Concise Clinical Review

Caring for Children with Drug-Resistant Tuberculosis

Practice-based Recommendations

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The management of children with drug-resistant tuberculosis (DR-TB) is challenging, and it is likely that in many places, the roll-out of molecular diagnostic testing will lead to more children being diagnosed. There is a limited evidence base to guide optimal treatment and follow-up in the pediatric population; in existing DR-TB guidelines, the care of children is often relegated to small "special populations" sections. This article seeks to address this gap by providing clinicians with practical advice and guidance. This is achieved through review of the available literature on pediatric DR-TB, including research studies and international guidelines, combined with consensus opinion from a team of experts who have extensive experience in the care of children with DR-TB in a wide variety of contexts and with varying resources. The review covers treatment initiation, regimen design and treatment duration, management of comorbid conditions, treatment monitoring, adverse events, adherence promotion, and infection control, all within a multidisciplinary environment.

Keywords: pediatrics; child; drug resistance

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

With increasingly available rapid diagnostic techniques, more children are likely to be diagnosed with drug-resistant tuberculosis. Guidance is lacking to assist the clinician in caring for children with drug-resistant tuberculosis.

What This Study Adds to the Field

This article draws on the published literature and available guidelines, combining this with the consensus opinion of authors who have extensive experience in the management of children with drug-resistant tuberculosis. It provides guidance on regimen selection, the management of comorbid conditions and adverse events, and how to monitor treatment response. It discusses the promotion of adherence, how to involve other disciplines, and the role of infection control.

(*Received in original form June 4, 2012; accepted in final form September 2, 2012*)

This work was supported by grant GHN-A-00-08-00004-00 from TREAT TB, USAID (J.A.S. and H.S.S.), the Sir Halley Steward Trust (J.A.S.), the South African Medical Research Council (H.S.S.), and the National Research Foundation of South Africa (H.S.S.).

Author Contributions: J.A.S. created the initial draft of the manuscript, revised the manuscript and approved the final version. J.J.F. revised and edited the manuscript and approved the final version. M.G. revised and edited the manuscript and approved the final version. H.D.C.B. revised and edited the manuscript and approved the final version. R.M.H. revised and edited the manuscript and approved the final version. F.A. revised and edited the manuscript and approved the final version. N.F. performed the systematic review of the literature, revised and edited the manuscript, and approved the final version. J.R.S. revised and edited the manuscript and approved the final version. H.S.S. revised and edited the manuscript and approved the final version.

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Am J Respir Crit Care Med Vol 186, Iss. 10, pp 953–964, Nov 15, 2012

Originally Published in Press as DOI: 10.1164/rccm.201206-1001CI on September 13, 2012
Internet address: www.atsjournals.org

The World Health Organization (WHO) estimates there are 650,000 prevalent cases of multidrug-resistant tuberculosis (MDR-TB) globally (*see* Table 1 for definitions) (1). Because children (< 15 yr of age) comprise up to 20% of the TB caseload in high-burden settings (2–4), the number of children with drug-resistant TB (DR-TB) is undoubtedly high. Data regarding this vulnerable population, however, are lacking; a recent systematic review of children with MDR-TB was only able to include eight studies from five countries (5). Few children with DR-TB are diagnosed, and fewer still are started on appropriate treatment. This failure of appropriate management occurs for several reasons. First, confirmation of the diagnosis for all forms of TB in children is limited by the difficulty in obtaining appropriate diagnostic specimens (6). In many contexts, WHO-endorsed, rapid genotypic tests are being rolled out (7, 8), and, for the majority of regions that did not previously carry out comprehensive culture and drug susceptibility testing (DST), the number of diagnosed cases of pediatric DR-TB will increase. Second, due to misperceptions regarding the toxicity of the second-line TB medications in children, some clinicians are hesitant to use these drugs to treat unconfirmed disease. Finally, there are few practice-based recommendations on the optimal care of children with DR-TB. Existing global guidelines relegate the care of pediatric DR-TB to a one- or two-page

"special populations" section within adult DR-TB guidelines or in general pediatric TB guidelines (2, 9, 10). Treatment recommendations for children with DR-TB are usually extrapolated from adult guidelines, which may not be appropriate because children have a different disease spectrum. Children generally metabolize drugs in a different way from adults (11) and have a different incidence of adverse events (5). Children vary in age from infancy to adolescents, with differing biomedical and psychosocial needs (12).

The purpose of this review is to fill this gap in the pediatric DR-TB literature by providing practice-based recommendations for the care of children with DR-TB. This review goes further than previous articles (13–15) because it incorporates the latest evidence and the implications of technological developments (e.g., molecular testing), systematically draws on the available literature, and combines this with the interpretation and experience of a team of experts who collectively have cared for hundreds of children with DR-TB on five different continents. Specifically, this article covers treatment initiation, regimen design and treatment duration, management of comorbid conditions, treatment monitoring, adverse events, adherence promotion, and infection control. These topics are discussed within the context of a multidisciplinary approach. This article does not discuss the pharmacology of the second-line drugs used or well children exposed to DR-TB because these topics are discussed elsewhere (16, 17).

METHODOLOGY

For each of the sections above, the articles identified from a recent systematic review, undertaken by a number of the authors of this article (5), were consulted (Table 2). This was complemented with additional literature relevant to the section. Recommendations from available guidelines were reviewed, and, where evidence was lacking, expert consensus was reached. This consensus was generated by a group of healthcare professionals and epidemiologists working within The Sentinel Project on Pediatric Drug-Resistant Tuberculosis (18). The writing committee for this article has more than two decades of clinical experience caring for children with DR-TB in a variety of countries, including Bangladesh, Ethiopia, Georgia, Haiti, India, Lesotho, Mexico, Pakistan, Peru, Russia, Rwanda, South Africa, and the United States.

