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INVITED COMMENTARY

Drug-Resistant Tuberculosis: Pediatric Guidelines

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Abstract The World Health Organization estimates that there are 650,000 prevalent cases of multidrug-resistant (MDR) tuberculosis (TB) globally, and since children (<15 years of age) constitute up to 20 % of the TB caseload in high-burden settings, the number of children with drug-resistant (DR) TB is likely to be substantial. Because bacterial burden at the site of disease is often low, diagnosis involves collection of multiple specimens and a laboratory capable of performing culture, although the Xpert MTB/RIF assay has improved sensitivity over smear examination. The basic principles of treatment for children are the same as those for adults with MDR-TB; however, the treatment regimen is often empiric and based on the drug susceptibility pattern of the source case, if available, or on past history of treatment. Additional challenges arise when MDR-TB is diagnosed and managed in the context of HIV coinfection. HIV-infected children are also treated with antiretroviral therapy medications, which have the potential to interact with second-line anti-TB drugs. Lack of pediatric formulations of second-line drugs and paucity of pharmacokinetic data make dosage challenging. However, when treated appropriately, children with DR TB have good outcomes.

Keywords Drug-resistant TB · MDR-TB · Children · Diagnosis · Treatment

Introduction

Antituberculosis drug resistance is a major public health problem that threatens progress made in tuberculosis (TB) care and control worldwide. Globally, 3.7 % (2.1 %–5.2 %) of new cases and 20 % (13 %–26 %) of previously treated cases are estimated to have multidrug-resistant (MDR) TB [1]. The World Health Organization (WHO) estimates that there are 650,000 prevalent cases of MDR-TB globally [2], and since children (<15 years of age) constitute up to 20 % of the TB caseload in high-burden settings [3, 4], the number of children with drug-resistant (DR) TB is undoubtedly high. Data regarding this vulnerable population, however, are lacking; a recent systematic review of children with MDR-TB was able to include only eight studies from five countries [5••]. Children serve as a "sentinel" of TB transmission in the community, and drug resistance in this group mirrors the situation in the adult population in the region.

Major obstacles to understanding the epidemiology of pediatric TB in general and DR-TB in particular include the difficulty of confirming the diagnosis (needing multiple specimens other than sputum and a laboratory capable of performing culture), a higher proportion of smear- and culture-negative and extrapulmonary TB in young children, and the low priority given to this group by public health programs. However, the occurrence of DR-TB among children has been documented by several groups [6, 7•, 8••, 9–11]. In the Western Cape, repeat surveys among children, done in 1997–1998, 2001–2002, and again in 2005–2006, showed that resistance to isoniazid (INH) or rifampicin (RIF) increased from 6.9 % to 12.9 % to 15.1 % and multidrug resistance from 2.3 % to 5.6 % to 6.7 % [12, 13]. Drug resistance among children has been documented in both pulmonary and extrapulmonary disease [14].

When children have MDR-TB, it is usually "primary resistance"—that is, they are infected with strains transmitted from adults with MDR-TB—rather than secondary resistance acquired as a result of suboptimal therapy or nonadherence [13]. The concordance between the *Mycobacterium tuberculosis* strain infecting the child and the adult index case varies from 45 % to 80 % in different studies, suggesting that children are exposed to TB both within and outside the household [15].

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Table 1 Tuberculosis (TB) diagnostic tests in use, recently endorsed by WHO and in later stages of development

