EXPERT OPINION ON PHARMACOTHERAPY, 2017
VOL. 18, NO. 15, 1595–1606
https://doi.org/10.1080/14656566.2017.1373090

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REVIEW

Current therapies for the treatment of multidrug-resistant tuberculosis in children in India

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ABSTRACT

Introduction: Multidrug-resistant tuberculosis (MDR-TB) is a serious life threatening condition affecting children as well as adults worldwide. Timely diagnosis and effective treatment, both of which are complex in children, are the prerogatives for a favorable outcome.

Areas covered: This review covers epidemiology, treatment regimen and duration, newer drugs and adverse events in children with MDR-TB. Special note has been made of epidemiology and principles of treatment followed in Indian children.

Expert opinion: High index of suspicion is essential for diagnosing childhood MDR-TB. If there is high probability, a child can be diagnosed as presumptive MDR-TB and started on empiric treatment in consultation with experts. However, every effort should be made to confirm the diagnosis. Backbone of an effective MDR-TB regimen consists of four 2nd line anti-TB drugs plus pyrazinamide; duration being 18–24 months. The newer drugs delamanid and bedaquiline can be used in younger children if no other alternatives are available after consultation with experts. Wider availability of these drugs should be ensured for benefit to all concerned. More research is required for development of new and repurposed drugs to combat MDR-TB. Children need to be included in clinical trials for such life-saving drugs, so that nobody is denied the benefits.

ARTICLE HISTORY
Received 31 March 2017
Accepted 25 August 2017

KEYWORDS
MDR-TB; 2nd line anti-tubercular therapy; children; bedaquiline; delamanid

1. Introduction

Globally, an estimated 3.9% of new tuberculosis (TB) cases and 21% of previously treated cases have multidrug-resistant TB (MDR-TB). In 2014, only 50% of MDR-TB patients who were identified and started on appropriate treatment were successfully treated and an estimated 190 000 people died of MDR-TB. As of 2015, extensively drug-resistant TB (XDR-TB) had been reported by 117 countries. An estimated 9.5% of people with MDR-TB develop XDR-TB [1].

Pediatric data on MDR-TB are not very well documented. Dodd PJ et al., used mathematical modeling to estimate the global burden of MDR TB in children. According to the authors' estimate, a median (IQR) 6.9% (6.6–7.1) of incident TB disease in children was isoniazid (INH) mono-resistant and 2.9% (2.7–3.1) was MDR. Of MDR TB in children, a median (IQR) 4.7% (4·3–5·1) was estimated to be XDR TB [2].

In India, the 2016 annual report of the revised national tuberculosis control program (RNTCP), reported MDR-TB among new pulmonary cases to be 2.2% (95% CI: 1.9–2.6%) [0.024 (95% CI: 0.021–0.029) millions] and 15% (11–19%) [0.047 (0.035–0.059) millions] among retreatment pulmonary cases [3] Data on children with MDR TB are limited. A cross-sectional hospital-based study from Mumbai in 2012 reported the incidence of drug-resistant TB (DR-TB) in children to be 6.8% (34 out of 500 children studied) [4]. In a study on presumed pediatric MDR-TB cases (n = 312) from Delhi, valid line probe assay results were available in 198 samples. Out of the 198 valid tests, 49 (24.7%) were confirmed to be MDR-TB, whereas 73 (36.9%) were either INH or rifampicin mono-resistant [5]. In a cohort of 403 Indian children from Delhi with probable pulmonary TB, 5.6% were found to be harboring MDR-TB [6]. Another paper from Delhi reported resistance to one or more 1st line anti-TB drugs in 20.5% children [7]. In a pilot project providing Xpert MTB/RIF to pediatric patients across the country, out of 8,370 pediatric presumptive TB cases, 614 cases were positive by Xpert MTB/RIF and 60 of these positive cases were found to be rifampicin resistant [8]. A retrospective study which evaluated the children referred to a tertiary care center in Mumbai during the period 2007–2013, reported the overall resistance of DR-TB to be 6.6% (86/1311), with an increasing trend of 5.6% (23 children) before 2010 to 7% (63 children) after 2010 [9]. The same study also observed an increasing resistance to 2nd line anti-TB drugs, especially fluoroquinolones [9/23 before 2010 to 59/63 after 2010] and ethionamide [6/23 children before 2010 to 31/63 after 2010]. A study from Chennai reported the incidence of MDR-TB to be 11.8% (2/17) as diagnosed by polymerase chain reaction (PCR)-based DNA sequencing [10].

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Article highlights

- MDR-TB is a serious problem affecting children all over the world today.
- In children, high index of suspicion is needed for diagnosing MDR-TB. Because of the paucibacillary nature of the disease and difficulty in obtaining appropriate specimens, many a times MDR-TB cannot be confirmed. However, in the presence of active TB not responding to 1st line ATT, with history of contact with confirmed or suspected case of MDR-TB, empiric treatment may be started. Every effort should be made to confirm the microbiological diagnosis of TB and resistance.
- Rapid diagnostic tests for confirmation of *Mycobacterium tuberculosis* in clinical samples and detection of resistance to rifampicin, INH, fluoroquinolones and second line injectables should be widely available and used for the timely diagnosis of MDR-TB in children, so that initiation of appropriate treatment is not delayed.
- An effective MDR-TB regimen consists of at least 5 drugs: four 2nd line anti-TB drugs which are likely to be effective and pyrazinamide.
- Delamanid can be considered from 3 years onwards after consulting with experts. Similarly, bedaquiline can be considered 12 years onwards on a case to case basis.
- Strict monitoring of adverse events is essential while a child is on 2nd line ATT.

This box summarizes key points contained in the article.