TREATMENT INITIATION

The diagnosis of DR-TB in children is either confirmed or presumed. Confirmed disease occurs when *Mycobacterium tuberculosis* is isolated from the child with phenotypic or genotypic resistance. In published studies of children with MDR-TB, the proportion of culture-confirmed cases ranges from 25% (19, 20) to 100% (21–28). Although a number of these investigations excluded presumed cases, it is clear from studies of drug-susceptible pediatric TB that confirmation is usually achieved in only about 25% of cases with clinical evidence of disease (29). This suggests that a significant proportion of children treated for DR-TB should be presumptively diagnosed. A presumptive diagnosis of DR-TB can be made on clinical symptoms or signs of TB and radiology, in combination with risk factors for drug resistance, such as contact with a confirmed or presumed DR-TB source (2, 10) or the failure to respond to a first-line regimen. The operational definition of failure is challenging and includes ongoing microbiological positivity, unresolving symptoms or signs of TB, persistent or deteriorating radiology, and poor weight gain or weight loss (10). Although the time course is different for each child, all children should show improvement by 2 months if therapy is effective.

Children with presumed DR-TB should be started on effective therapy as soon as possible to avoid progression to severe disease, worse clinical outcome, and ongoing transmission. However, empiric therapy for DR-TB may needlessly expose a child to toxic medications. Extensive efforts should, therefore, be made to confirm the diagnosis with intensive sampling from the child. Dependent on age of the child and health care

TABLE 1. PROPOSED DEFINITIONS FOR USE IN PEDIATRIC DRUG-RESISTANT TUBERCULOSIS

		Definition
Drug resistance	Mono-resistant	Resistance to one TB drug
	Polyresistant	Resistance to two or more TB drugs other than to both rifampin and isoniazid
	MDR	Resistant to rifampin and isoniazid
	Pre-extensively drug resistant	MDR-TB with resistance to either a fluoroquinolone or an injectable second-line TB drug but not both
	Extensively drug resistant	MDR-TB with resistance to both a fluoroquinolone and an injectable second-line TB drug
Episodes and treatment	Previous TB episode	Treatment taken for at least one month, after which there was a reported symptom-free period of $\geq$ 6 mo before the start of the current DR-TB episode (117)
	DR-TB episode	If DR-TB is subsequently confirmed, the episode begins when the child is first documented to have presented to the health care system, when the specimen was obtained that eventually confirmed DR-TB, or when the child commenced TB treatment
	Previous TB treatment	Any TB treatment before the initiation of DR-TB treatment for more than 1 mo
Reason for treatment	Confirmed DR-TB	Isolation of *Mycobacterium tuberculosis* from the child with genotypic or phenotypic demonstration of resistance
	Presumed DR-TB due to contact	DR-TB treatment started on the basis of symptoms, signs, radiology, and/or immunology consistent with TB together with a close, infectious source case with confirmed DR-TB or with risk factors for DR-TB
	Presumed DR-TB due to treatment failure	DR-TB treatment started on the basis of a clinical or radiological deterioration on effective, well adhered-to first-line therapy with the exclusion of other possible diagnoses or explanations
Outcome	Cure	Completion of treatment, clinical and radiological improvement, and three or more negative sputum cultures
	Probable cure	Completion of treatment with clinical and radiological improvement
	Treatment completed	Completion of prescribed treatment
	Default	Treatment interruption for $\geq$ 2 mo
	Died	Death for any reason while on MDR-TB treatment
	Treatment failure	Ongoing sputum culture positivity or clinical or radiological deterioration after 6 mo of an effective, well adhered-to therapy
	Transferred out	Transfer to another reporting region for ongoing care

Definition of abbreviations: DR = drug resistant; MDR = multidrug resistant; TB = tuberculosis.

TABLE 2. STUDIES DESCRIBING DRUG-RESISTANT TUBERCULOSIS TREATMENT IN CHILDREN

First Author	Year of Study	Location	Number of Children Included	Number Culture-Confirmed	Treatment Success (%)	Adverse Events
Seddon (23)	2003–2008	Cape Town, South Africa	111	111	88 (79)	NS
Leimane (60)	1998–2006	Latvia	76	NS	70 (92)	26
Schaaf (21)	1998–2001	Cape Town, South Africa	39	39	21 (54)	20
Drobac (35)	1999–2003	Lima, Peru	38	28	36 (95)	16
Feja (19)	1995–2003	NY	20	6	16 (80)	4
Satti (20)	2007–2011	Lesotho	19	5	15/17 (88)	18
Fairlie (22)	2008	Johannesburg, South Africa	13	13	7 (54)	2
Granich (118)	1994–2003	CA	10	NS	9 (90)	NS
Mendez Echevarria (36)	1994–2005	Madrid, Spain	8	5	8 (100)	4
Padayatchi (24)	1992–2003	Durban, South Africa	8	8	1 (13)	NS
Rose (28)	2007–2012	Cape Town, South Africa	7	7	4/4 (100)	3
Kjöllerström (27)	2011*	Lisbon, Portugal	4	4	4 (100)	3
Thomas (61)	2006–2007	Tuglea Ferry, South Africa	4	4	4 (100)	2
Schluger (25)	1983–1993	NY	2	2	2 (100)	NS
Pinon (55)	2010*	Turin, Italy	2	NS	1 (50)	0
Suessmuth (26)	2005	Hannover, Germany	1	1	1 (100)	NS

Definition of abbreviation: NS = not stated.
*Year of publication as year of study unclear.

resources, attempts can be made to obtain sputum samples, gastric aspirates, induced sputum samples, biologic fluid samples, nasopharyngeal aspirates, lymph node aspiration biopsy, or tissue biopsy (6, 29–32). With extensive sampling, the proportion of children with a confirmed diagnosis can rise to greater than 50% (33). Invasive methods, such as bronchoalveolar lavage, bronchoscopic biopsy, or open lung biopsy, may be in the child's best interest if a confirmed diagnosis can be made (34). All isolates confirmed as resistant to rifampin should be sent for full second-line DST assessment. In addition, if rifampin and/or isoniazid resistance is determined by a rapid molecular test, the results should be confirmed by phenotypic testing.

