New and Repurposed Drugs for Pediatric Multidrug-Resistant Tuberculosis

Practice-based Recommendations

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Abstract

It is estimated that 33,000 children develop multidrug-resistant tuberculosis (MDR-TB) each year. In spite of these numbers, children and adolescents have limited access to the new and repurposed MDR-TB drugs. There is also little clinical guidance for the use of these drugs and for the shorter MDR-TB regimen in the pediatric population. This is despite the fact that these drugs and regimens are associated with improved interim outcomes and acceptable safety profiles in adults. This review fills a gap in the pediatric MDR-TB literature by providing practice-based recommendations for the use of the new (delamanid and bedaquiline) and repurposed (linezolid and clofazimine) MDR-TB drugs and the new shorter MDR-TB regimen in children and adolescents.

Keywords: multidrug-resistant tuberculosis; *Mycobacterium tuberculosis*; child; adolescent; pediatric

Each year, approximately 33,000 children develop multidrug-resistant tuberculosis (MDR-TB, *Mycobacterium tuberculosis* with *in vitro* resistance to at least isoniazid and rifampin), but diagnosis and treatment remain problematic (1, 2). Although children have better treatment outcomes than adults with MDR-TB, global treatment success rates still remain unacceptably low and children suffer from the serious side effects of the older second-line MDR-TB drugs (3, 4). Unfortunately, children have limited access to the new drugs bedaquiline and delamanid and to the repurposed drugs clofazimine and linezolid that have shown improved interim outcomes and acceptable safety profiles in adults (5, 6). Children also have limited access to the

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shorter MDR-TB treatment regimen[1] that has shown promise in adult and adolescent patients (7, 8) and has been recommended by the World Health Organization (WHO) for selected individuals with MDR-TB (9).

This differential standard of care is due, in part, to the exclusion of children from most TB clinical trials (10). There is some consensus that adolescents should be included in adult TB efficacy trials, but it may not be necessary to repeat efficacy trials in younger children. It is important, however, that children of all ages be included in both pharmacokinetic and safety studies of TB drugs and new regimens, to ensure there is appropriate pediatric dosing and safety information (11). Such inclusion should be done quickly to prevent unnecessary delays in pediatric access to therapeutic advances.

While awaiting data from studies, front-line providers must make decisions about how to treat children with MDR-TB, including how to use the new and repurposed drugs. Despite positive experiences with these interventions in adults, there are no recommendations regarding their clinical use in children (12). This review fills a gap in the pediatric MDR-TB literature by providing practice-based recommendations for the use of new and repurposed drugs and novel regimens.

Some of the results of these studies have been previously reported in the form of abstracts (13–17).

Methods

Articles identified from a comprehensive literature review were consulted using a methodology previously described (18). Briefly, articles from a systematic review were complemented via a comprehensive literature search using PubMed and a review of recent WHO guidelines. A writing committee (E.P.H. and J.F.) wrote the initial draft and then incorporated comments from the remaining coauthors. In accordance with recommendations from an expert panel on inclusion of children in TB clinical studies, assessments of efficacy in adults were applied to children, although there may be limitations to this approach (11). However, data on safety and dosing in children were reviewed and considered separately from these data in adults. This was done as it is accepted that adult efficacy data can be applied to children; however, safety and dosing data need to be pediatric specific. Because there are limited published data on the use of new drugs and regimens in children, expert consensus was reached where evidence was lacking. The consensus was generated by clinical health professionals working within the Sentinel Project on Pediatric Drug-Resistant Tuberculosis (19). The process differed from that used by some normative bodies (e.g., the WHO) as it considered practice-based experience, and its target audience is clinical providers. The authors of this review have more than two decades of experience in caring for children with MDR-TB in the international context, including the use of new and repurposed drugs.

Treatment Recommendations

Summary recommendations are provided in Table 1. Clinical studies of new and repurposed drugs are summarized in Table 2. Information on formulations and procurement is summarized in Table 3. Because of length constraints, recommendations for the short MDR-TB regimen are available as an online supplement. For every medication and regimen discussed, it is recommended that informed consent be obtained, active pharmacovigilance be performed, and monitoring of patients be performed according to WHO recommendations for adult patients (20). Children should also receive adherence counseling, social support, and nutritional supplementation as recommended for the treatment of children with MDR-TB (21, 22).