Definitions

Multidrug-resistant tuberculosis (MDR-TB): MDR-TB is defined as tuberculosis caused by strains of *Mycobacterium tuberculosis* (MTB) which are resistant, *in vitro*, to at least isoniazid and rifampicin.

Mono-resistant TB: Resistance of the clinical isolate to only one first line antitubercular drug.

Rifampicin-resistant tuberculosis (RR-TB): Resistance of the clinical isolate to only rifampicin without resistance to other antitubercular drug.

Poly-resistant TB: Resistance of the clinical isolate to more than one first-line antitubercular drugs other than both isoniazid and rifampicin.

Extensively drug resistant TB (XDR-TB): In addition to multidrug resistance, if there is resistance to one fluoroquinolone and any of the second-line injectable (SLI) drugs (amikacin, kanamycin, capreomycin), the case is referred to as extensively drug-resistant TB (XDR-TB).

2. When to suspect MDR-TB?

Confirmed MDR-TB refers to cases of active TB where the microbiological isolate is resistant to rifampicin and INH as evidenced by phenotypic or genotypic testing methods.

MDR-TB is suspected in the following situations [11]:

(1) Close contact with a person known to have MDR-TB, including household and school contact
(2) Failure to improve clinically after 2–3 months of first-line TB treatment, including persistence of positive smears or cultures, persistence of symptoms, and failure to gain weight (radiological improvement is frequently delayed)
(3) History of antitubercular treatment within the past 6–12 months
(4) Close contact with a person who has died from TB, failed TB treatment, or is non-adherent to TB treatment

The term 'presumptive MDR-TB' is used to describe the cases which fulfill any of the above-mentioned conditions. Every attempt should be made to microbiologically confirm drug resistance in such patients. However, in many instances microbiological confirmation of drug resistance may not be available.

3. When to start treatment?

Conventionally, MDR-TB regimen is initiated when the drug susceptibility testing (DST) shows resistance to rifampicin and INH. However, in the pediatric population microbiological confirmation may not always be available, even in cases with high index of suspicion of MDR-TB. In cases where microbiological confirmation of drug resistance is not available, if the child is clinically unstable (temperature >40°C, hypoxia, respiratory distress, hemoptysis, severe anorexia, indicators of meningeal or disseminated TB) or there is high index of suspicion for drug resistance, a diagnosis of presumptive DR-TB may be made and *empiric 2nd line antitubercular therapy (ATT)* may be started while awaiting the culture and DST results. If the DST results are not available, empiric treatment may be followed for the whole duration.

4. Where to treat?

At present, ambulatory care for MDR-TB patients is preferred. Hospitalization may be required for initial stabilization of the patients if critically ill.

5. What regimen to start?

Standardized regimen for MDR-TB treatment is designed according to the drug-resistance surveillance data of the region and can be used before the results of DST of the patient is available. *Individualized regimen* should be used once the patient's DST results are available. In case of children, the regimen can be designed according to the DST profile of the adult index case of MDR-TB, as strain concordance between the child contact and adult index case has been reported to be as high as 88% [12].

5.1. Principles of designing a MDR-TB regimen

Designing an effective treatment regimen is also challenging because of the scarcity of pharmacokinetic (PK)/pharmacodynamics (PD) data of the 2nd line anti-TB drugs in children, heavy burden of pills, unavailability of child-friendly formulations and non-inclusion of children in most of clinical trials involving newer drugs and regimens. Until recently, the 2nd line anti-TB drugs to be used in MDR-TB regimen were divided into five groups [13]. The latest World Health Organization (WHO) guidelines published in 2016, have re-classified the 2nd line antitubercular drugs in four groups according to their importance and efficacy in the MDR-TB regimen (Table 1) [14]. Whenever a MDR-TB is being designed, the following principles should be kept in mind:

(1) MDR-TB regimen should be composed of at least five drugs likely to be effective, including four core second-line drugs plus pyrazinamide.
(2) An anti-TB drug is considered 'likely to be effective' when [11]:

Table 1. Classification of drugs to be used in MDR-TB regimen as per WHO guidelines, 2016 [1].

Groups	Medicine
A. Fluoroquinolones	Levofloxacin Moxifloxacin Gatifloxacin
B. 2nd line injectables	Amikacin Kanamycin Capreomycin
C. Other core 2nd line agents	Ethionamide/prothionamide Cycloserine/terizidone Linezolid Clofazimine
D. Add-on agents	
	D1 Pyrazinamide Ethambutol High dose isoniazid
	D2 Bedaquiline Delamanid
	D3 PAS Imipenem-Cilastatin Meropenem Amoxicillin-clavulanate Thioacetazone

- The drug has not been used in a regimen that failed to cure the individual patient
- DST performed on the patient's isolate indicates that the Mycobacteria strain is susceptible to the drug
- There is no known resistance to drugs with high cross-resistance to the drug in question (e.g. between amikacin and kanamycin)
- The possible source case's isolate is not resistant to the drug.
- Drug-resistance surveillance data demonstrates that resistance is rare to the drug in patients from that region with similar TB history.

(3) Amongst the four core drugs, one should be from group A (fluoroquinolones), one from group B (SLI) and at least two from group C (other core 2nd line agents) (Table 1).
(4) If a minimum of four core second-line TB medicines cannot be reached by using agents from groups A to C alone (Table 1), drugs from group D2 or group D3 are added.
(5) Pyrazinamide is added routinely unless there is confirmed resistance from reliable DST, or well-founded reasons to believe that the strain is resistant, or there is risk of significant toxicity. If pyrazinamide is compromised or cannot be used, the regimen may be strengthened with an additional agent from group C or D (preferably D2, or if not possible, from D3).
(6) Other agents from group D1 are added if they are considered to have added benefit (e.g. high-dose INH in patients with low-level INH resistance or inhA promoter region mutations.). High-dose INH refers to a dose range of 15–20 mg/kg/day. The total number of TB medicines included in the regimen need to balance expected benefit with risk of harms and non-adherence when the pill burden is high.
(7) All the drugs should be dosed at the higher end of the dosing range.