REGIMEN DESIGN AND TREATMENT DURATION

The WHO has placed the drugs used in the treatment of DR-TB into five groups; these groups are summarized in Table 3 (10). Group 1 drugs are considered first-line therapy, and the remainder are considered second-line therapy. Few of the second-line drugs are produced in pediatric formulations, and the pharmacokinetics are incompletely studied in young children (17). This means that optimal dosing is unknown and that tablets must be broken or cut, potentially leading to inaccurate dosages and blood concentrations that are subtherapeutic or toxic. The medications are often unpalatable, and a number of the drugs can cause vomiting and diarrhea (17). This may not only affect the amount of drug absorbed but also may deter adherence. Daily injectable drugs are usually given for the first few months of treatment (21–23, 35, 36), and the pill burden can be vast; the child may require multiple TB medications, antiretroviral therapy (ART), antibiotics, and vitamin and calorie supplements. In our experience, spreading the total daily dose over the course of the day can improve tolerability but makes directly observed therapy (DOT) challenging. Drugs can be mixed with different foods or drinks, and, in some situations, nasogastric or percutaneous endoscopic gastrostomy feeding may be appropriate. A programmatic dosing table is demonstrated in Table 4.

Guidelines suggest that the decision regarding which drugs to include in a DR-TB treatment regimen should be guided by the DST of the child's isolate. If this is not available, regimen composition should be guided by the DST pattern of the presumed source case (2, 9, 10, 37, 38). If DR-TB treatment is given for failure of a first-line regimen, the child should be assumed to have TB that is resistant to rifampin and isoniazid. For children with confirmed MDR-TB or those with a clear MDR-TB source case, there is no role for rifampin. However, if the child is failing first-line therapy or if there are multiple source cases, it may be appropriate to include rifampin for the first 6 months to treat potential drug-susceptible organisms. However, the drug–drug interactions seen with rifampin must be considered, especially in HIV-infected children, where protease inhibitor concentrations have been shown to be reduced with rifampin (39). There is some evidence in the laboratory and in adult subjects that the fluoroquinolones are less effective in rifampin-containing regimens (40, 41).

When designing a regimen to treat children with MDR-TB, the target should be to use at least four drugs that are likely to have activity against the infecting organism (Figure 1) (2, 38, 42). Because they are effective drugs with few adverse effects (43), any first-line drugs to which the organism has not been shown to be resistant should be used. Even when the organism is resistant to isoniazid, higher doses of isoniazid (15–20 mg/kg) have been shown to overcome resistance in children with MDR-TB (44). High-level resistance to isoniazid is usually caused by mutations in the *katG* gene, whereas low-level resistance is usually caused by mutations in the *inhA* promoter region. *InhA* mutations usually confer resistance to ethionamide (45). With increasing use of genotypic diagnostics, the implications of different mutations will become increasingly important (46–48).

The next step is to add a second-line injectable drug from group 2 and a fluoroquinolone from group 3 (42). In adult studies, the inclusion of fluoroquinolones is associated with improved outcome (49). The later-generation fluoroquinolones (levofloxacin and moxifloxacin) are more effective than earlier-generation treatments (ofloxacin) *in vitro* (50–52) but are poorly studied in children. Other drugs from group 4 are then added. Ethionamide or prothionamide should be used (if no *inhA* mutation is documented) because their metabolic pathways are similar and cross-resistance is total (51). The same is true for cycloserine and terizidone, and only one of these two should be used (51). *Para*-aminosalicylic acid (PAS) can be added if there are not sufficient effective drugs at this stage, but, in our experience, due to gastrointestinal intolerance, the other drugs from group 4 are usually used. Finally, agents from group 5 can be added if required. Drugs from group 5 are described as having relatively weak or uncertain activity against *M. tuberculosis* (2, 10). However, clofazimine and linezolid have, in recent adult

TABLE 3. DRUGS USED TO TREAT TUBERCULOSIS IN CHILDREN

Group	Group Name	Drugs	Dosage* (*mg/kg*)	Adverse Events
1	First-line oral agents	Isoniazid	10–15	Hepatitis, peripheral neuropathy
		Rifampin	10–20	Hepatitis, discoloration of secretions
		Ethambutol	15–25 (DR-TB: 20–25)	Optic neuritis
		Pyrazinamide	30–40	Hepatitis, arthritis
2	Injectable agents	Kanamycin	15–30	Ototoxicity, nephrotoxicity
		Amikacin	15–22.5	As above
		Capreomycin	15–30	As above
		Streptomycin	15–20	As above
3	Fluoroquinolones	Ofloxacin	15–20	Sleep disturbance, gastrointestinal disturbance, arthritis, peripheral neuropathy
		Ciprofloxacin	20 twice daily	As above
		Levofloxacin	7.5–10†	As above
		Moxifloxacin	7.5–10	As above but including prolonged QT syndrome
4	Oral bacteriostatic second-line agents	Ethionamide	15–20	Gastrointestinal disturbance, metallic taste, hypothyroidism
		Prothionamide	15–20	As above
		Cycloserine	15–20	Neurological and psychological effects
		Terizidone	15–20	As above
		Para-aminosalicylic acid	150	Gastrointestinal intolerance, hypothyroidism, hepatitis
5	Agents with unclear efficacy	Clofazimine	3–5	Skin discoloration, xerosis, abdominal pain
		Linezolid	10†	Diarrhea, headache, nausea, myelosuppression, neurotoxicity, lactic acidosis, pancreatitis, and optic neuropathy
		Amoxicillin-clavulanic acid	10–15 (amoxicillin component) three times a day	Gastrointestinal intolerance, hypersensitivity reactions, seizures, liver and renal dysfunction
		Imipenem/cilastatin		As above
		Thiacetazone	2.5	Stevens Johnson Syndrome in HIV-infected patients, gastrointestinal intolerance, hepatitis, skin reactions
		High dose isoniazid	15–20	Hepatitis, peripheral neuropathy, neurological and psychological effects
		Clarithromycin	7.5–15 twice daily	Gastrointestinal intolerance, rash, hepatitis, prolonged QT syndrome, ventricular arrhythmias

Definition of abbreviations: DR-TB = drug-resistant tuberculosis.

* Daily unless otherwise specified.