Method	Products	Intended and/or Typical Use	Level of Health System	Main Strengths	Main Weaknesses
In use					
Smear microscopy for acid-fast bacilli (light microscopy)	Noncommercial	Rapid, point-of-care test for TB case detection	Community	Requires moderate training; minimal infrastructure; minimal equipment	Low sensitivity
Culture on solid media	Many commercialized prepared media and reagents	TB case detection and as prerequisite to drug susceptibility	Referral laboratory	Good sensitivity	Slow time to growth
Chest radiograph	NA	TB case detection (pulmonary TB)	Referral	Indications and use not restricted to TB	Low specificity, low sensitivity, requires equipment, trained interpreter
Tuberculin skin test	Many commercialized reagents	Detection of M.tuberculosis infection	Community	Extensive practical and published experience	Sensitivity decreases with increasing immunocompromise, cross-reaction with BCG vaccine
Interferon release assays	QuantiFERON-TB Gold (Cellestis) T-SPOT.TB (Oxford immunotec)	Detection of M. tuberculosis infection	Referral to reference laboratory	Highly specific for M. tuberculosis	Requires moderate training and equipment; imperfect sensitivity, especially for immunocompromised persons
Trial of antibiotics directed against routine bacterial pneumonia pathogens	NA	TB case detection for persons with suspected pulmonary TB whose sputum smear results are negative	Community	May be clinically beneficial to patients with bacterial pneumonia	Poor discriminatory power engenders time delay in further evaluation of and care for patients with TB
Automated nonintegrated NAAT	Amplifed mycobacterium tuberculosis direct test (Gen-Probe); Amplicor M. tuberculosis test (Roche)	TB case detection (pulmonary TB)	Reference laboratory	Sensitivity between that of smear and culture; highly specific for TB	Require moderate training and equipment; labor intensive; potential for cross-contamination among specimens
Endorsed by the WHO					
Culture in liquid media	MGIT (Becton Dickinson) BacT/ALERT (BioMeneux); others	TB case detection and as prerequisite to drug-susceptibility testing	Referral laboratory	High sensitivity (higher than culture on solid media)	Slow time to detection (although faster than culture on solid media); high contamination rates in some settings
Strip-based species identification (detects TB-specific antigen in positive cultures)	Capilia TB (Tauns)	Species identification (TB versus not TB) in cultures positive for mycobacterial growth	Referral laboratory (with culture)	Accurate; requires minimal training; minimal equipment; minimal consumables	
Line probe manual amplification and hybridization	Genotype MTBRplus (HainLifescience); INNO-LiPA Mycobacteria (Innogenetics)	TB case detection and drug-susceptibility testing	Reference laboratory	Poor sensitivity in smear-negative specimens; relatively short time to result	Labor-intensive; potential for cross-contamination; requires extensive training
Xpert MTB/RIF	GeneXpert, Cepheid	Rapid TB detection and rifampin resistance	Point of treatment	Simplicity of use, increased sensitivity of TB detection in smear-negative TB	Poor specificity within subset of NTM samples

Diagnosis

The diagnosis of pediatric MDR-TB is often delayed due to reliance on the adult case definition and the need for bacteriologic confirmation [16]. Systematic approaches to the diagnosis of children with suspected drug resistance and consensus case definitions have been proposed recently [17, 18]. A diagnosis of TB in children can be made on clinical and radiological grounds in the majority of cases, when bacteriological confirmation is not possible. Depending on the age of the child, site of disease, and available facilities, attempts can be made to obtain sputum, gastric aspirates, induced sputum, biologic fluid samples, nasopharyngeal aspirates, lymph node aspiration biopsy, or tissue biopsy [19–23]. With extensive sampling, the proportion of children with a confirmed diagnosis can be >50 % [24]. Invasive methods, such as bronchoalveolar lavage, bronchoscopic biopsy, or open lung biopsy may sometimes be required [25].

Diagnostic Assays

Culture can be performed using solid media, such as the egg-based Lowenstein–Jensen or the agar-based Middlebrook medium, where the cultures are examined after 3–4 weeks, instead of 4–6 weeks using the classic method. Liquid media systems such as the radioactive (Bactec) or nonradioactive (MGIT), allow detection of growth in 8–14 days. Table 1 shows the TB diagnostic tests in use recently endorsed by the WHO [26].

Tuberculin skin testing, using purified protein derivative and chest radiography, is used as an adjunct to smear microscopy (and culture, if available); however, the former has poor sensitivity and specificity for active TB, and the latter is often not available at the point of primary patient care [26].