Some case reports on Indian children with MDR- or partial XDR-TB (MDR-TB with resistance to either fluoroquinolone or SLI) have outlined the same principles of treatment [15–17].

5.2. Individual drugs

Dosages for children are usually based on body weight and are generally extrapolated from adult data. However, PK for children, especially young children, is likely to be different from that of adults. During their growth and development, children experience considerable changes in their ability to absorb, distribute, metabolize, and excrete antibiotics. Not only are there obvious changes in body weight and length, but the relative contributions of water, fat, and protein also change, as do the relative size of the organs such as the liver and kidneys that play a major role in xenobiotic metabolism and excretion [18]. Furthermore, there is an increasing appreciation that the development of drug absorption and metabolizing enzyme systems is a dynamic process that is itself often subject to various maturational processes and polymorphic genetic influences [19,20]. Therefore, with the same dose per kg body weight, children may not attain serum drug concentrations of ATT comparable to adults.

5.2.1. Fluoroquinolones

This group of drugs has strong anti-TB activity – functions by inhibiting the DNA gyrase (topoisomerase II) of the bacteria. They can act on intracellular and dormant bacteria; they play an important role in achieving sterilizing cure [21]. Among the fluoroquinolones, the antimycobacterial activity is highest for moxifloxacin followed by levofloxacin and then ofloxacin, as evidenced by animal studies [22]. Use of gatifloxacin is not advised because of the many serious side effects such as dysglycemia [23]. Ciprofloxacin has hardly any anti-TB activity and should not be considered here [14,24]. Though moxifloxacin has been proved to have the maximum anti-TB activity amongst the fluoroquinolones [21,24], the safety profile of moxifloxacin in children has not yet been established. The cross-resistance between the fluoroquinolones have not been well established, hence if there is resistance to an older-generation fluoroquinolone, a newer-generation fluoroquinolone can be used in the MDR-TB regimen [13]. It is advisable to get DST done for the fluoroquinolone which is being used for the patient.

Data on PK of levofloxacin or moxifloxacin in children with MDR-TB are scarce. A study on 22 children receiving either treatment or prophylaxis for MDR-TB noted that the serum concentrations of levofloxacin, at a dose of 15 mg/kg, were lower than those observed in adults at the same dosage [25]. Another study on 23 children receiving moxifloxacin as part of MDR-TB regimen at a dose of 10 mg/kg/day, noted that serum concentrations of moxifloxacin achieved in children were lower than the adults receiving comparable dosage [26]. Inter-patient variability of levofloxacin is also a concern while deciding on the optimal dosage the drug. There are no prospective PD studies in children to determine the optimal

concentration target of fluoroquinolones in children with MDR-TB. A recent study utilizing Monte Carlo simulations have suggested using a higher dosage of moxifloxacin at 20 mg/kg/day to achieve the target area under curve (AUC_{0-24})/minimum inhibitory concentration (MIC) >122 [27].

There have been concerns regarding the use of fluoroquinolones in children due to the reports of arthropathy in animal models [28]. However, use in the pediatric population has not demonstrated any serious adverse events [29].

5.2.2. Second-line injectable (SLI)

Streptomycin is not considered as a 2nd line anti-TB drug, because of the high rate of resistance to it, and is not included in the MDR-TB regimens. Any of the injectables (kanamycin, amikacin, capreomycin), considered as SLI should be included in the intensive phase of the MDR-TB regimen. Kanamycin and amikacin act by inhibiting the bacterial protein synthesis. Capreomycin also inhibits protein synthesis of susceptible bacteria, but unlike the aminoglycosides, the site of action is the 70S subunit of ribosome and not the 30S subunit. Kanamycin and amikacin are cheaper than capreomycin. There is high cross-resistance between amikacin and kanamycin, less so with capreomycin; the cross-resistance between aminoglycosides and capreomycin is in the range of 70–80% [30]. Hence, if there is documented resistance to kanamycin or amikacin, capreomycin can be used instead. If there is resistance to all three SLI, streptomycin can be considered (if DST results show the mycobacterial isolate to be sensitive to streptomycin) as there is little cross-resistance between streptomycin and the other three group B drugs. These drugs are usually given intramuscularly, can be given intravenously for variable periods depending on the available intravenous access.

Irreversible ototoxicity with these drugs is a serious issue and needs careful monitoring. It has been demonstrated in animal models and adult PK/PD studies that the cumulative dose of the drug and the AUC is predictive of sensorineural hearing loss, rather than the maximum concentration achieved (C_{max})and dosing strategy (intermittent vs. daily) [31]. The incidence of ototoxicity increases sharply after 6 months of use [32]. The hearing loss starts from frequencies higher than the usual speaking range; hence audiometry (including frequencies higher than 8000 Hz) is better suited than clinical monitoring for early detection of ototoxicity [33]. Amikacin may have more potential for hearing loss than kanamycin. There is some evidence to suggest that capreomycin has less ototoxicity than amikacin [34]. A retrospective study on a Namibian cohort of adult MDR-TB patients showed that odds ratio of developing hearing loss with amikacin was 4.0 (95% CI: 1.5–10.8) as compared to kanamycin in similar setting [35].