† The stated dose is advised to be given twice a day for children <5 yr.

studies, demonstrated promising efficacy and can be considered useful drug options (53, 54). Increasing use of linezolid has also been seen in children, but the potential for toxicity must be considered (27, 28, 55). Novel agents such as delamanid (56), PA-824 (57), and bedaquiline (58) are in advanced stages of clinical trials. However, because no child-friendly formulations have been produced and no pediatric pharmacokinetic studies have been conducted, it will be a number of years before these drugs are available for use in children.

The decision on number of drugs and duration of therapy is dependent on the extent of disease and the degree of drug resistance as well as penetration to different body sites and treatment response. For children with cavitary or widespread disease with resistance to only rifampin and isoniazid, treatment is usually given for 18 months from the time of sampling of the first negative culture. Good outcomes have been reported in children treated with regimens of this duration, even in children with extensive disease (19, 21, 23, 36). Treatment normally includes an injectable drug given daily for the first 4 to 6 months. Limited evidence exists regarding the efficacy and reduced toxicity of giving three times a week (38). The systematic review of MDR-TB treatment in children suggests that in those studies where

TABLE 4. A PROPOSED DOSING TABLE FOR THE DRUGS USED IN THE TREATMENT OF DRUG-RESISTANT TUBERCULOSIS IN CHILDREN*

	Isoniazid	Pyrazinamide	Ethambutol	Ofloxacin			Levofloxacin†	Moxifloxacin	Terizidone	Ethionamide	PAS
Dosing range, mg/kg	15–20	30–40	20–25	15–20			7.5–10	7.5–10	15–20	15–20	150
Tablet size, mg	100	500	400	100	200	400	250	400	250	250	4,000
Weight, kg											
3–4.9	50 (½ tab)	125 (¼ tab)	100 (¼ tab)	100 (1 tab)	100 (½ tab)	100 (¼ tab)	†	‡	62.5 (¼ cap)	62.5 (¼ tab)	500 (⅛ sach)
5–6.9	100 (1 tab)	250 (½ tab)	100 (¼ tab)	150 (1½ tab)	100 (½ tab)	100 (¼ tab)	62.5 (¼ tab)	‡	125 (½ cap)	125 (½ tab)	1,000 (¼ sach)
7–9.9	150 (1½ tab)	250 (½ tab)	200 (½ tab)	200 (2 tabs)	150 (¾ tab)	200 (½ tab)	125 (½ tab)	‡	187.5 (¾ cap)	187.5 (¾ tab)	1,500 (⅜ sach)
10–13.9	200 (2 tabs)	500 (1 tab)	300 (¾ tab)	300 (3 tabs)	200 (1 tab)	200 (½ tab	125 (½ tab)	100 (¼ tab)	250 (1 cap)	250 (1 tab)	2,000 (½ sach)
14–19.9	300 (3 tabs)	500 (1 tab)	400 (1 tab)	400 (4 tabs)	300 (1½ tab)	300 (¾ tab)	187.5 (¾ tab)	200 (½ tab)	375 (1½ caps)	375 (1½ tab)	3,000 (¾ sach)
20–29.9	400 (4 tabs)	750 (1½ tab)	600 (1½ tab)	600 (6 tabs)	400 (2 tabs)	400 (1 tab)	250 (1 tab)	200 (½ tab)	500 (2 caps)	500 (2 tabs)	4,000 (1 sach)
30–39.9	400 (4 tabs)	1,000 (2 tabs)	800 (2 tabs)	800 (8 tabs)	600 (3 tabs)	600 (1½ tab)	312.5 (1¼ tabs)	300 (¾ tab)	625 (2½ caps)	625 (2½ tabs)	6,000 (1½ sach)
>40	400 (4 tabs)	1,500 (3 tabs)	1,200 (3 tabs)	1,200 (12 tabs)	800 (4 tabs)	800 (2 tabs)	375 (1½ tabs)	400 (1 tab)	750 (3 caps)	750 (3 tabs)	8,000 (2 sach)

Definition of abbreviations: PAS = *para*-aminosalicylic acid.

* If rifampin is given, dose as for drug-susceptible tuberculosis. A suspension is available for a number of the drugs in some contexts, which might be preferable for smaller children.

† For children younger than 5 yr of age, this dosage of levofloxacin should be given twice a day.

‡ Unable to create an appropriate fraction of a tablet for a child of this weight.

