Review

Epidemiology and management of childhood multidrug-resistant tuberculosis

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Practice points

- Children with drug-resistant tuberculosis (TB) have disease caused by strains that are currently circulating in the community providing a vital opportunity for surveillance.
- Consider drug-resistant TB whenever a child has symptoms and signs of TB and: they have been in contact with a source case who has known drug-resistant TB; the child has failed first-line therapy to which the child was adherent; or the source case has died of TB, failed therapy or defaulted.
- Strive for a microbiological diagnosis in all children suspected to have multidrug-resistant TB using extensive sampling if necessary.
- Treat with at least four drugs known to have an effect against the likely drug-resistant mycobacteria.
- Treat with an injectable second-line TB drug for the first 4–6 months.
- Explain the risk of adverse events prior to starting therapy and at every follow-up appointment.
- If patients experience adverse events, manage them promptly and proactively.
- With appropriate care, the vast majority of children with multidrug-resistant TB can be successfully treated.

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SUMMARY: Multidrug-resistant tuberculosis (TB) in children is mainly caused by transmission of drug-resistant strains causing infection and disease (i.e., primary drug-resistant TB) and, therefore, follows adult multidrug-resistant TB trends. Diagnosis is made by culture and phenotypic or genotypic drug susceptibility testing, either from the child's or the adult source case's *Mycobacterium tuberculosis* isolate. Treatment is mainly with second-line anti-TB drugs, building a regimen with four effective drugs; the principles of management are the same as for adults. Monitoring for adverse events is important as second-line drugs are more toxic than first-line treatment. With early diagnosis and treatment, outcome is better than in adults. New drugs and drug combinations are in development and should also be evaluated in children.

Epidemiology

Multidrug-resistant (MDR) tuberculosis (TB) in children, especially in those less than 5 years of age, is usually primary (transmitted) MDR disease. However, older children and adolescents may develop cavitary, adult-type TB, which is associated with higher bacillary loads and more natural drug-resistant mutations. The mismanagement of TB in these children, either by the healthcare provider or the patient, may lead to the development of drug resistance (i.e., secondary drug resistance) in their mycobacterial isolates. With high bacillary loads, development of resistance through selective drug pressure is more likely compared with paucibacillary disease (as in young children); for example, the mutation rate *in vitro* of isoniazid is one in 10^6 bacilli compared with rifampin, which is one in 10^8 bacilli [1,2]. Isoniazid resistance mostly develops first. As most drug-resistant TB in children is transmitted or new drug resistance (i.e., patient received no previous anti-TB treatment or treatment for <1 month), surveillance of drug resistance in children is a good indicator of transmitted *Mycobacterium tuberculosis* strains that are currently circulating in a community [3,4]. This is confirmed by several studies, which have shown that drug-resistant TB trends in adult populations are soon followed by the same trends in children [5,6].

The WHO estimated 650,000 prevalent cases of MDR-TB (i.e., resistance to at least isoniazid and rifampin) worldwide in 2010 [101]. Children comprise 10–15% of the TB caseload in many high-burden settings [7]; this is likely the same proportion for MDR-TB. This means, in the absence of accurate figures for children with MDR-TB, an estimation of MDR-TB in children could be between 65,000 and 97,500 prevalent cases. Treated cases published in the literature show that MDR-TB in children is grossly under-reported, with just over 300 cases described in a recent systematic review that included case series of more than five childhood MDR cases [8]. Surveillance data for drug-resistant TB in children is also scarce and, due to the nature of childhood TB (paucibacillary disease and difficulty obtaining specimens for microbiology), surveys are mainly limited to hospital settings where specimens can be obtained and drug susceptibility testing (DST) performed. Continuous surveillance data in one such setting, the Western Cape of South Africa, has shown an upward trend of MDR-TB in children from 5.4% during 2003–2005 to 8.9% during 2007–2009 (2-year periods) [9]. Other reported surveys of drug-resistant TB in children, published after 2000, are summarized in **Table 1**.