In a large, multicountry study in adults, Boehme et al. evaluated an automated tuberculosis assay (Xpert MTB/RIF) for the presence of *Mycobacterium tuberculosis* (MTB) and resistance to RIF. With a single test, this assay identified 98 % of patients with smear-positive and culture-positive TB (including more than 70 % of patients with smear-negative and culture-positive disease) and correctly identified 98 % of bacteria that were resistant to RIF [27•]. It has several advantages over conventional nucleic acid amplification tests, which have been licensed for nearly 20 years: simple to perform with minimal training, not prone to cross-contamination, requires minimal biosafety facilities, and has a high sensitivity in smear-negative TB (the last factor being particularly relevant in patients with HIV infection) [27•].The Xpert MTB/RIF assay has demonstrated sensitivity of 50 %–70 % in specimens like gastric aspirates and induced sputum [28••, 29].

Molecular line probe assays focused on rapid detection of RIF resistance alone or in combination with INH resistance are now widely used; examples are the INNO-LiPARif.TB kit (Innogenetics, Zwijndrecht, Belgium) [30], labeled for use on *M. tuberculosis* isolates grown on solid culture, and the Genotype MTBDR and Genotype MTBDRplus assays (Hain Lifescience, Germany) [31], labeled for use on isolates from solid and liquid culture, as well as directly on smear-positive pulmonary specimens. Both assays are complete, polymerase chain reaction (PCR)-based, hybridization assays simultaneously detecting *M. tuberculosis* complex and specific mutations in the *rpoB* gene conferring RIF resistance. The Genotype MTBDRplus assay also simultaneously detects specific mutations in the *katG* gene conferring high-level INH resistance, as well as those in the *inhA* conferring low-level resistance.

The molecular basis of resistance to INH and RIF (and some other drugs) is now understood (Table 2) [32]. Resistance to INH is due to mutations at one of two main sites, in either the *katG* or the *inhA* gene [33, 34]. Resistance to RIF is nearly always due to point mutations in the *rpo* gene in the beta subunit of DNA-dependent RNA polymerase [35]. These mutations are not directly connected, and so separate mutations are required for organisms to change from a drug-susceptible isolate to MDR-TB. However, genetic probes that detect drug resistance to RIF with >95 % accuracy is very suggestive of MDR-TB; <10 % of RIF resistance is monoresistant, and so RIF resistance is a marker for MDR-TB in >90 % of cases [36]. Whenever RIF and/or INH resistance is determined by a rapid molecular test, the results should be confirmed by phenotypic testing.

There must be recognition, however, that there will be a group of children who need treatment for MDR-TB in whom bacteriological confirmation is either pending or not possible. The category of "probable" MDR-TB will allow providers to initiate timely care within programmatic guidelines in order to decrease the morbidity and mortality of MDR-TB in children,

Table 2 [32] Genetic sites for drug resistance in tuberculosis

Drug	Target	Gene
Isoniazid	Catalase-peroxidase enzyme	*katG*
Isoniazid–ethionamide	Mycolic acid synthesis	*inhA*
Rifampicin	RNA polymerase	*rpoB*
Streptomycin	Ribosomal S12 protein	*rpsL*
	16S rRNA	*rrs*
Quinolones	DNA gyrase	*gyrA*
Pyrazinamide	Pyrazinamidase-nicotinamidase	*pncA*
Ethambutol	Arabinosyl transferase	*embcAB*
PAS	Thymidylate synthase thyA	*ThyA*
Kanamycin	Ribosomal RNA	*rrs*

Table 3 Drugs used to treat tuberculosis in children (5)

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, hypothyrodism
		Prothionamide	15-20	As above
		Cycloserine	15-20	Neurological and psychological effects
		Terizidone	15-20	As above
		Para-aminosalicylic acid	150	Gastrointestinal intolerance, hypothyrodism, hepatitis
5	Agents with unclear efficacy	Clofazimine	3-5	Skin discoloration, xerosis, abdominalpain
		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 reaction, seizures, liver and renal dysfunction
		Imipenem/cilastatin		As above
		Thiacetazone	2.5	Stevens Johnson Syndrome in HIV-infected patients, gastrointestinal intolerance, hepatitits, 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 arrtrythmias

Note. DR-TB=drug-resistant tuberculosis.

*Daily unless otherwise specified

+ The stated dose is advised to be given twice a day for children <5 years

while at the same time ensuring that any potential therapeutic "chaos" does not ensue.

