Treatment of Multidrug-resistant Tuberculosis Infection in Children

Andrea T. Cruz, MD, Anthony J. Garcia-Prats, MD,† Jennifer Furin, MD,‡ and James A. Seddon, MBBS,§*

Key Words: tuberculosis, infection, multidrug-resistant, pediatric, children

It is estimated that 2 million children (younger than 15 years of age) are infected with multidrug-resistant (MDR) strains of *Mycobacterium tuberculosis* (TB), known as MDR-TB infection.[1] Data on the natural history of TB infection—which are often extrapolated to MDR-TB infection—show that young children (younger than 5 years of age) with TB infection are at high risk (up to 25%) of progressing to TB disease within 2–3 years of exposure, with infants' risk of progression approaching 50%.[2] It is noteworthy that older children and adolescents (10–20 years of age) also have an increased risk of developing TB disease after infection. Most children who develop MDR-TB disease are not diagnosed and started on appropriate therapy; mortality is high. However, even if diagnosed and treated, individuals must tolerate long (up to 18–24 months) courses of therapy with multiple (4–6) second-line drugs associated with far more adverse effects (AEs) than the 6–9 months of treatment with first-line drugs for drug-susceptible (DS)-TB disease. Thus, treatment of MDR-TB infection (often referred to as "preventive therapy") to prevent progression to disease is critical.

KNOWLEDGE GAPS FOR IMPLEMENTATION

Treatment of TB infection with isoniazid, a low-cost medication for which there are extensive safety and efficacy data, has received little traction in many high-burden countries.[3] The situation for MDR-TB infection is more complex, as there are unresolved questions surrounding whether to give any drug treatment, the number of drugs that should be used, which drugs may be most effective, the duration of therapy and the optimal dose of medications for children of different ages.[4] Some of these issues will be addressed in ongoing clinical trials. The higher cost of many of these medications, the lack of child-friendly formulations and difficulties in identifying which children would benefit most from treatment are additional challenges. Not surprisingly, treatment of MDR-TB infection in children has been operationalized in few high-burden countries. Given the large potential benefit in high-risk young child contacts, however, MDR-TB infection therapy has been widely implemented in low-burden, high-resource settings.

SCREENING FOR INFECTION AND DISEASE

The most important aspects of caring for children with MDR-TB infection are to screen comprehensively for TB disease at baseline and to follow children closely. These activities are recommended by all guidelines, despite the highly variable guidance about whether to treat MDR-TB infection, and should be implemented in all settings regardless of the use of MDR-TB infection treatment.

The critical first step when evaluating a child after exposure to MDR-TB is to ensure that the child does not have TB disease at baseline. A thorough symptom screen and physical examination are needed, with the latter focusing on evaluation of anthropometry (eg, evaluating for weight stasis or decline across growth curves), lung findings, mental status, meningeal signs, peripheral lymphadenitis, organomegaly, spinal deformities and abdominal masses.

In most high-resource settings, a chest radiograph (CXR) is undertaken to rule out TB disease after exposure to both DS- and MDR-TB, before provision of TB infection. A CXR is a low-risk evaluation that may provide valuable information to guide clinical decision making, particularly in children with subclinical TB. If possible, a CXR (frontal and lateral) should be obtained to evaluate

Accepted for publication March 28, 2018.
From the *Department of Pediatrics, Baylor College of Medicine, Houston, Texas; †Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; ‡Department of Global Health and Social Medicine, Harvard Medical School, Boston, Massachusetts; and §Centre for International Child Health, Imperial College London, London, United Kingdom.
The authors have no funding or conflicts of interest to disclose.
Address for correspondence: Andrea T. Cruz, MD, MPH, Department of Pediatrics, Baylor College of Medicine, 6621 Fannin Street, Suite A2210, Houston, TX 77035. E-mail: acruz@bcm.edu.

ISSN: 0891-3668/18/3708-0831
DOI: 10.1097/INF.0000000000002087

for intrathoracic TB before initiation of therapy. Lateral films are advised for evaluation of intrathoracic lymphadenopathy, particularly in children in the first 2 years, where the thymic silhouette can make discernment of adenopathy difficult on the frontal CXR. Respiratory samples (via gastric aspiration or sputum induction with several samples collected over consecutive days) should be considered only if a child has symptoms or an abnormal CXR and should not otherwise be routinely obtained. For children exposed to MDR-TB, the risk of inadequately treating TB disease is possibly more serious than for DS-TB, and so the benefit of performing a CXR to rule out TB disease before starting TB infection treatment is likely greater. However, in circumstances where it is not possible to undertake CXR, a thorough symptom screen will detect the vast majority of children with TB disease, and the lack of a CXR should not stop the evaluation of children exposed to MDR-TB and the provision of MDR-TB infection treatment.