Extensively drug-resistant TB (XDR-TB; i.e., MDR-TB plus resistance to the fluoroquinolones and at least one of the second-line injectable drugs) has emerged with an even worse outcome than MDR-TB. Poor management of MDR/XDR-TB in adults and then transmission of this form of TB has been increasingly reported and, although only few cases have been described, children have not escaped this epidemic [10–12].

Another important and emerging form of drug-resistant TB is rifampin-resistant, isoniazid-susceptible (mono- or poly-rifampin-resistant) TB. Isoniazid monoresistance is traditionally considered the gateway to MDR-TB, but rifampin-resistant isoniazid-susceptible *M. tuberculosis* strains are increasing [13]. Due to the higher natural mutation rate of isoniazid compared with rifampin, these strains can more

Table 1. Results of antituberculosis drug resistance surveys among childhood tuberculosis cases reported after 2000.

Continent/country	Time of survey	Number of children (n)	Any drug resistance, n (%)	Isoniazid resistance, n (%)	Multidrug resistance, n (%)	Ref.
Africa						
Central African Republic	April 1998–June 2000	190 (DST in 165)	25 (15.2)	15 (9.1)	1 (0.6)	[70]
Egypt	NA	150 (DST in 73)	18 (24.7)	4 (5.4)	2 (2.7)	[71]
Madagascar	1997–2000	97	1 (1)	1 (1)	0	[72]
Madagascar	October 2005–July 2007	17 (DST in 14)	0	0	0	[73]
South Africa	March 2003–February 2005	320	41 (12.8)	41 (12.8)	19 (5.9)	[74]
South Africa	March 2005–February 2007	291 (DST in 285)	43 (15.1) – only isoniazid and rifampin	41 (14.4)	19 (6.7)	[4]
South Africa	March 2007–February 2009	294 (DST in 292)	45 (15.4)	41 (13.9)	26 (8.9)	[9]
South Africa	2008	204 (DST in 148)	23 (15.5)	21 (14.2)	13 (8.8)	[75]
Americas (North & South)						
USA	1993–2001	2432	NA	178 (7.3)	32 (1.3)	[76]
Colombia	2001–2009	123	NA (21.1)	NA	NA (6.5)	[77]
Peru	2005–2006	64	14 (21.9)	NA	2 (3.1)	[78]
Asia						
India	1996	201	NA	NA (10)	NA (3.5)	[79]
Thailand	2005–2006	41 (DST in 33)	NA	NA	1 (3)	[80]
Europe						
England and Wales	1999–2006	837	NA	78 (9.3)	19 (2.3)	[81]
Greece	1994–2004	77	16 (20.8)	12 (15.6)	3 (3.9)	[82]
Norway	1998–2009	19	5 (26.3)	5 (26.3)	0	[83]
Sweden	2000–2009	79	28 (35)	15 (19)	4 (5.1)	[84]

DST: Drug susceptibility testing; NA: Not available.
Data taken from [34].

rapidly progress to MDR-TB. In recent studies in the western Cape of South Africa, rifampin-resistant isoniazid-susceptible TB in both adults and children are increasing [14,15]. Data from 14 supranational TB reference laboratories worldwide demonstrated that the proportion of rifampin-resistant isoniazid-susceptible isolates by phenotypic DST varied widely (0.5–11.6%), but that the general rate was high [13]. In the same report, preliminary results of TB surveillance data from the USA indicate that 22% of reported rifampin-resistant isolates are isoniazid-susceptible. The development of new rapid diagnostic tools based on gene mutation analysis such as line-probe assays (LPAs) and GeneXpert may lead to misclassification of resistance if phenotypic DST is not carried out to determine isoniazid resistance. LPAs may falsely increase the number of rifampin-resistant isoniazid-susceptible cases, as isoniazid resistance may be missed. GeneXpert MTB/RIF results are frequently used as a surrogate for MDR-TB, thus underestimating rifampin-resistant isoniazid-susceptible TB. The latter assay will also miss all isoniazid-monoresistant isolates.