5.2.3. Ethionamide

Ethionamide and prothionamide have similar efficacy and safety profile and so only one of them should be used. They are both prodrugs which are activated by the mycobacterial ethA; they inhibit the mycolic acid synthesis by targeting *inhA*. Hence, in cases of *inhA* promoter region mutations, there may be cross-resistance between INH and ethionamide. Ethionamide and para-aminosalicylic acid (PAS) should be used together only if strongly indicated as they both share toxicity profile and can cause gastrointestinal disturbances and hypothyroidism.

Ethionamide is one of the most commonly used oral second-line antitubercular drugs from group C. In a study conducted by Thee et al., on 31 children (<12 years of age) receiving ethionamide in doses of 15–20 mg/kg/day, maximum serum concentration (C_{max}) achieved ranged from 3.79 µg/mL to 5.44 µg/mL at 1 month of therapy and time taken to reach C_{max}(T_{max})was 0.97–2 h in different age groups. C_{max} and T_{max} were lower in younger age group, otherwise the concentrations achieved were comparable to adults receiving the same dosage [36].

5.3. Cycloserine

Cycloserine is basically the analog of d-alanine. It is bacteriostatic in action; main mechanism of action being inhibition of cell wall synthesis by competitive inhibition of alanine racemase and d-alanine-d-alanine ligase [37]. Neuropsychiatric side effects of cycloserine are mediated by NMDA receptors; they are usually dose and concentration dependent [38] A systematic review on treatment outcome of MDR-TB in children reported adverse events related to cycloserine in only 6 out of 182 children [39]. Peripheral neuropathy associated with cycloserine is probably due to antagonism of pyridoxine metabolism; supplementation of pyridoxine is hence recommended with the use of cycloserine.

5.4. Linezolid

Linezolid is an oxazolidinone class of antibiotics; it acts by inhibiting the initiation of protein synthesis [40]. The novel mechanism of action and lack of cross-resistance to other antitubercular drugs has led to the consideration of linezolid as an important component of the armamentarium against MDR-TB. Based on the review of available evidence, linezolid has now been placed in group C by WHO. However, the toxicities such as anemia, thrombocytopenia, peripheral neuropathy, and optic neuritis should always be kept in mind. Anemia is suggested to be due to inhibition of mitochondrial protein synthesis leading to myelosuppression. Thrombocytopenia probably is immune mediated [41]. Though PK/PD studies of linezolid on children with TB are lacking, a Monte Carlo simulation study by Srivastava et al. has suggested that a dose of 10 mg/kg in babies over 3 months of age is adequate to achieve the targeted AUC_{0-24}/MIC ratio [27].

5.4.1. Clofazimine

Clofazimine is a riminophenazine antibiotic which is being repurposed as an antitubercular drug. Until recently, it was primarily used against *M. leprae*. However, now clofazimine has been shown to be a drug with good sterilizing action in cases of MDR-TB. Multiple mechanism of actions have been proposed for the antitubercular effect of clofazimine; it influences the intracellular redox cycling pathways leading to accumulation of reactive oxygen species, may reverse the effects of *M. tuberculosis* on phagocytic killing mechanism, act synergistically with

interferon-gamma and also cause membrane destabilization [42–45]. It has been currently included in Group C drugs, that is, other core second-line drugs, in guidelines published by WHO in 2016 [14]. Clofazimine can cause darkening of skin color which should be kept in mind; this possibility of change in skin color must be informed to the caregivers and patient before putting the patient on this drug. A meta-analysis of cohort studies on use of clofazimine in treatment of MDR and XDR-TB reported the pooled proportion of serious adverse events requiring discontinuation of the drug to be only 0.1% (95% CI: 0.0–0.6%) [46]. The availability and high cost of clofazimine do remain a cause of concern.

5.4.2. Para-aminosalicylic acid (PAS)

PAS is now relegated as other 2nd line antitubercular drugs as per the 2016 MDR-TB treatment guidelines of WHO and is to be added to the regime if the required number of likely to be effective drugs cannot be attained from the other groups [14]. Adverse events to PAS including gastrointestinal disturbances such as diarrhea, nausea often makes it a difficult medication to adhere to. The use of granular slow-release PAS has improved tolerance. There is some debate regarding the dosing interval of PAS. A study on HIV-infected as well as HIV-uninfected adults showed that the free trough concentration remained above the targeted MIC for >90% of dosing interval when 4 g every 12 hourly dosing schedule was used. With 8 g once-daily dosage, the trough concentration was not above the MIC [47]. Another report published by the same researchers also state that the percentages of time above MIC over the 24-h interval was lower in the 8 g once-daily dosing schedule as compared to 4 g twice daily schedule [48]. A recent review on the use of PAS has suggested that once-daily dose of 15 g of PAS will achieve higher maximum concentration and may aid in preventing resistance in accompanying drugs [49].

In a study comprising 10 children, mean C_{max} in children receiving PAS at 75 and 150 mg/kg doses, were 45.40 and 56.49 µg/ml, respectively. $AUC_{0\text{-}12}$ was 233.3 and 277.9 µg*h/ml, respectively. A dosage of 150 mg/kg (as single dose or divided in two doses) in children was found to be equivalent to 4 g twice-daily dosage in adults [50].

5.4.3. Carbapenem and clavulanate

Carbapenems are a group of drugs repurposed for treatment of MDR-and XDR-TB; they are included in the group D3 of new WHO classification of 2nd line drugs and are to be used only when a regimen cannot be compiled otherwise [14]. The drugs included in this group are ertapenem, meropenem, and imipenem-cilastin. WHO recommends that carbapenems and co-amoxiclav should be used together in a regimen [14]. The need for parenteral administration and the doubtful efficacy against *M. tuberculosis* make these drugs add-on agents and not core components of the MDR-TB regimen. There are some observational studies outlining the use of these drugs in children which have reported tolerability and acceptable safety profile when used for XDR-TB [51–53].

The dosage and adverse events associated with the 2nd line antitubercular drugs are described in Tables 2 and 3.