As for CXR, in high-resource settings, tests of infection (tuberculin skin tests) or interferon gamma release assays) are routinely performed to decide who to treat for TB infection. With certain caveats, this is likely the optimal strategy as it targets the intervention at those most likely to benefit and avoids toxicity/unnecessary pill burden in the others. Children of all ages with positive test results are then offered TB infection treatment. Tests of infection may not be reliable in some high-risk children (eg, HIV-infected, malnourished), and they may not be available in many high-burden settings. A validated exposure screening scale[5] could be used in lieu of tests of infection, keeping in mind that using this score to make decisions whether to treat TB infection or not has not been studied. A strategy of providing TB infection treatment for drug-susceptible TB, based on household exposure, without tests of infection is cost-effective in high-burden settings.[6]

FOLLOW-UP

Whether or not therapy for MDR-TB infection is initiated, children should be followed regularly, ideally for up to 2 years, as it is during this period that most children will progress to disease. They should be evaluated regularly for symptom screening and physical examinations. Anthropometrics (eg, height, weight) should be measured to evaluate for failure to thrive or weight stasis. CXRs may be considered at baseline and if the child were to develop symptoms. After this period, families should be instructed on symptoms that should prompt immediately seeking medical attention. Of note, there are no uniformly accepted guidelines on the frequency or extent of evaluation in follow-up. Studies in Europe have found wide variation in the duration and evaluation that child contacts of MDR-TB cases receive.[7] Children receiving MDR-TB infection therapy should be seen every few months to assess adherence and to evaluate for AEs and the development of symptoms of TB disease. Caregivers should be instructed on what symptoms should prompt communication with the clinic for a more urgent visit to assess for AEs.

REGIMENS

In hyperendemic settings, children may have multiple exposures to adults with different drug susceptibility patterns, leading to the practice in some settings of treating child contacts of MDR-TB patients with isoniazid alone, in the event that the child was infected with a susceptible *Mycobacterium tuberculosis* isolate. This strategy is likely to be inadequate if the child is infected with an MDR organism.[8]

There are several regimens that could be considered for the MDR-TB infection treatment (Table).[4,9,10] Medication(s) should have the following characteristics: (1) good antimycobacterial effects; (2) resistance should be unlikely based on known susceptibilities for the isolate in the child's identified source case; (3) well tolerated; (4) safe; and (5) adequate data on drug dosing in children. Ideally, a child-friendly formulation should exist. This constellation of characteristics effectively rules out several categories of medications, including injectable agents, cycloserine, clofazimine, linezolid and para-amino salicylic acid because of AEs. Two newer drugs, delamanid and bedaquiline, are better tolerated than other second-line drugs and may be integrated into MDR-TB infection regimens in the future once optimal dosing and safety is determined in the youngest children. While there are few data on the development of secondary drug resistance during treatment for MDR-TB infection, data from isoniazid use in the treatment of DS-TB infection indicate that acquisition of isoniazid resistance while on therapy is exceedingly low, and there is no reason to suspect that this will be different for MDR-TB infection.[11]

As such, the focus for MDR-TB infection therapy has been on higher-generation fluoroquinolones, alone or with a second medication. While adults and children receiving fluoroquinolone-containing regimens noted AEs in up to one third of cases, these AEs usually were not of sufficient severity to warrant treatment discontinuation.[12] In contrast, several studies have found that patients receiving pyrazinamide-containing regimens reported AEs in up to two thirds of cases, with over one-half resulting in treatment discontinuation.[12] Pediatricians should be cognizant that children generally tolerate TB medications better than adults. In one study in Micronesia, 95% of children with MDR-TB infection completed therapy with a fluoroquinolone with either ethambutol or ethionamide.[9] Eighty percent of South African MDR-TB child contacts completed treatment in an observational study of a fluoroquinolone, ethambutol and isoniazid; no child suffered an AE requiring treatment discontinuation.[10] A recent systematic review and meta-analysis estimated TB incidence risk reduction with therapy for MDR-TB infection is up to 90%[12] and found that all treatment regimens were cost-effective compared with no treatment. It also found that for children, fluoroquinolone monotherapy was the most cost-effective.[12] There are no data on the optimal duration of therapy for MDR-TB infection. Courses of 6–12 months have been used most often.

There will be times when no obvious therapeutic regimen can be crafted, and expert opinion should be sought on optimal management in these scenarios. These situations may include (1) the source case isolate is resistant to the fluoroquinolones; (2) the isolate is only susceptible to agents to which the child has had hypersensitivity reactions; or (3) susceptible agents have unacceptable drug interactions with a child's existing medications. If not treated, these children should be carefully followed for the development of symptoms.