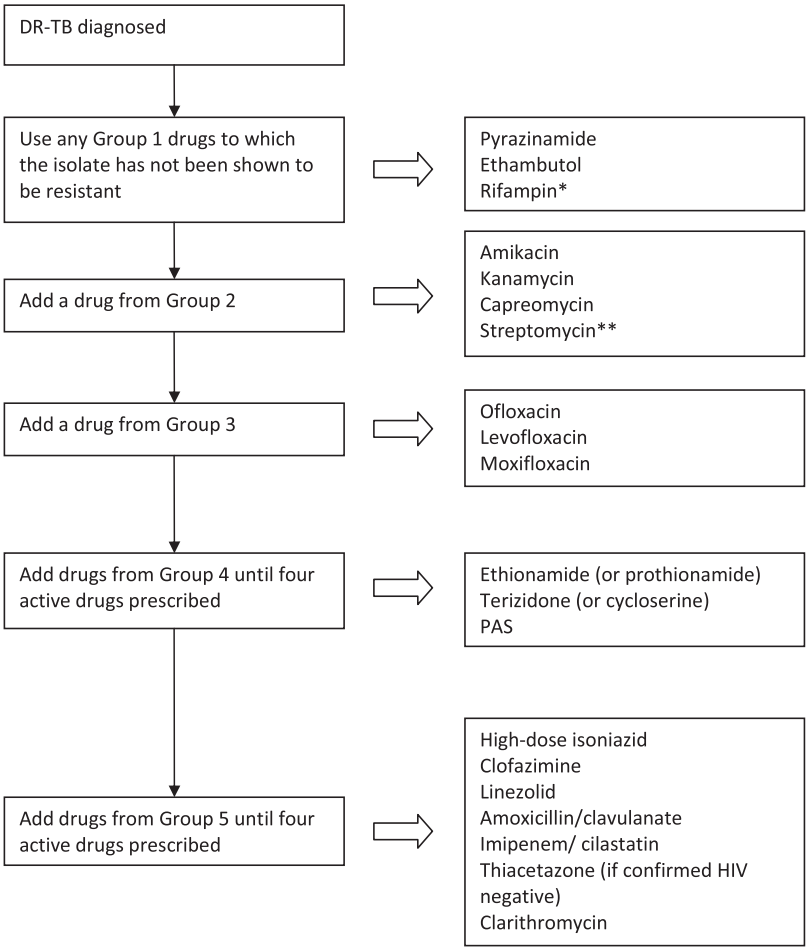

Figure 1. An algorithm to aid in the construction of a drug-resistant tuberculosis (DR-TB) treatment regimen for children. *Consider including rifampin for 6 months if the child is treated for failure of first-line therapy if no *Mycobacterium tuberculosis* isolate is obtained or if there are multiple potential source cases. **Consider streptomycin if the isolate is found to be resistant to amikacin, kanamycin, and capreomycin but is demonstrated to be susceptible to streptomycin.

injectable drug use was more common, treatment outcomes were better (5). The WHO has recently recommended that adults should be given injectable drugs for 8 months because longer durations are associated with better outcomes (59). This may be appropriate for older children with extensive disease, but for most children 4 to 6 months of treatment is likely to be sufficient (5). For children with limited, paucibacillary disease (e.g., isolated intra- or extrathoracic lymph node involvement) and with susceptibility to the second-line drugs, it is likely that the child can be treated for 12 to 15 months in total, dependent on response. In such situations, a shorter duration (e.g., 3–4 mo) of the injectable medication or no injectable medication at all is likely to be sufficient. Although evidence for such shorter regimens is lacking and these regimens are of unproven efficacy, good treatment outcomes have been seen in some studies (21, 36, 60). If the isolate is extensively drug resistant (XDR) or pre-XDR (*see* Table 1 for definitions), treatment relies on less effective drugs, and, in reported studies of children with extensive resistance, more drugs have been used and treatment has lasted for a minimum of 24 months (23, 27, 28, 61). In the treatment of XDR-TB, consideration can be given to the inclusion of streptomycin (if the isolate is susceptible to streptomycin) because cross-resistance between second-line injectables is incomplete (62).

There is limited available evidence to inform the management of TB in children caused by isolates resistant to isoniazid alone. A single study of children with isoniazid mono-resistant TB describes good treatment outcomes using three to four drugs (63). Guidelines for children suggest treatment for 6 to 12 months with rifampin, pyrazinamide, and ethambutol (2, 38, 42). In cases of extensive disease or for tuberculous meningitis (TBM), a fluoroquinolone and one other drug can be added. A study assessing the treatment of 18 children with rifampin mono-resistant TB (RMR-TB) demonstrated good outcomes when children were treated with 4 months of amikacin and for a total of 18 months using a further four or five drugs (64). Guidelines suggest that RMR-TB can be treated with isoniazid, pyrazinamide, ethambutol, and a fluoroquinolone for 12 to 15 months (2). In cases of extensive disease, an injectable agent can be used for the first few months, another drug can be added, and treatment can be extended to 18 months. If genotypic tests are used to perform DST, most national programs advise treating RMR-TB in adults and children with an MDR-TB regimen because these tests do not identify all of the mutations conferring isoniazid resistance (65).

In addition to TB drugs, guidelines suggest that children with TB should be given pyridoxine if they are HIV infected, malnourished, breast fed, or are being given terizidone, cycloserine, or high-dose isoniazid (2) because pyridoxine deficiency is common (66). Most experts put all children being treated for DR-TB on multivitamin supplements. Steroids have been demonstrated to improve outcome in children with TBM (67–69) and are additionally advised for airway obstruction and pericardial TB (2, 38). Nutritional and metabolic requirements should be assessed because these children are commonly malnourished (22, 23, 35) and have often been in a catabolic state before the diagnosis of DR-TB. They may also have high calorific requirements due to the ongoing tissue damage, repair, and inflammation.

Other adjunctive treatments include bronchoscopy and surgery. In cases of intrathoracic lymph node disease in children,

with external pressure on the airways leading to compression and respiratory compromise, assessment by bronchoscopy is advised (70, 71). In cases of extensive resistance, where the disease is localized to one anatomical lobe or part of the lung, surgical resection may still have a place. If there is extensive destruction and fibrosis, it may be difficult for some drugs to penetrate into lesions with poor vascularization. Enucleation of the nodes may be required bronchoscopically or surgically to relieve the pressure on the airway and debulk the lymph node lesion (70, 72).

MANAGEMENT OF COMORBID CONDITIONS

Comorbid medical conditions can increase the risk of TB in children and affect treatment outcomes. Examples include HIV infection (73), diabetes (74), and malnutrition (75). Rates of HIV infection in pediatric MDR-TB cohorts range from 0% (19, 60) to 54% (22). All children diagnosed with TB, whether DR or not, should be offered testing for HIV infection after counseling and consent from parents or guardians and, if old enough, the child. Important practical considerations in the cotreatment of pediatric TB and HIV infection include the timing of initiation of ART, Immune Reconstitution Inflammatory Syndrome (IRIS), drug–drug interactions (76, 77), and overlapping toxicities of ART and TB therapy (17). Generally, it is recommended that children with DR-TB and HIV infection be started on ART within 2 weeks of initiating TB therapy (10, 78, 79). This will decrease the likelihood of adverse drug reactions while allowing rapid initiation of immunorestorative therapy. The management of TBM in this situation is complex and requires further investigation. A study in adults with TBM suggested that delayed ART initiation may be beneficial (80). IRIS occurs within the first few weeks of ART when a resurgent immune system begins to recognize *M. tuberculosis* antigens (81–83) and, when severe, may respond well to corticosteroids. Differentiating IRIS from treatment failure can be challenging but, decreasing HIV viral load and improving CD4 count should point to IRIS. Little data exist on the interactions between ART and second-line TB therapy in adults (76, 77), and even less data are available for children (17). In general, our experience suggests that stavudine should be avoided, and concomitant use of tenofovir and an injectable requires regular testing of renal function and electrolytes.

