younger than 18 years as there is no data available and the manufacturer's programme for compassionate use excluded paediatric patients.

CONCLUSIONS AND RESEARCH NEEDS

MDR-TB in children is a recognized problem and treatment guidelines are now available from WHO. However, more evidence is needed on the use of new and repurposed drugs in children with MDR-TB, especially the identification of factors which determine the optimal duration of treatment for children; PK studies to determine optimal drug dosing and safety. Since prevention is much better than treatment, there is an urgent need for evidence guiding preventive chemotherapy for children and adolescents in contact with a confirmed MDR-TB in the household.

REFERENCES

1. World Health Organization. Global Tuberculosis Report 2016 [Internet]. Geneva: World Health Organization; 2016 [acesso 2017 Ago 31]. Disponível em: http://www.who.int/tb/publications/global_report/en/
2. Jenkins HE, Tolman AW, Yuen CM, Parr JB, Keshavjee S, Pérez-Vélez CM, et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. Lancet. 2014;383(9928):1572-9. PMID: 24671080 DOI: http://dx.doi.org/10.1016/S0140-6736(14)60195-1
3. Dodd PJ, Sismanidis C, Seddon JA. Global burden of drug-resistant tuberculosis in children: a mathematical modelling study. Lancet Infect Dis. 2016;16(10):1193-201. DOI: http://dx.doi.org/10.1016/S1473-3099(16)30132-3
4. Seddon JA, Schaaf HS. Drug-resistant tuberculosis and advances in the treatment of childhood tuberculosis. Pneumonia (Nathan). 2016;8:20. DOI: http://dx.doi.org/10.1186/s41479-016-0019-5
5. World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2nd ed. Geneva: World Health Organization; 2014.
6. World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis 2016 update. Geneva: World Health Organization; 2016.
7. du Cros P, Swaminathan A, Bobokhojaev OI, Sharifovna ZD, Martin C, Herboczek K, et al. Challenges and solutions to implementing drug--resistant tuberculosis programmes for children in Central Asia. Public Health Action. 2015;5(2):99-102. DOI: http://dx.doi.org/10.5588/pha.15.0007
8. World Health Organization. Active tuberculosis drug-safety monitoring and management (aDSM): Framework for implementation. Geneva: World Health Organization; 2015.

9. World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis. Interim policy guidance. Geneva: World Health Organization; 2013.
10. World Health Organization. The use of delamanid in the treatment of multidrug-resistant tuberculosis. Interim policy guidance. Geneva: World Health Organization; 2014.
11. Tadolini M, Garcia-Prats AJ, D'Ambrosio L, Hewison C, Centis R, Schaaf HS, et al. Compassionate use of new drugs in children and adolescents with multidrug-resistant and extensively drug-resistant tuberculosis: early experiences and challenges. Eur Respir J. 2016;48(3):938-43. DOI: http://dx.doi.org/10.1183/13993003.00705-2016
12. World Health Organization. The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents: Interim policy guidance. Geneva: World Health Organization; 2016.