Delamanid

Efficacy and safety in adults. Delamanid (Otsuka Pharmaceutical, Tokyo, Japan) is a nitroimidazole shown to be effective when added to an MDR-TB regimen in a randomized, placebo-controlled phase IIb trial (23). In this phase IIb trial, patients were randomized to receive an optimized background regimen (OBR) with either placebo or delamanid added for 8 weeks. After the initial 8 weeks, there was a 4-week period of continued OBR treatment, and then all participants were offered open-label delamanid for an additional 24 weeks. When participants who received at least 6 months of delamanid were compared with participants who received less than 2 months of delamanid, there were statistically significant differences seen in the time to culture conversion, the rates of culture conversion at both 8 and 24 weeks, and treatment success, with those who had at least 2 months of therapy doing better (24). The drug was well tolerated with mild to moderate QTc prolongation (12.1 ms) observed but no clinical cardiac complications (25). This study led to conditional marketing approval for delamanid in the European Union and Japan in 2013 and later in South Korea (26). A phase III randomized, placebo-controlled trial of delamanid has completed enrollment and the period of study drug administration; treatment outcome results are expected in 2017–2018 (27).

Delamanid was recommended by the WHO in 2014 for treatment of adults with MDR-TB. WHO guidelines state that delamanid may be given to adults with MDR-TB in whom a four-drug regimen plus pyrazinamide cannot be constructed due to resistance or significant intolerance to other medications and that delamanid be given to adults at "high risk" of poor treatment outcomes. These guidelines stress that delamanid should be used as part of programmatic management of MDR-TB under the following conditions: (*1*) proper patient inclusion; (*2*) close clinical and programmatic monitoring; (*3*) used as part of a regimen that follows WHO guidelines; (*4*) due process followed for informed consent; and (*5*) active monitoring and management of adverse events. The WHO guidelines offer no recommendation on the use of delamanid in persons less than 18 years old, noting that there was insufficient evidence to make such a recommendation at the time of review in 2014 (28).

Dosing and safety in children. Otsuka has led a pediatric development program for delamanid, with enrollment in phase I and II pediatric trials beginning in 2013. Since the WHO interim guidelines were published in 2014, two studies of pharmacokinetics and safety in HIV-uninfected children as young as 6 years old have been presented at international meetings (13, 14). These studies follow an age de-escalation protocol in which the drug is first given to older

[1] "Shorter regimen" refers to the 9- to 12-month regimens that have been assessed under operational research conditions and are often referred to as the "Bangladesh" or "9-month" regimen.

Table 1. Summary Recommendations for New and Repurposed Drugs and Regimens for Multidrug-Resistant Tuberculosis in Children and Adolescents

Delamanid

Recommended dose

>35 kg: 100 mg twice daily
20–34 kg: 50 mg twice daily
<20 kg: consult with expert
Duration: 24 wk; longer duration could be considered on a case-by-case basis (no alternative drug option)

Indications for use: *children ⩾6 yr old and ⩾20 kg*

- Confirmed MDR-TB when a four-drug regimen plus pyrazinamide cannot be constructed owing to resistance or significant intolerance
- Probable MDR-TB with a source case with known or suspected additional resistance to second-line agents
- Confirmed or probable MDR-TB with a high risk of treatment failure

Indications for use: *children <6 yr old and <20 kg*

It is recommended that consultation with expert clinicians be sought before administering delamanid to children in this age range via consultation with the European Respiratory Society–hosted TB Consilium (https://www.tbconsilium.org) or the Sentinel Project on Pediatric Drug-Resistant Tuberculosis (tbsentinelproject@gmail.com)

Contraindications

- Baseline QTc interval greater than 500 ms that does not correct with medical management
- Allergy to delamanid or metronidazole
- Prior treatment with nitroimidazole agents (i.e., pretomanid/PA-824)

Monitoring

Baseline: ECG to assess QTc interval and albumin in addition to standard MDR-TB assessments
Follow-up: Monthly ECG to assess for QTc prolongation (although less frequent monitoring could be considered after 8 wk in children with a normal baseline and follow-up QTc intervals if access to electrocardiographic monitoring is a challenge) in addition to standard MDR-TB assessments

Bedaquiline

Recommended dose

Adolescents ⩾12 yr old who weigh 33 kg or more: 400 mg daily for 14 d followed by 200 mg given three times weekly for an additional 22 wk
Duration: 24 wk; longer duration could be considered on a case-by-case basis

Indications for use: *children ⩾12 yr old and who weigh >33 kg*

- Confirmed MDR-TB in whom a four-drug regimen plus pyrazinamide cannot be constructed because of resistance or significant intolerance and where delamanid is not available
- Probable MDR-TB with a source case with known or suspected additional resistance to second-line agents and where delamanid is not available