For children with DR-TB and diabetes, more frequent glucose monitoring is indicated because TB disease and some TB drugs (i.e., rifampin, ethionamide, PAS, and fluoroquinolones) can disrupt glycemic control. Malnourished children should be treated according to established protocols (84), and malnutrition should be prevented by the provision of nutritional support to children and their families.

MORBIDITY ASSOCIATED WITH DR-TB

Chronic pulmonary disease may exist concurrent with pulmonary DR-TB or can occur later due to chronic lung inflammation and tissue damage. Experience in the field suggests that peak flow testing or more extensive spirometry should be performed with appropriate infection control precautions if the child is old enough to cooperate. Breathing exercises and physiotherapy are advised to improve function, and, because there is frequently a reversible component, a trial of bronchodilators is often merited.

Little is published regarding osteo-articular DR-TB in children. The few case series of spinal DR-TB disease in children describe relatively good treatment outcomes (85, 86). Children should be followed by orthopedic surgeons because deformities can deteriorate with the growth of the child. Spinal lesions particularly need to be monitored for many years because spinal growth can exaggerate any deformity, with the potential to compress the spinal cord and cause neurological damage. In settings where there are no orthopedic specialists, nurses and community members can assist with limb and spine splinting and with physiotherapy. Reports of DR-TBM in children describe very poor outcomes (24, 87). TBM can cause devastating neurological damage, and affected children should have access to intensive physiotherapy and occupational therapy during and after their illness. Developmental assessments and level of functioning should be determined at the end of therapy, and children should be followed to monitor progress and to provide support. The care of severely disabled children is challenging, and parents should be supported with access to care services and with assistance with funding applications for resources to which they are entitled.

Although most of the adverse events of the drugs reverse on termination of therapy, the effects on hearing (88) and vision are often permanent. These can have a significant impact on the child's development and quality of life (89, 90). Hearing loss in adults treated for MDR-TB is common (91), but in children it is poorly described. One study assessing hearing loss documented ototoxicity in 7% of children treated for MDR-TB (35). Another study found hearing loss in 25% of children (92). Adverse effects on vision and hearing should be quantified, and appropriate aids to improve function should be given to the child. The child may need physical intervention, such as hearing aids, or they may need extra school support or financial assistance. A final area of morbidity that is seldom addressed is the psychological aspect of the condition and its treatment. Drug-susceptible TB has been shown to be emotionally difficult for children (12), and it is likely to be worse for DR-TB. Children receive treatment for extended periods, and TB is stigmatizing in some contexts. It may be necessary for the child to be admitted to hospital initially, but ambulatory treatment is possible for the majority of these patients (35), sparing the child separation from friends, families, and communities.

TREATMENT MONITORING

Children should be monitored for three reasons: *1*) to determine response to therapy, *2*) to identify adverse events early, and *3*) to promote adherence. A suggested monitoring schedule that can be adapted to local conditions and resources is demonstrated in Table 5. Response to therapy includes clinical, microbiological, and radiological monitoring (2). It is advised that children be clinically assessed on a regular basis to identify symptoms or signs that might signal response, including activity levels, respiratory function, and neurological development (2). Height and weight should be measured regularly and plotted on an appropriate percentile chart (93). For children with pulmonary disease, respiratory samples should be collected. For older children who are able to expectorate, the adult schedule is suggested, with monthly sampling (10). For younger children, with an initial positive smear or culture result, we advise that samples initially be taken monthly. After culture conversion this can be performed every 2 to 3 months. Significant rates of "cure" rather than simply "treatment completed" have been reported in children treated for MDR-TB, implying that this kind of optimal ongoing microbiological testing is possible, even in young children (21, 23, 26, 35, 60). For those with negative smear and culture samples at treatment initiation, samples should be obtained if the clinical or radiological situation changes. All samples should be sent for culture and DST in addition to smear microscopy. Finally, regular radiological monitoring with chest radiograph (CR) is advised for children with

TABLE 5. A PROPOSED MONITORING SCHEDULE TO DETERMINE RESPONSE AND DETECT ADVERSE EVENTS WHEN TREATING DRUG-RESISTANT TUBERCULOSIS IN CHILDREN

		Month										
	Baseline	1	2	3	4	5	6	9	12	15	18	Ongoing
All children												
HIV status	●											
Toxicity (symptoms, signs)	●	●	●	●	●	●	●	●	●	●	●	●
Height and weight	●	●	●	●	●	●	●	●	●	●	●	●
Audiology*	●	●	●	●	●	●	●					
Color vision testing†	●	●	●	●	●	●	●	●	●	●	●	●
CR‡	●			●			●					
TB culture and DST§	●	●	●	●	●	●	●					
Creatinine and potassium*	●	●	●	●	●	●	●					
TSH, T_4‖	●			●			●	●	●	●	●	●
Hematology (FBC with differential)¶	●	●	●		●		●	●	●	●	●	●
HIV infected												
LFTs, cholesterol	●						●			●		●
CD4 count and viral load	●						●			●		●

Definition of abbreviations: CR = chest radiograph; DST = drug susceptibility test; FBC = full blood count; LFT = liver function test; TB = tuberculosis; TSH = thyroid-stimulating hormone.

* Monthly while on an injectable and at 6 mo after termination of injectable.

† If on ethambutol.

‡ If any pulmonary involvement or at any point if the child deteriorates clinically. To be repeated at the end of treatment.

§ Monthly if old enough to expectorate. If unable to expectorate and initially smear or culture positive, monthly until culture converted then three times monthly. If initially smear and culture negative, perform if the child deteriorates clinically. For extrapulmonary TB, samples should be taken to make the diagnosis and if the child deteriorates clinically.

‖ If on ethionamide, prothionamide, or PAS.

¶ If on linezolid or HIV infected.

pulmonary disease (2) with additional radiology if the child develops new or worsening clinical signs or symptoms. It can be useful to have a CR at the end of therapy to provide a baseline for follow-up. Although CR improvement is an important indicator of successful treatment response, complete resolution may not occur, and a normal CR is not required to complete therapy. In the majority of reported cases, however, significant CR resolution at the end of therapy was observed (21).