Children with signs and symptoms of active TB disease who, in addition, have the following risk factors should be considered as having "probable" MDR-TB and started on MDR-TB treatment, even in the absence of bacteriological confirmation [8••]:

1. Close contact with a known case of MDR-TB;
2. Close contact with a person who died whilst on TB treatment;
3. Close contact with a person who failed TB treatment;
4. Failure of a first -line regimen;
5. Previous treatment with second-line medications.

Treatment

The basic principles of treatment regimen design for children are the same as for adults with MDR-TB [37]. One major difference for children is that their treatment is often empiric and based on the drug susceptibility pattern of the source case, if available, or on past history of treatment.

Depending on country guidelines, the regimen used is either individually constructed or a standardized one, such as the Category IV regimen recommended by WHO [18].

The basic principles are the following:

- Use any first-line medication to which susceptibility is documented or likely (high-dose INH could be included routinely, unless high-level INH resistance or Kat-G mutation is documented).
- Use of at least four second-line drugs to which the strain is likely to be sensitive; one of these agents should be an injectable, one should be a fluoroquinolone, and PZA should be continued.
- All doses should be given using DOT (directly observed therapy) to ensure that patients adhere to treatment.
- Treatment duration should be for 18–24 months, at least 12 months after the last positive culture/smear with minimal disease or 18 months with extensive (lung cavities or widespread parenchymal involvement) disease.

Table 3 shows the five groups of drugs recommended by WHO for use in treating DR-TB in children [5••]. The pharmacokinetics and toxicity of drugs in children differ considerably from those in adults. Almost every aspect of pharmacokinetics (absorption, distribution, metabolism, excretion) is subject to age-related change. Young children often require a higher mg/kg bodyweight dosage of a drug to achieve the same pharmacokinetic exposure as in adults. Current dosing recommendations are based on adult mg/kg doses [18].

For children, amikacin is usually given in preference to kanamycin, since it has a lower minimum inhibitory concentration and the available ampoule sizes are smaller, preventing wastage. Capreomycin is usually reserved for the treatment of extensively DR (XDR) TB. The fluoroquinolones have a central role in the management of MDR-TB in children. Resistance to early generation fluoroquinolones (ofloxacin) may not necessarily imply resistance to later generations (moxifloxacin or levofloxacin) [38]. Few studies have assessed the pharmacokinetics of fluoroquinolones in children; the available data are largely from studies in older children with cystic fibrosis [39].

The second-line drugs are rarely produced in pediatric formulations or appropriate tablet sizes, necessitating breaking, splitting, crushing, or grinding. Hence, dosing may be inaccurate, and subtherapeutic or toxic levels are possible. The taste of the medications is often unpalatable.

Adherence to treatment is a critical factor in the management of MDR-TB, and adverse events associated with second-line drugs could have a severe impact on adherence [40]. In general, children tolerate drugs better than do adults, and most side effects

Table 4 Overview of anti-TB drugs in the clinical pipeline [54]

Drug	Trial Phase	Potential to Shorten Treatment	Acceptable Toxicity Profile	Active Against MDR- TB	Useful in HIV-Infected Patients with TB	Active Against Latent TB[a]	Interaction with Rifampin
High-dose rifampin	II	Yes	To be established	Limited	Yes, but not coadministered with protease inhibitors	Yes, but not first choice	NA[b]
High-dose rifapentine	II	Yes[c]	To be established	Limited	To be established	Yes	NA
Moxifloxacin	III	Yes	Yes	Yes	Yes	Yes[c]	Yes; reduced AUC of moxifloxacin by 30 %
Gatifloxacin	III	Yes	Yes (caution: dysglycemia in elderly)	Yes	Yes	Unkown	Possible
TMC207	II	Yes[c]	To be established	Yes	Unknown	Unknown	Yes; reduced serum TMC207 concn by 50 %
PA-824	II	Doubtful	Yes (moderate increase in creatinine observed)	Yes	Unknown	Yes[c]	No
OPC-67683	I/II	Yes[c]	To be established	Yes	Unknown	Unknown	No
SQ109	I/II	Yes[c]	To be established	Yes	Unknown	Unknown	Synergism in vitro
LL3858	I	Yes[c]	Unknown	Yes	Unknown	Unknown	Synergism in vitro

• [a] Latent TB is the situation in which a host is infected with *Mycobacterium tuberculosis* but has not developed symptoms.