Table 2. Dosage of the 2nd line antitubercular therapy in children [13].

Drug	Daily dose, mg/kg/day	Dosing interval	Maximum daily dose in mg
Kanamycin	15–30	OD	1000
Amikacin	15–30	OD	1000
Capreomycin	15–30	OD	1000
Moxifloxacin	7.5–10	OD	200
Levofloxacin	<5 years: 15–20, >5years: 10–15	BD OD	500
Ethionamide	15–20	BD	1000
Cycloserine	10–20	BD	1000
PAS	200–300	BD/TDS	12g
Linezolid	<10 years: 20 ≥10 years: 300 mg	BD OD	600
Clofazimine	2–3	OD	200
Co-amoxyclav	80 (of amoxicillin)	BD	4 g of amoxycillin
Meropenem	20–40	TDS	6000
High dose isoniazid	15–20	OD	900

Vitamin B6 (pyridoxine) should be given to all MDR-TB patients receiving cycloserine, high dosage of INH or linezolid to prevent neurological side effects. Usual dose used is 1–2 mg/kg/day.

6. Duration of treatment

The usual duration of a conventional regimen for MDR-TB is 18–24 months. The intensive phase consisting of the SLI drug is usually of 6–9 months; 6 months of intensive phase being effective in most cases. In case the child is culture positive to begin with, there should be at least 12 months of treatment after the last positive culture/smear with minimal disease or 18 months with extensive disease [54].

Example of a standardized MDR-TB regimen:
Any drug still likely to be susceptible from Group D1 (pyrazinamide has to be added) + one injectable from Group B + one fluoroquinolone from Group A + 2 drugs from Group C
Group D2 and D3 drugs to be added only if designing a regimen is otherwise not possible.
If patients are started on the basis of rifampicin resistance detected by Xpert MTB/RIF, INH may be included in the MDR regimen until DST to INH can be done to determine if the INH should be continued.
Thus, MDR regimens should include at least pyrazinamide, a fluoroquinolone, an injectable anti-TB drug, ethionamide and cycloserine.
e.g. Inj kanamycin (6–9 months) + pyrazinamide + ethambutol + levofloxacin + ethionamide + cycloserine

6.1. Shorter duration of MDR-TB treatment regimen

Shorter MDR-TB regimen is being studied in adult MDR-TB patients; this regimen is of 9–12 months' duration and the drugs to be given are 4–6 months of 7 drugs (kanamycin, moxifloxacin, ethionamide, clofazimine, pyrazinamide, high-dose INH, ethambutol), followed by 5 months of 4 drugs (moxifloxacin, clofazimine, pyrazinamide, and ethambutol). WHO, in the latest guidelines in 2016, suggests that the same principle can be extrapolated from adults to children. Children with MDR-TB/rifampicin-resistant TB (RR-TB) in whom

Table 3. Adverse events associated with the 2nd line antitubercular therapy in children.

Drug	Common adverse events	Rare adverse events
Kanamycin Amikacin Capreomycin	Nephrotoxicity, Ototoxicity (hearing loss), Vestibular toxicity (vertigo, ataxia, dizziness), Electrolyte abnormalities, including hypokalemia, hypocalcaemia, and hypomagnesaemia.	Neuropathy, Rash
Moxifloxacin Levofloxacin	Nausea and bloating, Headache, dizziness, insomnia or tremulousness	Tendon rupture, Arthralgia, QT prolongation, hypoglycemia
Ethionamide	Gastrointestinal upset and anorexia, metallic taste, hepatotoxicity; Endocrine: Gynecomastia, alopecia, acne, impotence, menstrual irregularity, and reversible hypothyroidism; Neurotoxicity	
Cycloserine	CNS toxicity: inability to concentrate, lethargy, seizures, psychosis, suicidal ideation; Peripheral neuropathy; Dermatological changes: eruptions and Stevens–Johnson syndrome.	
PAS	Gastrointestinal symptoms, Hypothyroidism – reversible	Hepatotoxicity, coagulopathy
Linezolid	Myelosuppression; Diarrhea and nausea; Optic and peripheral neuropathy (irreversible); Lactic acidosis	
Clofazimine	Orange/red discoloration of skin, conjunctiva, cornea and body fluids; Dry skin, pruritus, rash, ichthyosis, xerosis; Gastrointestinal intolerance; Photosensitivity.	Retinopathy, Severe abdominal symptoms, bleeding and bowel obstruction; QT prolongation.
High-dose isoniazid	Hepatitis; Peripheral neuropathy; Hypersensitivity reactions.	Optic neuritis, arthralgias, CNS changes, drug-induced lupus, diarrhea, and cramping with liquid product.

the following exclusion criteria have been ruled out can be considered for the shorter regimen [14]:

(1) Previously treated with second-line drugs. Exposure to SLIs (like amikacin) and fluoroquinolones (like levofloxacin) which are not included in the shorter regimen, but may cause cross-resistance to the drugs used, is considered an exclusion criteria.
(2) Confirmed or suspected resistance to fluoroquinolones and/or SLI agents
(3) Intolerance to any of the drugs included in the shorter regimen
(4) Increased risk of toxicity to any of the drugs included in the shorter regimen
(5) Extrapulmonary TB

Observational studies in adults from multiple countries have shown that patients who met specific inclusion criteria for receiving the shorter MDR-TB treatment regimens had a statistically significant higher likelihood of treatment success than those who received longer conventional regimens (89.9 vs. 78.3%) when success was compared with treatment failure/relapse/death [55–57]. However, none of these studies have included children. Recently, there is a case report of 14-year-old boy from Karakalpakstan treated successfully with the shorter regimen [58]. Long-term follow-up data to reliably account for relapses have yet to be generated.