Indications for use: *children <12 yr old or who weigh <33 kg*

It is recommended that consultation with expert clinicians be sought before administering bedaquiline to children in this age range via consultation with the ERS-hosted TB Consilium (https://www.tbconsilium.org) or the Sentinel Project on Pediatric Drug-Resistant Tuberculosis (tbsentinelproject@gmail.com)

Contraindications

- Baseline QTc interval greater than 450 ms that does not correct with medical management
- Patient or family history of cardiac arrhythmias
- Severe cardiac disease
- Allergy to bedaquiline

Monitoring

Baseline: ECG to assess QTc interval in addition to standard MDR-TB assessments
Follow-up: Monthly ECG to assess for QTc prolongation in addition to standard MDR-TB assessments

Linezolid

Recommended dosing

Children ⩾12 yr: 10 mg/kg once daily
Children <12 yr of age: 10 mg/kg twice daily
Duration: entire course of treatment as long as the child tolerates it

Indications for use

- Confirmed or probable MDR-TB as part of the core second-line regimen
- If adverse events cannot be monitored, linezolid is best used in patients with additional resistance or intolerance to other second-line medications

Contraindications and monitoring

- Avoid in children with significant anemia, leukopenia, or thrombocytopenia
- Avoid in children with significant peripheral neuropathy
- Monthly screening for peripheral neuropathy and monthly complete blood counts should be assessed while the child is receiving linezolid

Clofazimine

Recommended dosing

2–3 mg/kg given daily for a maximum daily dose of 100 mg or every other day in smaller children (gelcaps cannot be split)
Duration: entire course of treatment as long as the child tolerates it

(Continued)

Table 1. (*Continued*)

Indications for use
• Confirmed or probable MDR-TB as part of the core second-line regimen
Contraindications and monitoring
• Avoid in children with a baseline QTc interval greater than 500 ms that does not correct with medical management
• Baseline and monthly ECGs to assess QTc interval
Shorter MDR-TB regimen ("9- to 12-mo regimen")
Recommended doses
As per published guidelines. Of note, there are no pediatric safety data yet on the doses of moxifloxacin (12 mg/kg) used in this study
Duration: 9–12 mo, depending on culture conversion and/or clinical response
Indications for use
• Probable or confirmed MDR-TB in which resistance to second-line drugs is unlikely
• Probable or confirmed MDR-TB with no previous second-line drug treatment in the child or source case
Contraindications and monitoring
• Avoid in children with known resistance to any component of the shortened regimen except isoniazid
• Avoid in children whose source cases have known resistance to any component of the shortened regimen except isoniazid
• Avoid in children with an allergy to any of the medications in the shortened regimen
• Baseline and monthly ECG to assess QTc interval

Definition of abbreviations: ERS = European Respiratory Society; MDR-TB = multidrug-resistant tuberculosis; TB = tuberculosis.

children and, when shown to be safe with established dosing, it is given to younger children. Although age bands were used to design the study, the ultimate dosing recommendations are based on weight, and weight should guide the dose selection for children. For children at least 13 years of age and weighing at least 35 kg, a dose of 100 mg twice daily was safe and achieved adequate serum concentrations. For children 6–12 years of age and weighing 20–34 kg, a dose of 50 mg of delamanid twice daily achieved adequate serum concentrations. A safety and pharmacokinetics study of delamanid in children 3–5 years old is currently enrolling patients; when dosing and safety are established, then children and infants less than 3 years of age will be evaluated. A pediatric dispersible formulation of delamanid is being assessed as part of these trials. In addition, studies in children who are HIV coinfected are planned. Delamanid is available for pediatric patients at least 6 years of age and with a body weight greater than 20 kg via compassionate use from Otsuka. Of note, there are more pediatric data on the safety and dosing of delamanid than for some other second-line drugs that are frequently used to treat children for MDR-TB, such as cycloserine and clofazimine (29).

Recommendations for delamanid use in children. Delamanid may be included in the treatment regimens of children at least 6 years old and who weigh at least 20 kg for the same indications as for adults: those with MDR-TB in whom a four-drug regimen plus pyrazinamide cannot be constructed due to resistance or significant intolerance *or* those with a high risk of treatment failure. Because MDR-TB may be difficult to bacteriologically confirm in children, delamanid may be used in children if they have an MDR-TB source case with known or suspected resistance to second-line agents. Children at high risk for treatment failure include those with immunocompromising conditions (e.g., HIV, diabetes, malnutrition) or those with extensive disease (defined as extrapulmonary TB other than isolated lymphadenitis; or pulmonary TB with bilateral infiltrates and/or cavities) (4). Children in this age and weight group receiving standard MDR-TB therapy and who develop significant toxicity in response to any of their medications should have the causative agent discontinued and delamanid started as a substitute. Avoid adding a single drug to a failing regimen.