Diagnosis of drug-resistant TB in children

The diagnosis of drug resistance in childhood TB is dependent on microbiological investigations of specimens obtained either from the child or the source case likely to have infected the child [16]. A definite diagnosis of drug-resistant TB is confirmed only if there is microbiological proof of drug resistance (i.e., DST) in a *M. tuberculosis* isolate obtained from the child. Clinical findings and chest radiographs are the same for drug-susceptible and -resistant TB cases and cannot distinguish between these entities [5]. However, taking a good history in a child presenting with symptoms and signs of TB disease may assist in

identifying children at risk of drug-resistant TB. This includes a history of:

- Known contact with an adult with infectious drug-resistant pulmonary TB, in which case the child has a risk of approximately 80–90% of having the same drug-resistant organism [17,18];
- Known contact with an adult source case who is failing treatment or who has recurrent TB with unknown DST results;
- Known contact with an infectious source case who has died on first-line anti-TB treatment with unknown DST results;
- The child failing anti-TB treatment to which he/she is fully adherent [16,19];

Contact tracing of children exposed to an adult with MDR-TB is therefore an important way of early identification of children at risk of MDR-TB [20,21]. In all suspected cases, it is important to try and obtain specimens for culture and DST from the adult source case and the child with suspected TB. For the latter, multiple specimens from different sites should be obtained, preferably before starting treatment. Phenotypic DST is determined by assessing bacterial growth in the presence of antibiotic-containing media, while genotypic DST is determined by the identification of mutations known to confer drug resistance. The WHO, as well as many national guidelines, endorse empiric drug-resistant TB treatment in children (i.e., not to wait for confirmation by culture and DST, but to start treatment on the basis of suspicion of drug-resistant TB to prevent further deterioration in the clinical condition of the child) if there is a high suspicion of drug-resistant TB in the child, especially if the child has known contact with an adult with drug-resistant TB [102,103].

The gold standard for TB diagnosis is obtaining a positive culture for *M. tuberculosis* from the TB case. In children, this is more difficult than in adults as they mainly have paucibacillary TB, and specimens, especially sputum, are difficult to obtain. Positive culture for *M. tuberculosis* is obtained in approximately 20–40% of children with TB disease [22,23], dependent on the extent of disease. In infants with severe TB disease or children with expansile TB pneumonia, this may be as high as 70–90% [24–26]. To improve diagnostic yield from respiratory samples, different methods can be used to obtain specimens, such as early-morning fasting gastric aspirates, induced sputum or expectorated (if old enough) sputum, nasopharyngeal aspirates and bronchoalveolar lavage (if bronchoscopy is clinically indicated) [27]. In extrapulmonary TB, specimens are often more difficult to obtain, but fine-needle aspiration biopsy from peripheral lymph nodes [28], cerebrospinal fluid, pleural and pericardial effusion, and ascitic tap fluid, synovial and other biopsy specimens, and even ear swabs in cases of otorrhoea [29], can be sent for culture and DST.

Confirmation of drug resistance is by culture and either phenotypic or genotypic DST. Culture and phenotypic DST by conventional solid media is slow (weeks to months). Liquid medium culture, such as Mycobacterial Growth Indicator Tube (MGIT 960; Becton Dickenson, MD, USA), is more rapid (1–4 weeks in the case of pediatric specimens, which are often paucibacillary), with DST taking a further 2–3 weeks. Rapid genotypic methods are now commercially available, which provide results within hours to days. Both LPAs and GeneXpert methodologies have been approved by the WHO [104].

The best known LPA, GenoType® MTBDRplus (Hain Lifescience, Nehren, Germany) can identify the *M. tuberculosis* complex directly on sputum smear microscopy specimens positive for acid-fast bacilli (AFB) and also identifies resistance to rifampin (*rpoB* gene mutations) and isoniazid (*inhA* promoter region and *katG* gene mutations) on the same assay. A second version of this LPA has recently been launched, which is said to be more sensitive and can also identify *M. tuberculosis*, as well as rifampin and isoniazid resistance, even in many AFB smear-negative specimens. In children and smear-negative adult TB cases, where culture of *M. tuberculosis* and DST still provides the best yield, LPA can be carried out on cultured isolates to expedite DST results for at least isoniazid and rifampin. LPA for second-line DST is available mainly for the fluoroquinolones and aminoglycosides (GenoType MTBDR*sl*), but these are not as accurate as for isoniazid and rifampin [30]. Limitations of LPAs are that a good laboratory setup, with well-trained staff, is still needed and cross contamination is a risk in the preparation of assays.