The major concern in implementing the shorter regimen in a country like India is the high level of existing resistance to the drugs included in the regimen (such as fluoroquinolones, ethionamide), the requirement of excluding resistance to all the drugs included in the shorter regimen and ensuring the continued availability of all the drugs in the shorter regimen [9,59]. The high incidence of extrapulmonary TB in children may also hamper the use of this regimen.

7. Monitoring

Regular monitoring of a child on MDR-TB regimen is essential for the following reasons [54]:

(1) To assess symptomatic improvement such as improvement in fever, cough, lymph node swelling.
(2) To assess nutritional improvement as in weight gain.
(3) To monitor bacteriological conversion by gastric lavage/induced sputum.
(4) To monitor for toxicities of the 2nd line ATT.

7.1. Suggested monitoring schedule

Table 4 illustrates a model monitoring schedule that can be adopted for a child on MDTR-TB regimen.

8. Use of steroids

Corticosteroids are to be used in certain conditions such as central nervous system TB, tubercular pericarditis, and airway compression due to tubercular lymph nodes [60]. A recent Cochrane review states that corticosteroids are beneficial in reducing mortality in patients with tubercular meningitis (TBM), though corticosteroids do not have any benefit in reducing the neurological disability associated with TBM [61]. A large randomized controlled trial demonstrated no significant difference in composite outcome of death, cardiac tamponade, or constrictive pericarditis between adult patients receiving prednisolone or placebo. However, the

Table 4. Suggested monitoring schedule for a child on MDR-TB regimen.

Parameters	Baseline	1 mo	2 mo	3 mo	4 mo	5 mo	6 mo	3 monthly thereafter
Clinical	✓	✓	✓	✓	✓	✓	✓	✓ (every month)
Anthropometry – weight	✓	✓	✓	✓	✓	✓	✓	✓ (every month)
Induced sputum/GA for culture#	✓	✓	✓	✓	✓	✓	✓	✓ (every month till culture conversion, then three monthly)
CXR	✓			✓			✓	✓ (at the end of therapy)
Toxicity monitoring	✓	✓	✓	✓	✓	✓	✓	✓ (every month)
SGOT/SGPT	✓			✓			✓	✓
Creatinine	✓	✓	✓	✓	✓	✓	✓	
Potassium	✓	✓	✓	✓	✓	✓	✓	
TSH, fT4*	✓			✓			✓	✓
Hb/TLC**	✓	✓	✓		✓		✓	✓
Audiometry***	✓	✓	✓	✓	✓	✓	✓	✓ (6 months after stopping injectable)
ECG##	✓	✓	✓	✓	✓	✓		
Vision****	✓	✓	✓	✓	✓	✓	✓	✓
HIV	✓							

GA: gastric aspirate; CXR: chest X-ray; SGOT: Serum glutamic oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase; TSH: thyroid-stimulating hormone; fT4: free T4 hormone; Hb: hemoglobin; TLC: total leukocyte count; HIV: human immunodeficiency virus; MDR-TB: multidrug-resistant tuberculosis.
*If on ethionamide/PAS; **if on linezolid; ***till on injectable second lines; ****if on ethambutol/linezolid; ##if on delamanid, bedaquiline, moxifloxacin or clofazimine; #if culture negative to begin with, repeat culture to be done if clinically indicated.

rate of constrictive pericarditis and hospitalization were lower in the group receiving prednisolone as compared to those receiving placebo. There was an increase in human immunodeficiency virus (HIV)-related cancers in the prednisolone group [62].

9. New drugs

We have already discussed about the drugs repurposed for use in MDR-TB, that is, linezolid, clofazimine, and carbapenems.

Two new drugs which have been endorsed by WHO for treatment of MDR-TB in select group of patients: bedaquiline and delamanid. Bedaquiline is approved by the US Food and Drug Administration (US FDA), whereas delamanid has been approved by European commission and in Japan and South Korea.

9.1. Bedaquiline

Bedaquiline is a member of the diarylquinoline group, with inhibitory activity against mycobacterial ATP synthase. It was first approved for use in MDR-TB by US-FDA in 2012 and recommended by WHO since 2013. It has been approved for use under the national program of India for a select group of adult patients in six public hospitals in Delhi, Mumbai, Chennai, Guwahati, and Ahmedabad under strict pharmacovigilance [60]. Phase II clinical trial is registered to determine PK of bedaquiline as part of regimen for MDR-TB in children [63]. As of now, WHO does not recommend the use of bedaquiline below 18 years of age [64,65]. However, the Sentinel Project on Pediatric Drug-Resistant Tuberculosis, a global conglomerate of TB researchers and clinicians, have proposed that bedaquiline can be considered in children ≥12 years under the following circumstances [66]:

(1) Resistance to SLIs and/or fluoroquinolones.
(2) Failing MDR-TB regimen.
(3) Significant intolerance to SLIs and/or fluoroquinolones.
(4) A four-drug regimen cannot be designed with the other available drugs.

In children <12 years of age, bedaquiline may be considered on a case-to-case basis after careful consideration by experts on childhood MDR-TB. However, in such cases delamanid is a better option [66].

The suggested dose for body weight 20–32 kg is 200 mg once a day for 14 days followed by 100 mg thrice weekly for a total duration of 6 months. For body weight above 32 kg, dosage are 400 mg once a day for 14 days followed by 200 mg thrice weekly for next 22 weeks [66]. Common adverse events recorded are nausea, arthralgia, headache, hepatotoxicity. QT prolongation is a serious adverse event, especially when coadministered with other anti-TB drugs with potential for QT prolongation like fluoroquinolones, especially moxifloxacin [67], and clofazimine. Before starting bedaquiline, a baseline ECG should be checked for normal QT; monthly monitoring thereafter is preferred.