Delamanid can be considered on a case-by-case basis in children less than 6 years old and who weigh less than 20 kg, if the children meet the criteria previously described and no suitable alternatives are available. Although studies of delamanid in this age group are ongoing, there may be cases in which the benefits of including delamanid outweigh the risk (30). As with other second-line drugs, the delamanid dose for this age and weight range would have to be extrapolated from the dosages used in older children and adults (31). Until the dispersible tablet is available, administration of delamanid to younger children might involve crushing and mixing the drug, which could affect its stability and bioavailability, although this is true for most second-line drugs. It is recommended that consultation with expert clinicians be sought before administering delamanid to children in this age range. Such consultation is available through the European Respiratory Society–hosted TB Consilium (https://www.tbconsilium.org) (32) or through the Sentinel Project on Pediatric Drug-Resistant Tuberculosis (tbsentinelproject@gmail.com).

As with adults, programs treating children with delamanid should meet the five conditions recommended by the WHO for its use in adults (28). All children should undergo the standard baseline testing for MDR-TB treatment. They should also undergo a baseline ECG to assess the QTc interval[2] and a baseline serum albumin level. Children with a baseline QTc interval greater than 500 milliseconds should not be started on delamanid until the interval is corrected by medical management (33). Delamanid is metabolized by albumin and there may be higher rates of adverse events in children with hypoalbuminemia; therefore children with serum albumin levels less than 2.8 g/dl should receive protein supplementation during delamanid

[2]The QTc interval is a measure of cardiac myocyte readiness for depolarization. A prolonged QTc interval (defined as greater than 500 ms) may be a risk factor for the development of fatal cardiac arrhythmias. The most commonly used correction for the QT interval in children is by the Fridericia correction (QTcF).

therapy. Children with an allergy to delamanid or metronidazole or who have been treated with other nitroimidazole drugs (i.e., pretomanid/PA-824) should not be treated with delamanid. While receiving delamanid, children should undergo a monthly ECG to assess for QTc prolongation, although less frequent monitoring after 8 weeks could be considered in children with a normal baseline and follow-up QTc intervals if access to electrocardiographic monitoring is a challenge. Combination with drugs that also prolong the QTc interval should be done with caution, and substitution of levofloxacin (which has less effect on the QTc interval) for moxifloxacin is advised. Official recommendations are for delamanid to be given for 24 weeks total, although longer courses of therapy have been given to adults and children with limited therapeutic options. In the initial phase IIb trials in adults, a substantial number of individuals (192 of 421) received 8 months of delamanid without any additional safety signals (23). Phase I studies in adults show that delamanid did not have any significant drug–drug interactions with antiretroviral therapy, including tenofovir, efavirenz, and lopinavir–ritonavir (15).

Replacement of the injectable agent with delamanid? Children tend to tolerate second-line medications better than adults do; however, the second-line injectable medications are problematic (34). Although there are currently no data to support the routine substitution of delamanid for a second-line injectable agent within the MDR-TB regimen, providers could consider using delamanid instead of the injectable drug in the initial regimen in children with MDR-TB. This substitution could substantially benefit children given the risk of permanent sensorineural hearing loss in children (reported in up to 25% of children) due to the second-line injectable agents and the pain and hospitalization requirements that are associated with daily intramuscular injections (34). These drugs have been assessed only when given in combination with other agents; it is therefore challenging to tease out the individual contribution of specific drugs in an MDR-TB regimen (35, 36). However, there is higher quality evidence for the inclusion of delamanid than there is for the inclusion of the injectable given that delamanid has been assessed in randomized placebo-controlled clinical trials for MDR-TB whereas the injectable agents have not. There also exists substantial clinical experience in treating children with nonsevere MDR-TB disease with an injectable-sparing regimen, with good results (3).