ADVERSE EVENTS

In children treated for MDR-TB, toxicity is common, occurring in up to 40% of cases (5). Significant adverse events, however, and ones that necessitate stopping or changing treatment are less common. The toxicity of the first- and second-line TB drugs has been well described in other reviews and is summarized in Table 3 (17, 38, 43). This section therefore focuses on the monitoring and management of adverse events, specifically in children. A suggested monitoring schedule is shown in Table 5, and management of adverse events is described in Table 6. Due to renal, thyroid, auditory, and visual adverse events possible with second-line TB drugs, we advise that, before initiating therapy, children have their hearing and vision tested as well as their renal and thyroid function. Children old enough to cooperate (usually from about 5 yr of age) can be assessed using Ishihara charts and by pure tone audiometry (94). Otoacoustic emissions can be used to test the hearing in younger children, but visual testing is challenging for this age group. Clinicians should, however, be reassured that the incidence of ocular toxicity in children is very rare (0.05%) when ethambutol is given at the recommended dosage (95). Toxicity is dose related, and studies in adults demonstrate that ocular toxicity increases exponentially with increasing dose (96).

One of the cornerstones of TB care in adults and in children is that TB drugs should be provided without cost to the family. This is particularly pertinent in any campaign against drug resistance. Drugs to alleviate adverse events, such as analgesics, antiemetics, antipruritics, and drugs to manage diarrhea, are likely to improve adherence and, in our practice, are also provided free of charge. Children should be assessed clinically for adverse events on a regular basis by their healthcare provider and on a daily basis by a DOT supporter and/or caregivers after training in the recognition of signs and symptoms of adverse events (35). Thyroid function should be checked regularly if the child is on a potentially thyrotoxic drug because thyroid dysfunction is common in children treated with ethionamide (97, 98). Renal function and hearing should also be tested the child is taking an injectable drug; hearing loss frequently complicates pediatric treatment (35, 92). There is no need to monitor full blood count or liver function routinely. Transient elevations in transaminase levels are common at the start of TB therapy in children and are rarely associated with significant adverse events (43). Due to the increased risk of myelosuppression, a regular full blood count is advised if the child is receiving linezolid (99).

PROMOTING ADHERENCE

DOT is a key component of successful treatment in children, and the use of community health workers (CHWs) or DOT supporters can be valuable for promoting adherence and identifying adverse events early (100, 101). DOT is a comprehensive package of support and assistance rather than a paternalistic observation of ingestion (102). Although young children, in effect, always receive their treatment under DOT, in a programmatic sense DOT implies treatment given under the supervision of someone outside the family. DOT should be made as easy as possible; CHWs and DOT supporters can be used to give the medications at a convenient location, such as at home or at a nearby clinic (100). In our experience, long waiting times, peer pressure, unsympathetic staff, and stigmatization at health facilities can deter attendance at clinic and impair overall adherence. If children are old enough to understand, it is important to invest time and effort in educating them about the disease and allow them to take responsibility for their illness and their treatment. Adolescents can be at high risk of severe disease, and adherence can be challenging, with associated poor treatment outcomes (10, 103).

TABLE 6. THE MANAGEMENT OF ADVERSE EVENTS IN THE TREATMENT OF DRUG-RESISTANT TUBERCULOSIS IN CHILDREN*

Adverse event	TB Drugs Possibly Responsible	ART Drugs Possibly Responsible	Monitoring	Management
Hearing loss (88)	Amikacin, kanamycin, capreomycin		PTA or OAE assessed and classified using ASHA guidelines (94)	If any hearing loss is detected, strong consideration should be given to stopping/switching the injectable drug.
Renal impairment (88)	Amikacin, kanamycin, cpareomycin,	Tenofovir	Blood testing	1. Evidence of mildly elevated creatinine should prompt retesting. 2. Markedly elevated creatinine or potassium should lead to the cessation of all nephrotoxic drugs
Visual impairment (95)	Ethambutol		Clinical or Ishihara Chart	Any deterioration in visual fields or color vision should lead to stopping or switching the ethambutol.
Hypothyroidism (97)	Ethionamide, prothionamide, PAS		Blood testing	1. If T4 is low, continue medications and supplement with 0.05 mg thryoxine supplement daily. 2. Continue to monitor T4 and consider increasing supplementation to 0.1 mg daily.
Hepatitis (43)	Rifampin, isoniazid, pyrazinamide,† ethionamide, prothionamide	Nevirapine, efavirenz, PIs	Clinically and blood testing	1. Clinical suspicion of hepatitis (vomiting not directly associated with medications, abdominal pain or jaundice) should lead to immediate cessation of all hepatotoxic drugs. 2. Investigation into nondrug aetiologies (hepatic viruses, etc.) should take place. 3. Treatment should continue with medications that are less hepatotoxic (ethambutol, injectables, fluoroquinolones, terizidone/cycloserine, and PAS). 4. The hepatotoxic TB drugs can be reintroduced one by one every 2 d. 5. Given that the child is on treatment for DR-TB the relative merits of reintroducing isoniazid, rifampin and pyrazinamide should be considered.
Rash	All TB drugs	Nevirapine, efavirenz	Clinical	1. Mild reactions: symptomatic relief 2. Stevens Johnson reactions: immediate cessation of all drugs (including all TB and HIV medications) until the symptoms have resolved. 3. Sequential reintroduction can then occur. Restart the TB medications one by one every 2 d and monitor response. If the child was on ART, once TB treatment is reestablished all ART medications should be restarted at the same time to prevent the development of resistance. 4. Once TB and ART drugs are established, other agents can be added. Cotrimoxazole is an important, but rare, cause of severe skin reactions.
Vomiting	Ethionamide, prothionamide, PAS, ethambutol	Zidovudine, PIs	Clinical	If nausea and vomiting compromise drug delivery, it may be prudent to split the dose of ethionamide/prothionamide or give it at a separate time from the other drugs.
Diarrhea	PAS, ethionamide, prothionamide	Zidovudine, PIs	Clinical	1. PAS is usually given twice a day, but if diarrhea is severe, the dosage can be reduced or the drug given in smaller quantities more frequently. 2. If diarrhea is profuse, regular monitoring of hydration status and serum potassium should be conducted. 3. CHWs or DOT supporters can be trained to provide oral rehydration solutions for those with vomiting or diarrhea.
Peripheral neuropathy (119)	Isoniazid, linezolid	Stavudine, didanosine	Clinical	1. Mild reactions: increase the dose of pyridoxine or reducing the dose of the offending TB drug. 2. If severe or persisting in spite of above, the TB drug should be stopped.
Neuropsychiatric effects (120)	Terizidone, cycloserine, isoniazid, fluoroquinolones	Efavirenz	Clinical	1. As a first step, it is important to verify that the child has been prescribed and is receiving the correct dose because overdosing can be associated with adverse events 2. The next step is to reduce the dosage of the drug felt most likely to be responsible and monitor the effect. 3. If this does not help, then the drug should be stopped. 4. If no resolution then the drug should be reintroduced, and the next most likely drug should be reduced in dose. If necessary, treatment should be stopped.
Joint problems (121)	Pyrazinamide, fluoroquinolones‡		Clinical	1. Analgesia 2. Reducing dose or stop one of potentially offending drugs
Metabolic problems	Linezolid	Stavudine, didanosine, zidovudine	Clinical and blood tests	Lactic acidosis is life-threatening and if determined, all potentially implicated drugs should be stopped
Bone marrow suppression (122)	Linezolid	Zidovudine	Clinical and blood tests	The responsible drug should be switched or stopped