The second commonly used genotypic test for the identification of both *M. tuberculosis* and rifampin susceptibility is the GeneXpert.

GeneXpert is marketed as a point-of-care test because of the simplicity of the method. Sputum specimens are currently the only samples approved for use with this method, but there is evidence that other specimens (e.g., gastric aspirate and cerebrospinal fluid) may also be possible to use [31,32]. A sputum specimen is obtained from the patient, deposited in the provided cartridge and placed in the machine, which provides the final result. Although training to carry out these tests is relatively simple and the laboratory facilities required are minimal, the machines need maintenance and calibration, precluding their use as a point-of-care test. The roll-out of commercially available Xpert MTB/RIF machines (Xpert® MTB/RIF System, Cepheid, CA, USA) by the WHO and other organizations has been pushed strongly, but care must be taken in areas where culture methodology is available, as while the sensitivity in sputum AFB-positive patients is excellent, the yield in smear-negative child cases is only approximately 61% compared with culture [33]. Currently, it is recommended only as a test to replace sputum smear microscopy, not to replace culture. The advantage of DST for rifampin, in addition to identifying *M. tuberculosis*, is that it helps to identify possible MDR-TB cases early. It does not, however, identify isoniazid resistance.

Drug treatment of MDR-TB in children (including XDR-TB & rifampin-resistant, isoniazid-susceptible TB)

Children with culture-confirmed MDR-TB should be treated according to the DST result of their own isolate, while children with presumptive MDR-TB, based on contact with a known adult MDR-TB source case, should be treated according to the DST result of the source case's isolate [102]. For children failing adherent first-line therapy, a source case may not be known and a DST result may not be available from either the child or a source case. In such cases, MDR-TB should be assumed and the use of all previous TB drugs, as well as the regional drug resistance pattern (or where the patient originates from), should be taken into account when deciding on or building an effective treatment regimen [34,35].

The treatment principles of MDR-TB in adults and children are the same. A regimen should contain four active drugs, that is, drugs to which the DST shows susceptibility and/or to which the patient or source case is naive [16,35]. The WHO has divided the currently available TB drugs into five groups, summarized in **Table 2** [102]. A regimen to treat MDR- and XDR-TB cases is built as follows (recommended dosages for children are included in **Table 2**):

- Start with first-line drugs to which the isolate is still susceptible (or DST not done), that is, ethambutol and/or pyrazinamide. Note, however, that more than 50% of MDR-TB isolates are resistant to either or both of these drugs. Therefore, these drugs should not be relied on in treatment [102,35–37];
- Add a second-line injectable agent from group 2. Cross-resistance is almost complete between kanamycin and amikacin, while in approximately 30–40% of resistance to second-line aminoglycosides, susceptibility to capreomycin (a polypeptide) may be retained [38]. The choice of second-line agent to use first is controversial, but amikacin has the lowest minimal inhibitory concentration for *M. tuberculosis* and it comes in smaller-sized ampoules; therefore this is often preferred in children [39]. In XDR-TB, if resistance to all second-line injectables is found, there remains a chance that streptomycin may still be effective and could be used if DST shows susceptibility [38]. Streptomycin is, however, not used for MDR-TB treatment, as more than 50% of MDR isolates are resistant to streptomycin;
- Add a fluoroquinolone. These are the most effective second-line drugs for the management of MDR-TB, but they are likely to have no effect in XDR-TB cases, although there is some controversy about later-generation fluoroquinolones (moxifloxacin and gatifloxacin) still having an effect if resistance to ofloxacin is evident. Levofloxacin and moxifloxacin are the currently preferred fluoroquinolones in the MDR-TB regimen [39]. The 400-mg tablet size of moxifloxacin often precludes its use in younger children in contexts where solutions cannot be prepared. The use of fluoroquinolones are generally safe in children and musculoskeletal complications are rare [40];
- Add oral second-line drugs from group 4 to get to a total of four active/effective drugs. These are ethionamide/prothionamide, cycloserine/terizidone and para-aminosalicylic

Table 2. The drug groups according to the WHO classification†, individual drugs in each group, dosages and most important adverse events of each drug used to treat childhood tuberculosis‡.