Bedaquiline

Efficacy and safety in adults. Bedaquiline (Janssen Pharmaceuticals, Beerse, Belgium) is a diarylquinoline that was effective when added to an MDR-TB regimen in a randomized, placebo-controlled phase IIb trial (37). In this phase IIb trial, patients were randomized to receive an OBR with either placebo or bedaquiline for 24 weeks. When compared with placebo, bedaquiline was associated with significantly reduced time to culture conversion, increased rates of culture conversion at 24 weeks, and increased cure rates (38). The drug was associated with moderate QTc prolongation (15.7 ms), and although there were higher rates of cure and lower rates of failure and loss to follow-up in the bedaquiline group, there was also a significantly higher rate of all-cause mortality (although the number of deaths was small) in the bedaquiline group compared with the placebo group (39). This study led to conditional approval of bedaquiline for the treatment of MDR-TB by the U.S. Food and Drug Administration (FDA) in 2012 and subsequently by a number of other stringent regulatory authorities in the European Union, South Africa, and India (40). In 2013, the WHO and the U.S. Centers for Disease Control and Prevention (CDC) published interim guidelines on the programmatic use of bedaquiline in specified adult patients with MDR-TB (41, 42). The STREAM-II (Evaluation of a Standard Treatment Regimen of Antituberculosis Drugs for Patients with MDR-TB) trial, which is a phase III randomized, placebo-controlled trial of bedaquiline, began enrolling patients in May of 2016 (27). A number of observational cohort studies confirming the efficacy and safety of bedaquiline have been reported from a variety of settings (5, 6). There are currently more than 3,000 individuals receiving bedaquiline worldwide (43).

The WHO and CDC guidelines state that bedaquiline may be offered to adults with MDR-TB in whom a four-drug regimen plus pyrazinamide cannot be constructed for reasons of resistance or significant intolerance to other medications. The WHO guidelines also stress that bedaquiline should be used as part of programmatic management of MDR-TB under the same five conditions as delamanid, although they specify the need for a signed informed consent for bedaquiline. The WHO guidelines state there was not sufficient evidence to make a recommendation regarding bedaquiline use in persons less than 18 years old at the time the evidence was reviewed in 2013 (41). The CDC also stated that there is insufficient evidence to provide guidelines for the use of bedaquiline in children, but that its use can be considered on a case-by-case basis, given the high mortality and limited treatment options for MDR-TB (42).

Dosing and safety in children. Bedaquiline has not yet been formally assessed in children less than 18 years old. However, a Janssen Pharmaceuticals safety and pharmacokinetics study in children (ages 5–11 yr) and adolescents (ages 12–18 yr) opened for enrollment in South Africa in May of 2016 (27). Younger children will be included in this trial, based on the data obtained from older children and following an age de-escalation protocol. A 20-mg dispersible tablet formulation will be assessed in this trial. A second trial of bedaquiline in HIV-infected and uninfected children sponsored by the U.S. National Institutes of Health (NIH) IMPAACT (International Maternal Pediatric Adolescent AIDS Clinical Trials) network, is being planned and may begin enrolling in 2016 (44). A compassionate use protocol for children is also being developed by Janssen Pharmaceuticals.

There has been some programmatic experience using bedaquiline in adolescents not exceeding 12 years of age (16, 17). When adolescents weighing at least 33 kg have been given bedaquiline, they have received the same dosages that are given to adults: 400 mg daily for 14 days followed by 200 mg three times weekly for 22 weeks.

Recommendations for bedaquiline use in children. Bedaquiline could be considered for the treatment of children at least 12 years old and weighing at least 33 kg for the same indications extrapolated from adults: those with MDR-TB in whom a four-drug regimen plus pyrazinamide cannot be constructed due to resistance or significant intolerance. Bedaquiline may be included in treatment regimens for children with

Table 2. Summary of Ongoing, Planned, or Completed Pediatric Studies Involving New Drugs, Repurposed Drugs, and New Regimens*