Definition of abbreviations: ART = antiretroviral therapy; ASHA = American Speech-Language-Hearing Association; CHW = community health worker; DOT = directly observed therapy; OAE = otoacoustic emissions; PAS = *para*-aminosalicylic acid; PTA = pure tone audiometry; TB = tuberculosis.

* Data from references 9, 10, 15, 17, 38, and 42.

† Hepatitis to pyrazinamide is both dose-dependent and idiosyncratic.

‡ Tendon rupture has been reported in adults being treated with fluoroquinolones, but there have been no reports in children.

If the child is not old enough, the parents must be prepared appropriately. The child and family should be warned about the possibility of all adverse events and what to do if they occur (2). These adverse events should be managed proactively and promptly. Creative mechanisms should be used to encourage adherence, with reward systems appropriate to the child's age; mobile telephone technology has been used successfully in adults and could play an important role in the adolescent age group (104).

INFECTION CONTROL

Children traditionally have been considered to pose a low infection control risk because they generally have paucibacillary disease and limited tussive force. However, as the diagnosis of DR-TB is frequently delayed in children (5, 21, 35), those with diagnosed DR-TB tend to be older than those with drug-susceptible disease (105, 106) and have more severe pathology. In one pediatric MDR-TB cohort, over 60% of children were sputum smear positive (23). Infection control should therefore form a vital part of any management strategy (107).

From the drug-susceptible TB literature, it is clear that children pose a limited infection risk to others, other than when they have extensive, adult-type disease (108, 109). The impact of drug resistance is unclear. In household studies, drug resistance does not appear to alter infectiousness (110–114) other than when drug resistance is not detected promptly or suitable treatment is delayed for other reasons. Experienced clinicians would generally suggest that smear-positive children should sleep in a room separate from others. As long as they are culture positive, they should not sleep in the same room as the most vulnerable, such as HIV-infected persons or the very young. If the climate allows, children should be encouraged to spend as much of their time outside as possible. Play, eating, and schooling areas should attempt to facilitate this. When outside, it is reasonable to allow children to play and eat without a mask. Where it is not possible to spend long periods of time outside, windows should be kept open, passive air extraction systems should be put in place, and areas with sufficient resources should have active air flow management systems installed. Children without pulmonary disease are unlikely to pose an infection risk unless there is an uncovered area with pus discharging.

Staff should protect themselves when interacting with infectious children. If the child is sputum smear positive, staff should wear a fit-tested respirator with a filter efficiency of 95% or greater (e.g., N95, N99, or N100). More comprehensive guidance on infection control measures to use in healthcare facilities has been documented by the WHO and the Centers for Disease Control (115, 116).

MULTIDISCIPLINARY CARE

Multidisciplinary care is a crucial component of the successful management of children with DR-TB. In addition, the child and caregiver should be engaged as active members of the health care team. We have found input from pharmacists to be invaluable in providing appropriate medications, formulations, and advice concerning interactions and pharmacokinetics. Support from a dietician is frequently helpful in monitoring and planning calorie intake and the correct balance of nutrients, vitamins, and minerals. Physiotherapy and occupational therapy are of benefit not only for children with neurodevelopment involvement but also for those with respiratory and musculo-skeletal deficit. Social services should assess home circumstances and support the caregiver to look after a child who may have complex medical needs and must take multiple medications. They must also assist the family in securing any funding or grants that they are eligible for to assist in the process of home-based care. In cases of neglect, abuse, or drug and alcohol use, child placement with alternative caregivers may be necessary. In areas of limited resources, many of these key tasks can be performed by CHWs. Ongoing education is important, and children should be encouraged to return to school when they are no longer infectious.

DR-TB DEFINITIONS IN CHILDREN

For clinical practice and programmatic reporting, treatment characteristics and outcome must be defined in a standardized manner. It is important to define and record if the child has been previously treated and what that treatment was and also to determine if the child has previously experienced a TB disease episode. For the current episode, the reason for treatment initiation is important, as is the site of disease. Proposed clinical definitions are provided in Table 1.

CONCLUSIONS

Treating children with DR-TB is challenging. However, it is possible to achieve excellent outcomes in a wide range of settings and with varying resources. The child and family should be actively engaged in the treatment process and supported by the healthcare team. They should be treated with at least four drugs that are likely to be effective, and the child should be monitored carefully for adverse events and response to treatment. It is likely that more and more children will be diagnosed with DR-TB in the future.

Author disclosures are available with the text of this article at www.atsjournals.org.

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