• [b] NA, not applicable.

• [c] Results from preclinical data.

are mild and manageable with counseling and symptomatic drugs. The published information on treatment outcomes for children with MDR-TB suggests that when appropriately treated, outcomes are as good if not better than in adults [41•].

MDR-TB and HIV Coinfection

In settings with a high burden of TB and HIV, up to 40 % of children with MDR-TB are also HIV infected [42]. However, there are few reports of DR-TB/HIV cotreatment in pediatric patients [43–45]. The combination of MDR-TB and HIV can have serious psychological effects. Both conditions are stigmatized and are perceived to carry poor prognosis. The second- and third-line TB regimens demonstrate their own distinct cumulative toxicities with concomitant antiretroviral administration; the nephrotoxicity associated with tenofovir may be compounded by the antituberculous aminoglycosides, and the peripheral neurotoxicity induced by stavudine and didanosine and psychiatric disturbances associated with efavirenz may be exacerbated by the antituberculous agent cycloserine. Additionally, the pill burden and gastrointestinal distress associated with drug-susceptible TB regimens are even greater with MDR-TB and XDR-TB regimens [46, 47].

Studies have demonstrated that, even in a setting of high HIV prevalence, it is possible to achieve favorable outcomes among children treated for MDR-TB using early empiric treatment delivered through a comprehensive community-based program [16, 41•, 48–50]. Four pediatric XDR-TB patients with HIV coinfection were successfully cured with cotreatment in South Africa [43]. Another study in South Africa examined outcomes in 111 children with MDR-TB, including 43 children with HIV coinfection, most of whom initiated ART prior to or during MDR-TB treatment. In that report, 82 % of patients achieved favorable outcomes, and 5 of the 13 deaths occurred before confirmation of MDR-TB and initiation of appropriate treatment [45].

Supportive Care

In addition to TB drugs, guidelines recommend that children with TB should be given pyridoxine if they are HIV infected, malnourished, or breast fed or are being given terizidone, cycloserine, or high-dose INH [51, 52]. Most experts put all children being treated for DR-TB on multivitamin supplements. Nutritional and metabolic requirements should be assessed, because these children are commonly malnourished, and supplements should be provided when necessary [44, 45]. Physiotherapy and occupational therapy may be of benefit for children with respiratory and musculo-skeletal deficit. Social workers should assess home circumstances and support the caregiver to look after a child who may have complex medical needs and must take multiple medications.

New TB Drugs

There are six novel drugs in four new classes in clinical trials, including TMC207 (Bedaquiline), OPC-67683 (Delamanid), PA824, SQ109, and Oxazolidinones (PNU-100480 and AZD5847) [53].

Table 4 shows the overview of anti-TB drugs in the clinical pipeline [54]. These agents are anticipated to shorten and improve the treatment of drug-resistant, and possibly drug-susceptible, tuberculosis—used either separately or in novel combinations. A recent study from South Africa evaluated several novel combinations in an early bactericidal activity study, which measures decline in sputum colony counts per day among patients with sputum smear-positive pulmonary TB, and got encouraging results [55•].

Conclusions and Future Directions

MDR-TB in children is often an underrecognized and neglected problem. Although accurate prevalence or incidence data are not available, wherever surveillance has been done, the rates have been found similar to those for adults in the region. Diagnosis should be presumptive, based upon a number of clinical and epidemiologic factors, in situations where bacteriologic confirmation is not available. While principles of treatment are similar to those for adults, lack of pediatric formulations and paucity of information on pharmacokinetics of second-line drugs in children make treatment challenging. Outcomes are good when appropriate therapy is initiated, even in the presence of HIV coinfection. Research is urgently required to establish optimal dosing schedules of second-line drugs, investigate shorter, more patient-friendly, fully oral regimens for treatment and prevention, and initiate dose-finding and safety studies of newer anti-TB molecules (e.g., Bedaquiline, PA 824, and Delamanid).

Compliance with Ethics Guidelines

Conflict of Interest Navaneetha Pandian Poorana Ganga Devi and, Soumya Swaminathan declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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