If a HIV-positive child receiving efavirenz is started on bedaquiline, efavirenz should be replaced with nevirapine as efavirenz reduces the serum concentration of bedaquiline [68].

9.2. Delamanid

Delamanid, a nitro-dihydro-imidazooxazole, is a new addition in the fight against TB. The mechanism of action is incompletely understood; it probably acts by inhibiting mycolic acid synthesis [69]. The absorption of delamanid is better when administered with food. Data on safety, efficacy, and PK of delamanid in children are still forthcoming as number of clinical trials are in the process of recruiting patients and have not published their results [70,71]. Currently, only case reports and case series describing the efficacy and safety of delamanid in children are available. A case series published in 2016, describes 19 children administered delamanid on compassionate basis, 5 from India; interim outcome in the form of culture conversion was favorable in all children. Serious adverse event requiring stopping of delamanid was reported in one child [72]. The WHO interim policy recommendations (2016) states that delamanid may be added to background regimen for MDR-TB/RR-TB in children ≥6 years of age with >20 kg body weight under the following conditions [73]:

a. When the core regimen for MDR-TB with pyrazinamide and at least four 2nd line drugs deemed to be still effective cannot be completed either due to intolerance to drugs or resistance.
b. When there is resistance to fluoroquinolones and/or SLI.
c. Failing MDR-TB regimen with extensive disease (bilateral pulmonary involvement, cavities) – delamanid should not be the only agent added to a failing regimen.
d. Proper adherence can be ensured and monitored.
e. Proper pharmacovigilance for adverse events and drug–drug interaction is in place.
f. Informed consent has been taken from the parent/legal guardian of the concerned child.

For children between 3 and 6 years of age, the Sentinel Project on Pediatric Drug-Resistant Tuberculosis suggests that delamanid can be given after careful consideration by experts on a case-to-case basis [66]. Experts have also suggested that in view of the high rate of sensorineural deafness and local pain form the injectables, delamanid can be used to replace the injectables in the MDR-TB regimen [66].

The dose recommended for delamanid is 50 mg BD for age 6–11 years of age or 20–34 kg body weight and 100 mg BD for 12–17 years of age or >35 kg body weight, for 6 months (intensive phase) to be given after meals.

There should be a baseline ECG for QT monitoring and serum albumin levels available. Serious adverse event to be aware of is QT prolongation. Caution should be applied while combining delamanid with other drugs that have the potential of prolonging QT. There is no noted interaction of delamanid with the antiretroviral agents [74]. Hypoalbunemia may increase the potential of delamanid to prolong QT; albumin levels should also be monitored while prescribing delamanid [75].

10. Drugs in pipeline

In addition to bedaquiline and delamanid, there are few newer drugs that have shown some promise and are undergoing various phases of clinical trials. These drugs include pretomanid (class – nitroimidazole) and sutezolid (class – oxazolidinone), Q2O3, and TBA 354 [66]. All clinical trials of these drugs are in adult patients; no data on safety and efficacy in children have yet been generated. Pretomanid has been used in combination with moxifloxacin and pyrazinamide in phase III trial and was associated with high rates of hepatotoxicity. Sutezolid, has shown promising results till phase IIb trial as a companion drug; phase III trial is awaited. Q203 is still in early phase of development [76].

11. Adjunct immunotherapy

Interferon- gamma, IFN-γ (intramuscular, subcutaneous, aerosolized) [77,78], mesenchymal stromal cells [79,80], thalidomide [81] are some of the immunomodulators that have been or are being experimented with to improve the immune response in patients with DR-TB. However, further research and convincing inputs are required before any of them are included in the MDR-TB regimen in children.

12. Indications of surgery

Lung resection with adequate chemotherapy may be helpful in carefully selected patients (localized disease) in centers with adequate resources and expertise, as this may help in getting rid of the intractably pathological part and reduce the bacterial load needed to be eliminated. Adjunct resection surgery may also reduce the chances of relapses [82,83].

13. Extrapulmonary TB – central nervous system TB (CNS TB)

In case of CNS TB, some special considerations have to be kept in mind while designing the regimen:

(1) Drugs with good penetration into CSF: INH, pyrazinamide, prothionamide/ethionamide, cycloserine, linezolid.
(2) Drugs with variable penetration: fluoroquinolones (best – moxifloxacin).
(3) Drugs with penetration in the presence of inflamed meninges: kanamycin, amikacin, and streptomycin.
(4) Drugs with poor penetration: PAS and ethambutol.

14. Regimen for XDR-TB

A regimen for XDR-TB (with resistance to fluoroquinolones and SLI in addition to INH and rifampicin) is very complex and such patients should be treated in centers with experienced physicians available. Availability of SL-LPA (second line – Line Probe Assay) and reliable culture DST against second-line drugs will be required which are not easily available across India. The basic principles of treatment remain the same as for MDR-TB patients. To have at least 4–5 new drugs likely to be effective, drugs from group C and D are usually required including newer drugs such as linezolid, clofazimine, and delamanid. Choice of fluoroquinolones in XDR-TB is restricted due to resistance to one of the fluoroquinolones. In XDR-TB, standardized treatment regimen includes capreomycin for 6–12 months on the premise that the mycobacterial strain may still be susceptible to it [13,60]. The final designing of XDR-TB regimen should depend on the number of drugs that are likely to be effective in a particular patient.

15. Regimen for rifampicin-resistant TB

All TB patients infected with strains resistant to rifampicin should be treated using a full MDR-TB regimen, with or without INH depending on DST results. If *inhA* promoter region mutation is documented, high-dose INH can be given and ethionamide needs to be replaced with another drug.