Drug/ Regimen	Study/Reference Number	Design	Status of Study	Findings
Bedaquiline	Janssen-sponsored PK, safety, and tolerability trial in children and adolescents/ NCT02354014	A phase II, open-label, multicenter, single-arm study to evaluate PK, safety, tolerability, and antimycobacterial activity of TMC207 in combination with a background regimen of MDR-TB medications for the treatment of children and adolescents 0 mo to <18 yr of age who have confirmed or probable pulmonary MDR-TB	Enrolling 11–17 yr; will begin enrolling 5–10 yr with IRB approval; will enroll younger cohorts once data available from older cohorts	Pending
	IMPAACT PK and safety/P1108	Phase I/II, open-label, single-arm study to evaluate PK, safety, and tolerability of bedaquiline in combination with optimized individualized MDR-TB therapy in HIV-infected and HIV-uninfected infants, children, and adolescents with MDR-TB disease	Not yet open to enrollment	Pending
	NiX trial/NCT02333799	A phase III open-label trial assessing the safety and efficacy of bedaquiline plus PA-824 plus linezolid in subjects with pulmonary infection of either XDR-TB or treatment-intolerant/nonresponsive MDR-TB (NiX-TB)	Enrolling, includes adolescents ages 14 yr and older	Pending
	Observational cohorts	Bedaquiline is being given to adolescent patients as part of programmatic management of MDR-TB, compassionate use protocols, and operational research projects in multiple countries	Cohort data collection and analysis is ongoing	Pending
Delamanid	Otsuka-sponsored long-term safety, efficacy, and pharmacokinetic study of delamanid in pediatric patients with MDR-TB/NCT01859923	Phase II, open-label, multiple-dose trial to assess the safety, tolerability, PK, and efficacy of delamanid in pediatric patients with MDR-TB and receiving therapy with an optimized background regimen of anti-TB drugs over a 6-mo treatment period	Enrollment completed for cohorts age 6+ yr; enrollment open for cohort age <6 yr	Plasma concentrations in the pediatric patients were within the range observed in the open-label trial in adults. Delamanid was well tolerated after 6 mo of therapy in the 12-to 17-yr age group
	Otsuka-sponsored short-term pharmacokinetic and safety trial of delamanid to determine the appropriate dose for pediatric patients with MDR-TB	Phase I, open-label, multiple-dose, and age de-escalation trial to assess the PK, safety, and tolerability of delamanid (OPC 67683) in pediatric patients with MDR-TB receiving therapy with an optimized background regimen of anti-TB drugs	Enrollment completed for cohorts aged 6–11 and 12–17 yr; enrollment for cohort aged 3–5 yr open	Median delamanid exposures were higher in the population of patients ages 6–17 yr compared with adults but within the ranges observed in the adult population. Delamanid was well tolerated in the short term in these cohorts

(Continued)

Table 2. (*Continued*)

Drug/ Regimen	Study/Reference Number	Design	Status of Study	Findings
	Observational cohorts	Delamanid is being given to pediatric patients as part of compassionate use protocols and operational research projects in multiple countries	Cohort data collection and analysis is ongoing	Early results from 19 pediatric patients receiving delamanid as part of multidrug therapy for MDR-TB show that the drug is well tolerated and appears to be efficacious
Linezolid	Pharmacokinetics and toxicity of the second-line anti-TB drugs in HIV-infected and uninfected children	Prospective, longitudinal, hospital-based, observational PK study in HIV-infected and uninfected children aged 0–15 yr who are routinely receiving chemotherapy or chemoprophylaxis for the treatment or prevention of DR-TB	By the end of 2014, a total of 230 participants had already been enrolled; target enrollment is 318 children	Pending
	NiX trial/NCT02333799	A phase III open-label trial assessing the safety and efficacy of bedaquiline plus PA-824 plus linezolid in subjects with pulmonary infection with either XDR-TB or treatment-intolerant/nonresponsive MDR-TB (NiX-TB)	Enrolling, includes adolescents ages 14 yr and older	Pending
	Observational cohorts	Linezolid is being given to pediatric patients as part of programmatic management of MDR-TB and operational research projects in multiple countries	Cohort data collection and analysis is ongoing	
Clofazimine	Pharmacokinetics and toxicity of the second-line anti-TB drugs in HIV-infected and uninfected children	Prospective, longitudinal, hospital-based, observational PK study in HIV-infected and uninfected children aged 0–15 yr who are routinely receiving chemotherapy or chemoprophylaxis for the treatment or prevention of DR-TB	By the end of 2014, a total of 230 participants had already been enrolled; target enrollment is 318 children	Pending
	Observational cohorts	Clofazimine is being given to pediatric patients as part of programmatic management of MDR-TB and operational research projects in multiple countries	Cohort data collection and analysis is ongoing	Pending
Shorter regimens	Observational cohorts	Shortened regimens are being given to pediatric patients as part of programmatic management of MDR-TB and operational research projects in multiple countries	Cohort data collection and analysis is ongoing	Case reports show that the shortened regimens are safe and effective in the limited number of pediatric patients who have received them

Definition of abbreviations: DR-TB = drug-resistant tuberculosis; IMPAACT = International Maternal Pediatric Adolescent AIDS Clinical Trials; IRB = institutional review board; MDR-TB = multidrug-resistant tuberculosis; PK = pharmacokinetics; TB = tuberculosis; XDR-TB = extensively drug-resistant tuberculosis.