Drugs	Dosage in mg/kg daily: unless otherwise specified (maximum dose in mg)	Adverse events§
Group 1: first-line oral anti-TB drugs		
Isoniazid	10–15 (300)¶	Hepatitis, peripheral neuropathy, skin rashes and hematological effects
Rifampin	10–20 (600)	Hepatitis, discolouration of secretions and GI effects
Ethambutol	15–25 (1250)	Optic neuritis and skin rashes
Pyrazinamide	30–40 (2000)	Hepatitis and hyperuricemia with arthralgia
Group 2: injectable anti-TB drugs†		
Kanamycin	15–20 (1000)	Ototoxicity and nephrotoxicity
Amikacin	15–20 (1000)	As above
Capreomycin	15–20 (1000)	As above and hypokalemia
Streptomycin	15–20 (1000)	As above
Group 3: fluoroquinolones		
Ofloxacin	15–20 (800)	Sleep and GI disturbance, arthralgia, arthritis, peripheral neuropathy and hallucinations
Levofloxacin	7.5–10# (750)	As above
Moxifloxacin	7.5–10 (400)	As above but including prolonged QT syndrome
Group 4: oral bacteriostatic second-line drugs		
Ethionamide	15–20 (750)	GI disturbance, metallic taste, hypothyroidism, hepatitis and peripheral neuropathy
Prothionamide	15–20 (750)	As above
Cycloserine	15–20 (750)	Neurological and psychological effects
Terizidone	15–20 (750)	As above
Para-aminosalicylic acid	150 (can be divided into two doses) (8–12 g)	GI intolerance, hypothyroidism, hepatitis and hypersensitivity reaction
Group 5: drugs with unclear role in drug-resistant TB treatment		
Clofazimine	3–5 (300)	Skin discolouration, xerosis and abdominal pain
Linezolid	10 twice-daily in <10 years 300–600 total daily in >10 years†† (600)	Diarrhoea, headache, nausea, myelosuppression, neurotoxicity, lactic acidosis, pancreatitis and optic neuritis
Amoxicillin–clavulanic acid	10–15 (amoxicillin component) three-times daily	GI intolerance, hypersensitivity reactions, seizures, liver and renal dysfunction
Imipenem/cilastatin	Not known	As above
Thiacetazone	2.5	Stevens–Johnson syndrome in HIV-infected patients, GI intolerance, hepatitis and skin reactions
High-dose isoniazid	15–20 (in low-level isoniazid-resistant cases) (400)	Hepatitis and peripheral neuropathy, as well as neurological and psychological effects
Clarithromycin	7.5–15 twice-daily (1000)	GI intolerance, rash, hepatitis, prolonged QT syndrome and ventricular arrhythmias

†Data taken from [102].
‡Only daily therapy and no intermittent therapy for childhood multidrug-resistant tuberculosis.
§Data taken from [85].
¶Data taken from [109].
#Optimal dosage not established. Higher dosage for children <5 years of age advised: either 10 mg/kg twice-daily [86] or 15 mg/kg once-daily [87].
††Data taken from [12].
GI: Gastrointestinal; TB: Tuberculosis.

acid (PAS). In case of *inhA* promoter region mutation conferring isoniazid resistance, which can be identified by the GenoType MDRTBplus assay, cross-resistance to ethionamide/prothionamide is present and these drugs should not be relied upon as effective drugs [41,42].

In cases with isolates resistant to a high number of drugs, including XDR-TB, the number of effective drugs from the abovementioned groups may not be sufficient. Group 5 drugs include drugs with uncertain activity against *M. tuberculosis*, but some of these are likely to be effective, especially linezolid and clofazimine

[12,43]. One advantage of linezolid is that it also penetrates the blood–brain barrier in the case of CNS TB. Isoniazid at high doses has been shown to have an advantageous effect in adult MDR-TB cases [44]. The present authors have used high-dose isoniazid in the majority of their MDR-TB cases, depending on the mutation conferring isoniazid resistance, either high-dose isoniazid (for *inhA* promoter region mutations, which confer cross-resistance to ethionamide) or ethionamide (for *katG* gene mutations, which usually confer high-level isoniazid resistance, but are susceptible to ethionamide) may be effective in treatment [41]. Other drugs from group 5 have uncertain value and if used, two drugs are probably needed to provide the benefit of one effective drug [102].