16. HIV and MDR-TB

A systematic review published in 2015 states that the mortality in children with MDR-TB and HIV infection is twice as compared to the HIV-uninfected children with MDR-TB [84]. There are some special considerations to be kept in mind while managing HIV and MDR-TB coinfection [13,54].

- All children diagnosed with presumed or confirmed MDR-TB should be screened for HIV infection.
- Xpert MTB/RIF should be performed as the first line of investigation for microbiological confirmation and detection of rifampicin resistance in all children with probable TB and HIV infection.
- Starting MDR-TB treatment is the priority in HIV-infected children with MDR-TB who are antiretroviral therapy (ART) naïve.
- ART has to be started in all children receiving MDR-TB treatment irrespective of CD4 count, usually within 2–4 weeks of starting 2nd line ATT.
- Care has to be taken while planning the regimens, keeping in mind the drug interactions and overlapping toxicities of ART and ATT.
- Careful monitoring has to be done for overlapping toxicities such as drug rash (caused by most of the ART and ATT as well as co-trimoxazole), peripheral neuropathy (stavudine and INH, linezolid, cycloserine), central nervous system toxicities (efavirenz and cycloserine, INH), hepatotoxicity (most of the ART and pyrazinamide, INH, bedaquiline), gastrointestinal symptoms (most of ART and ethionamide, PAS), pancreatitis (stavudine and linezolid), renal toxicity (tenofovir and SLIs), bone marrow suppression (zidovudine and linezolid), and arthralgia (protease inhibitors and pyrazinamide).
- Important drug interaction that has to be considered include that of bedaquiline with efavirenz or protease inhibitors, delamanid and lopinavir/ritonavir.
- Stavudine and tenofovir should be avoided in children receiving 2nd line ATT.
- Maintaining adherence to treatment is important in HIV-infected children with MDR-TB as high pill burden and adverse events may prove as deterrent for the same.

17. MDR-TB regimen without injectables

The 2016 WHO update on management of MDR-TB [14] does suggest that in mild form of the disease, injectables can be removed from the MDR-TB regimen. However, more research is needed before we can do away with SLIs or replace them with newer drugs like delamanid. If fluoroquinolone resistance is demonstrated, an SLI certainly has to be included in the MDR-TB regimen.

18. Nutritional counseling

Nutritional status should be monitored at every visit for a MDR-TB patient and judicious nutritional advice regarding locally available, affordable food items should be provided [54].

19. Conclusion

MDR-TB is a serious problem in children which need to be handled with the same urgency as in adults. A high index of suspicion is required for diagnosing MDR-TB in children and in many a cases empiric treatment has to be started in the absence of bacteriological confirmation. Designing an appropriate regimen and monitoring adherence and adverse events are the keys to a successful outcome.

20. Expert opinion

MDR-TB in children is a serious problem which needs timely diagnosis and appropriate treatment. As bacteriological confirmation may not always be forthcoming, a high index of suspicion is required to diagnose MDR-TB in children. The diagnosis of MDR-TB and the indications of initiating 2nd line anti-TB drugs should be carefully redefined in national programs to include children in whom microbiological confirmation is not available. Cases of active TB with a history of contact with suspected or confirmed MDR-TB patient or failing first line of anti-TB treatment can be started on empiric 2nd line ATT. However, every effort should be made to confirm the microbiological diagnosis of TB and drug resistance.

Designing the appropriate regimen for a child with MDR-TB is a complex process. Issues of difference in PK from adults, heavy pill burden, lack of child-friendly formulations and dependence on caregiver for adherence are some of the problems that are encountered while constructing a MDR-TB regimen for children. Standardized regimens are good to begin with, but regimen should be individualized subsequently based on the respective DST results. One may also rely on the DST result of the adult MDR-TB source case as there is usually high concordance between the child contact and the adult source case in terms of susceptibility to anti-TB drugs.

The shorter duration MDR-TB regimen (9–12 months) holds promise, however, the patient selection has to be stringent and proper safety and efficacy data in children are warranted before accepting this regimen.

With the increased use of repurposed drugs like linezolid and clofazimine in childhood MDR-TB, more data and confidence have been generated regarding their safety and efficacy in such children. Current guidelines have categorized linezolid and clofazimine as core 2nd line anti-TB drugs, while relegating PAS as one of the other drugs which can also be used. PAS may still be a useful drug in the treatment of MDR and XDR-TB, as resistance to PAS is less likely to develop than to other 2nd line agents such as linezolid as PAS is not commonly used for any other infection.

Two new drugs have been approved for use in adult MDR-TB patients along with the background regimen – bedaquiline and delamanid. More data are available for use of delamanid in children; currently delamanid is recommended to be used in children above 6 years and ≥20 kg body weight. If required, delamanid can be used on a case-to-case basis in children between 3 and 6 years of age. Bedaquiline, on the other hand, has a more restricted utility in children. It can be considered for use in children older than 12 years of age only after deliberation by experts. Both these drugs have to be added to a background MDR-TB regimen and should never be a stand-alone drug added to a failing regimen. Careful monitoring should be done for cardiac abnormalities in the form of QT prolongation for both these drugs. Drug- drug interaction should also be kept in mind; other drugs with a potential of prolonging QT should be very cautiously added

with bedaquiline or delamanid. Wider availability of both the drugs is a prerequisite if the benefits are to be shared by all.

Vigilant monitoring for adverse events is essential while a child is on the 2nd line ATT.

Some newer drugs for TB are in the pipeline, but none that will be available for use in recent future. We need more focused research for newer and repurposed drugs for the treatment of MDR-TB. Also, steps should be taken to include children in these studies, so that we do not deny life-saving therapy to children.

Funding

A Mukherjee receives personal support from Wellcome Trust/India Alliance

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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