*Adapted from the RESIST-TB site (http://www.resisttb.org/?page_id=1602) and from the 2016 TAG Pipeline Report (http://www.pipelinereport.org/2015/tb-pediatrics).

probable MDR-TB if they have a source case who meets these criteria. Children in this age group receiving standard MDR-TB therapy and who develop clinically significant toxicity in response to any of their medications should have the causative agent discontinued and bedaquiline started as a substitute, but it should not be added as a single drug to a failing regimen. The adult dose of bedaquiline should be given (400 mg daily for 14 d and then 200 mg three times per week for 22 wk).

Bedaquiline could be considered in children less than 12 years old if the children meet the criteria described previously and no suitable alternatives are available. Delamanid, however, is the preferred novel agent in this population, given that there

Table 3. Formulations and Procurement of New and Repurposed Drugs for Multidrug-Resistant Tuberculosis

Drug	Formulation	Procurement	Cost and Funding	Comments
Delamanid	50-mg tablet	GDF	1,700 USD for 6-mo course	This price is available for GF-eligible countries GF grants will cover the cost of GDF-procured delamanid Countries not eligible for GF can obtain delamanid from Otsuka Single-patient compassionate use still available from Otsuka*
Bedaquiline	100-mg tablet	GDF	USAID donation for GF-eligible countries. Tiered pricing for non–GF-eligible countries: 6-mo course of 188 tablets is 900 USD for low-income countries and 3,000 USD for middle-income countries	Information on the USAID donation program can be found at http://www.stoptb.org/news/stories/2014/ns14_025.asp
Linezolid	600-mg tablet; 20-mg/ml suspension	GDF; country-specific	2.50–6.00 USD for each 600-mg tablet (64); country-specific	GF will support the procurement of linezolid
Clofazimine	50-mg gelcaps; 100-mg gelcaps	GDF	1.10 USD for each 100-mg tablet; 0.55 USD for each 50-mg tablet	GF will support the procurement of clofazimine
Shortened regimen	All components except gatifloxacin are available via the GDF			

Definition of abbreviations: GDF = Global Drug Facility; GF = Global Fund for AIDS, Tuberculosis, and Malaria; USAID = U.S. Agency for International Development; USD = U.S. dollars.
*For additional information on compassionate use of delamanid, contact Alexandra Martin at amartin@otsuka-onpg.com.

are more data on safety and dosing of delamanid. As with other second-line drugs, the bedaquiline dosage for these lower age and weight ranges would have to be extrapolated from adult dosages. Furthermore, there is no currently available pediatric formulation of bedaquiline, and administration of this drug to younger children would involve crushing and mixing of the drug, which could affect stability and bioavailability. It is recommended that consultation with expert clinicians be sought before administering bedaquiline to children in this age range.

As with adults, programs treating children with bedaquiline should meet the five conditions recommended by the WHO (41). All children being considered for bedaquiline should undergo the baseline testing normally undertaken before MDR-TB treatment but should also undergo a baseline ECG to assess the QTc interval. Contraindications for bedaquiline use are a baseline QTc interval greater than 450 milliseconds that does not correct with medical management, a patient or family history of arrhythmia, or severe cardiac disease. While receiving bedaquiline, children should undergo a monthly ECG to assess for QTc prolongation and should also have monthly potassium levels determined. As with delamanid, caution should be used when other QTc-prolonging medications are used and levofloxacin should be substituted for moxifloxacin. Guidelines recommend that bedaquiline be given for 24 weeks total, although longer courses have been given to individuals with limited therapeutic options (45).

Studies in adults show that bedaquiline should not be given with efavirenz, as efavirenz reduces bedaquiline levels. Therefore, children receiving antiretroviral therapy and for whom bedaquiline is being considered should be switched to a regimen containing nevirapine or raltegravir for the duration of bedaquiline therapy (46). If a nevirapine- or raltegravir-containing regimen is not appropriate, a triple nucleoside reverse transcriptase inhibitor (NRTI) regimen could be considered, keeping in mind the lower potency of such regimens. Of note, lopinavir–ritonavir is used in adults receiving bedaquiline, but two- to threefold higher concentrations of bedaquiline are predicted and have been observed when the two are given together (47). Although the clinical implications of this are unknown, this combination should be avoided if possible in children until more data and experience are available.