In some country guidelines, rifampin mono- and poly-resistant TB cases are managed as MDR-TB cases, especially in view of genotypic DST being performed, but isoniazid is a highly effective drug and should not be withheld as it can replace other, more toxic drugs in the treatment regimen [103]. The WHO recommends at least isoniazid, other active oral first-line drugs (ethambutol and pyrazinamide) and a fluoroquinolone plus an active injectable agent in all patients with more extensive rifampin mono- and poly-resistant TB [102].

HIV infection & MDR-TB

All children suspected of TB in high HIV-prevalence areas (prevalence of >1%) or children at risk of HIV infection should be screened for such [105]. In children dually infected with MDR-TB and HIV, early initiation of antiretroviral therapy (ART), that is, usually within the first 2–8 weeks of anti-TB treatment, is essential to improve outcome if they are not yet on ART [106,45]. Knowledge of the pharmacokinetic interactions between ART and second-line anti-TB drugs are incomplete. As rifampin is not used in second-line MDR-TB treatment regimens, drug–drug interactions are expected to be less severe. However, unexpected interactions might occur [46]. As for drug-susceptible TB patients coinfected with HIV, cotrimoxazole preventive treatment and pyridoxine supplementation should be added to the treatment [19,47]. Pyridoxine dosage should be increased if cycloserine/terizidone is included in the treatment (usually 25 mg per 250 mg of cycloserine/terizidone).

Duration of drug treatment

The optimal duration of MDR-TB treatment in children is unknown, but it likely differs with the type of TB and severity (uncontained vs contained) of the disease [48]. Early primary disease, such as uncomplicated mediastinal lymphadenopathy or limited lung parenchymal infiltration, has low bacillary load and could probably be treated for 12–15 months [35,49]. Children with more extensive infiltrates on chest radiograph and those with cavitary disease or severe forms of extrapulmonary disease should be treated for 18 months after the first negative culture [35]. A recent study of adults with MDR-TB, however, found that 9 months of treatment with certain second-line drugs was effective, but this needs to be confirmed in further studies [43]. The duration of the second-line injectable drug, which in resource-limited areas is mostly administered intramuscularly, could, in the present authors' experience, probably also be shortened to 4 months in children with limited (paucibacillary early primary) disease and, in the majority of children with MDR-TB, should not exceed 6 months. Studies on optimal treatment duration are, however, urgently needed.

Adherence management of drug treatment

MDR-TB treatment should always be given as daily, directly-observed treatment. Different models have been tried, including community-based, primary healthcare clinic-based and initial hospital-based treatment [6,50,51]. All models are successful as long as treatment is observed and the child adheres to it. In some settings, primary healthcare staff are reluctant to provide daily intramuscular injections to children who are then admitted for the duration that the injectable drug is administered [51].

An important and often neglected part of adherence management is regular counseling of parents/caregivers and children about the disease, duration of treatment and possible adverse events [16]. Families often need socio-economic support in the form of grants, food parcels and/or travel assistance to visit clinics or hospitals, especially if caregivers also have TB themeselves [102]. For children with TB/HIV coinfection it is important that comprehensive integrated care should be provided at a single facility and point in time to reduce the burden on families.

Adverse events

Second-line anti-TB drugs are usually more toxic than first-line drugs, but children tolerate these drugs better than adults. Both clinical observation (e.g., for arthralgia/arthritis, hepatitis and peripheral neuropathy) and special investigations (e.g., hearing evaluation, renal function and thyroid function tests) are needed for timely identification of adverse events. Common adverse events are summarized in **Table 2**. Care should be taken when concomitant drugs, such as antiretroviral drugs, are provided, which could cause similar or additional adverse events. Recent reviews discuss this in more detail [39,46].

Clinical evaluation for adverse events should be carried out with every visit (at least twice-monthly) and caregivers should be aware of what to look out for, especially regarding hepatitis. Hearing evaluation should be carried out on a monthly basis while on ototoxic drugs, that is, aminoglycosides or capreomycin, as hearing loss is common and irreversible, which could influence speech development in young children [52,53]. If hearing loss occurs, alternative drugs should be sought to manage the MDR-TB, such as linezolid or PAS if not already used, but this is often not possible due to the drug-resistance patterns of the isolate. Hearing evaluation should continue until 6 months after discontinuation of the injectable drug, as hearing loss may continue. Blood tests for renal function should be carried out on a monthly basis while on injectable drugs, with monthly, full blood counts if linezolid is used, as well as thyroid function tests being carried out every 2–3 months while on ethionamide/prothionamide and/or PAS [12,54].

Monitoring progress

Children with MDR-TB should be followed-up at least twice-monthly. This should include clinical evaluation of symptoms, signs and anthropometry, including evaluation for adverse events, as well as radiological and microbiological monitoring (follow-up cultures for *M. tuberculosis*) [16,35]. In culture-confirmed cases, monthly cultures to determine conversion to negative culture are indicated and a cure is established only if, in adults, at least five negative cultures are documented. In children, this may be difficult and fewer negative cultures at least a month apart toward the end of treatment have been used to document cure [51]. Culture-negative presumptive MDR-TB cases are mainly followed clinically and radiologically, but microbiological follow-up may be indicated if there is no improvement or progression of disease.

Nutritional support is essential in MDR-TB cases. Both TB and coexisting diseases (e.g., HIV infection) may cause malnutrition; children with MDR-TB may have advanced disease with severe malnutrition and TB is also associated with poverty [19]. Furthermore, anti-TB drugs, such as ethionamide and PAS, may have gastrointestinal adverse effects including nausea and anorexia. Pyridoxine levels may be affected by anti-TB and antiretroviral drugs; supplementation of pyridoxine (vitamin B_6) is recommended [47].

Outcome of MDR-TB in children

Despite limited data, outcome of MDR-TB and even XDR-TB in children is good if the diagnosis is made early and timely, and appropriate anti-TB treatment is initiated and completed. In a recent meta-analysis of more than 300 children with mostly confirmed MDR-TB, the cure- and treatment-completion rate was >80% [8]. In a study of culture-confirmed, mostly smear-positive MDR-TB cases, outcome was good, despite the fact that many of the deaths occurred before appropriate MDR-TB treatment could be started [51]. In a report of seven children with mostly XDR-TB, treated with second-line regimens including linezolid, the outcome was also excellent [12]. However, outcome for MDR tuberculous meningitis is generally poor [55,56].

Prevention of MDR-TB in child contacts of adults with infectious MDR-TB

There are currently two main schools of thought on the management of contacts of MDR-TB cases. First, some experts prefer not to give preventive therapy, but to follow-up the contacts for a period of 2 years and treat as MDR-TB if the contact develops disease [102,107]. Second, some see value in providing preventive therapy, usually two oral drugs to which the source case's isolate is susceptible, for 6–12 months, together with clinical follow-up for 2 years [57]. As there are no randomized controlled trials to advise health workers or experts on the management of MDR-TB contacts, published guidelines from different countries and organizations, which mainly present 'expert opinion', present both these views. In the most recent such guidelines, those of the European Centres for Disease Control, the opinion starts to swing in

favor of providing preventive treatment in high-risk contacts (e.g., young children), following provisional data from a study by the US Centers for Disease Control in Chuuk, Micronesia. In this study, none of the contacts receiving preventive treatment with two drugs to which the source case was susceptible (including a fluoroquinolone) developed TB, while a large number of those who did not receive preventive therapy developed MDR-TB [107]. This confirms a previous observational study in children carried out in South Africa [20]. Preventive treatment in the presence of resistance to the fluoroquinolones is difficult; in these cases, high-dose isoniazid may be an option if the source case's isolate has an *inhA*-promoter mutation or if low-level isoniazid resistance has been confirmed [57]. The most important component of the management of contacts of infectious MDR- and XDR-TB cases is evaluation for TB disease and regular follow-up for 2 years [107].