Regimens combining bedaquiline and delamanid. Case reports of successful use of the combination of bedaquiline and delamanid in adults are emerging (48, 49). Treatment regimens containing both bedaquiline and delamanid in children could be considered on a case-by-case basis, if no other treatment options exist, in consultation with expert clinicians. The use of combined delamanid and bedaquiline in this population should follow more recently proposed guidelines, which recommend it be used only when an effective regimen cannot otherwise be designed; the clinical center has expertise with treatment of MDR-TB; the patient and caregivers are counseled as part of informed consent for both drugs;

pharmacovigilance is in place; and an independent, qualified organization considers the use of both drugs to be appropriate (50).

Linezolid

Linezolid is an oxazolidinone antibiotic indicated for the treatment of gram-positive bacteria that has been effective for treating MDR-TB in adults in multiple observational studies (51, 52) and in a delayed-start randomized controlled trial (53). The main factor limiting wider use is the drug's toxicity profile, especially bone marrow suppression, and that an optimal dose has not been established in adults (54, 55). Bone marrow suppression is reversible on cessation of linezolid. The outcome of peripheral neuropathy on drug cessation is more variable; it may not be reversible, although it is unclear whether resolution may be seen with longer follow-up.

There have been studies of linezolid in children with MDR-TB showing the drug is effective, but safety issues have been reported with longer durations and higher doses, including hematologic toxicity and peripheral neuropathy (56–58). Linezolid has been recommended in children when close clinical monitoring is possible, and the WHO recommends that linezolid be included in the treatment regimens of children with confirmed or probable MDR-TB as part of the "other core second-line agents" that can be used to build a treatment regimen of at least four effective drugs (9, 59). However, because of the risk of adverse events, if the patient cannot be monitored, linezolid is best used in patients with additional possible resistance or intolerance to other second-line medications. Linezolid has excellent penetration into the cerebrospinal fluid, and thus should be considered for MDR-TB meningitis. Dosages of 10 mg/kg once daily for children at least 12 years old and of 10 mg/kg twice daily for children less than 12 years are recommended because younger children have increased metabolism of the drug (not to exceed a maximum dose of 600 mg daily). Children should be closely monitored for adverse events, especially for peripheral neuropathy, anemia, thrombocytopenia, lactic acidosis, and optic neuropathy. Linezolid should be given for the entire duration of therapy or for as long as it is tolerated. It can be safely given with antiretroviral therapy, although there should be close monitoring due to potential for overlapping toxicity if used with NRTIs, given the potential for both linezolid and NRTIs to inhibit mitochondrial protein synthesis (60).

Clofazimine

Clofazimine is a lipophilic riminophenazine antibiotic, traditionally used for leprosy treatment. It was effective for treating MDR-TB in adults in observational studies and in a nonplacebo randomized controlled trial (61, 62). There is a resurgence of interest in it, given its use in shorter MDR-TB regimens. Although there have been no formal studies of clofazimine in children with TB, there is substantial experience in using it to treat children with leprosy. In a leprosy trial of 422 children in China and India, clofazimine was well tolerated (63). The main adverse events associated with clofazimine include prolongation of the QTc interval, and reversible skin pigmentation. The WHO has included clofazimine as part of the "other core second-line agents" that can be used to build a treatment regimen of at least four effective drugs (9). A dose of 2–3 mg/kg per day (maximum dose, 100 mg daily) is recommended for children; however, there is limited published pharmacokinetics to support this dose. Clofazimine comes in 50- and 100-mg gelcaps that cannot be split, and therefore if lower doses are needed children could be given doses every other day because of the drug's long half-life. Children receiving clofazimine should have monthly ECGs assessed when possible, especially when more than one QTc-prolonging agent is used. Children and their caregivers should be advised about associated skin color changes, which may take a long time to resolve. Clofazimine should be given for the entire duration of therapy or as long as it is tolerated. It can be safely given with antiretroviral therapy.

Conclusions

The use of new and repurposed drugs for the treatment of MDR-TB has improved interim outcomes and helped manage toxicity in adults. Years after they have been recommended for adults, children facing the same challenges have not benefited from these therapeutic advances. This has caused a concerning disparity, in which vulnerable children with MDR-TB are left behind. This is occurring even in the setting of a robust pediatric drug development program for delamanid and multiple calls to action for inclusion of children in clinical research for MDR-TB. These practice-based recommendations can assist front-line providers treating children with MDR-TB and provide a base for national TB programs and the donor community to further support the use of new and repurposed drugs in the pediatric population, especially as additional data on safety and optimal dosing of these drugs in children continue to emerge. Children and adolescents with MDR-TB have had to endure the problems with the current treatment regimen for far too long, and it is time they too benefit from these exciting developments. ■

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

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