Infection control

Children may pose an infection risk if their respiratory specimens are smear-positive for AFB by microscopy or if they have cavitary pulmonary disease and an active cough [51]. If admitted to hospital, they should be isolated until they are on effective anti-TB therapy, do not cough actively and their respiratory specimens are smear microscopy negative for AFB on at least two occasions 2–4 weeks apart [58,108]. The greater risk of transmission in health facilities is likely posed by accompanying or visiting adults who may have infectious pulmonary TB, especially if they are unaware of the diagnosis and are not on effective anti-TB therapy [59,60]. When children are diagnosed with drug-resistant TB, household members should be screened for prevalent cases (reverse-contact tracing). Children who have infectious TB should not go back to school until rendered noninfectious by a TB expert [58].

Conclusion

The burden of childhood MDR-TB is likely underestimated. MDR-TB in children follows the pattern seen in adult cases, as children usually have transmitted MDR-TB. Early diagnosis and empiric MDR-TB treatment is possible if source cases are identified and their isolates' MDR results are taken into account. MDR-TB is only confirmed if a culture and DST is obtained from a child's own specimen. Children tolerate second-line anti-TB drugs well, but adverse events should be carefully monitored for and acted upon. Outcome, if diagnosed timeously, is generally good. New drugs and shorter regimens are needed to treat highly resistant TB, but ultimately an effective vaccine preventing TB disease should be the goal.

Future perspective: old & new drugs, drug combinations, immunotherapy & vaccines

The armamentarium of existing second-line anti-TB drugs is limited. In the case of childhood drug-resistant TB, problems exist with these drugs because pharmacokinetic data on them are limited, and child-friendly formulations, both in size (mg) of tablets and actual formulations, are rarely available [39].

A number of promising new anti-TB drugs are currently being evaluated in Phase II and III adult MDR-TB trials. The diarylquinoline, TMC207, recently renamed bedaquiline, has a novel mechanism of anti-TB action by inhibiting mycobacterial ATP synthase. Bedaquiline showed early bactericidal activity (EBA), although slightly delayed, similar to isoniazid and rifampin against *M. tuberculosis* [61]. In the first Phase II trial, TMC207 has shown effectiveness in adult studies of MDR-TB cases by reducing time to sputum culture-negative conversion and also by preventing the development of resistance to other second-line drugs, especially the fluoroquinolones, all with minimal adverse events [62,63]. PA-824, a new nitroimidazo-oxazine under evaluation as an anti-TB agent, also showed excellent EBA against *M. tuberculosis* with minimal adverse events [64]. Delamanid (OPC-67683), a mycolic acid biosynthesis inhibitor, is active against *M. tuberculosis* at a low minimal inhibitory concentration. In a Phase II trial, it was safe, well tolerated and showed significant, exposure-dependent EBA over 14 days [65]. Other novel drugs such as SQ109, a 1,2-diamine related to ethambutol, but with a different mechanism of action and no cross-resistance, and the new oxazolidinones, PNU-100480 and AZD-5847, which seem to be as active as linezolid but with less toxicity, are also currently being evaluated [66]. Ideally, a completely new drug-combination regimen for the treatment of MDR- and XDR-TB will become available, using mostly novel drugs; one such regimen, a combination of PA-824, moxifloxacin and pyrazinamide, holds much promise

[67]. However, although some new drug combinations have synergistic activity, others, such as bedaquiline and PA824, may be antagonistic [67]. For childhood MDR-TB, these new anti-TB drugs will all need to be evaluated in children for safety, tolerability and pharmacokinetics (dose ranging).

Drugs may not be enough to fight the increasing drug-resistant TB epidemic. Reports of *M. tuberculosis* resistant to all available drugs are increasing. Alternative strategies are sought, such as immunotherapy and vaccines, to boost the effect of current anti-TB drugs [68,69]. Ultimately, prevention of TB disease by an effective vaccine, given at a young age, would be ideal.

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