CONSIDERATIONS FOR THE HIV-INFECTED CHILD

The approach to the HIV-infected child should generally follow that for HIV-uninfected children, with a few additional considerations. HIV infection is a risk factor for progression from infection to disease. Although effective antiretroviral therapy with immune reconstitution substantially reduces that risk, there may remain a slightly higher risk than uninfected children even when the CD4 count is normal. HIV-infected children may have a higher risk of false-negative tests of infection, particularly if they have low $CD4^+$ cell counts. HIV-infected children with MDR-TB infection are high priority group for provision of treatment. Potential drug–drug interactions and additive or overlapping toxicities between HIV-infected children's antiretroviral therapy regimen and medications used for MDR-TB infection should be carefully considered. Most of the second-line antituberculosis drugs, including the fluoroquinolones, do not have clinically significant drug–drug interactions with most antiretroviral therapy, and there is no evidence to date that HIV-infected children have a higher risk of AEs from MDR-TB infection treatment.[10]

TABLE 1. Regimens for the Treatment of TB Infection Presumably Caused by Multidrug-Resistant (MDR) Isolates*

Drug	Dosage (mg/kg/dose)† (maximum dose)	Potential AEs	Drug Interactions With ARVs and Other TB Medications‡	Specific AEs With ARVs and Other TB Medications
Fluoroquinolone (FQ) alone	Lfx: 15–20 (max: 750 mg) Mfx: 7.5–10 (max: 400 mg)	Arthropathy, myelosuppression, peripheral neuropathy; prolongation of the QT interval (more with moxifloxacin than with other FQs)	Mfx concentration reduced by ritonavir and buffered didanosine; increased by atazanavir	Hepatitis: nevirapine, efavirenz, PIs QT prolongation: PI, efavirenz Psychiatric symptoms: efavirenz
Fluoroquinolone + EMB	FQ: see above EMB: 15–25 (max: 1600 mg); 40-55 kg: 800 mg; 56–75 kg: 1200 mg; >75 kg: 1600 mg	FQ: see above EMB: optic neuritis§; dose adjustment needed in renal impairment	FQ: see above EMB: few available data	See FQ above
Fluoroquinolone + ethionamide	FQ: see above Ethionamide: 15–20 (max: 1000 mg)	FQ: see above Ethionamide: vomiting, hepatitis, hypothyroidism	FQ: see above Ethionamide: few available data	Hepatitis: nevirapine, efavirenz, PIs GI intolerance: AZT, PIs Neuropathy: d4T, ddI Psychiatric: efavirenz Should be administered with pyridoxine (B6)
Fluoroquinolone + PZA	FQ: see above PZA: 30–40 (max: 2000 mg); 40–55 kg: 1000 mg; 56–75 kg: 1500 mg; >75 kg: 2000 mg	FQ: see above PZA: hepatotoxicity, nausea, vomiting, joint pain, rash, elevated serum uric acid. Up to 66% discontinued therapy because of AEs in one pediatric study	FQ: see above PZA: few available data	See FQ above
Fluoroquinolone + EMB + high-dose isoniazid	FQ: see above EMB: see above Isoniazid: 15–20 (max: 400 mg for children younger than 5 yr of age; 500 mg for children ≥5 yr)	FQ, EMB: see above Isoniazid: hepatotoxicity, nausea, vomiting	See above	See FQ above
PZA + EMB	See above	Hepatotoxicity, nausea, vomiting, joint pain, rash, elevated serum uric acid	Few available data	Few available data
Bedaquiline¶	400 mg/d for 2 wk, then 200 mg 3×/wk for 6 mo; data on dosing for children who weigh <33 kg are based on expert opinion	Hepatotoxicity, nausea, pancreatitis; joint pain; prolongation of the QT interval	ARVs (lopinavir, efavirenz), antifungals (ketoconazole), other TB medications (moxifloxacin, clofazimine)	QTc prolongation with bedaquiline and lopinavir/ritonavir (monitor carefully)
Delamanid¶	20–34 kg: 50 mg twice daily ≥35 kg: 100 mg twice daily <20 kg: consult with experts 100 mg/dose twice daily	Nausea, vomiting, dizziness; prolongation of the QT interval	Ethambutol (increased levels); lopinavir (increases delamanid levels)	Mild QTc prolongation with delamanid and lopinavir/ritonavir

*The optimal duration of therapy is unknown. While longer (~12 month) courses of therapy often are recommended, completion often is limited by adverse events and adherence.

†Frequency is daily unless otherwise specified.

‡Drug interactions do not include those of the specific regimen with isoniazid and rifampin.

§Ethambutol is metabolized much faster in children than in adolescents and adults; providers should not avoid using EMB in young children in whom visual acuity testing cannot be performed.

¶Not studied for the treatment of tuberculosis infection; the doses specified are those recommended for the treatment of TB disease.

AE indicates adverse event; ARV, antiretroviral therapy; AZT, zidovudine; ddI, didanosine; d4T, stavudine; EMB, ethambutol; GI, gastrointestinal; Lfx, levofloxacin; Mfx, moxifloxacin; Ofx, ofloxacin; PI, protease inhibitor; PZA, pyrazinamide.

ONGOING RESEARCH

Three clinical trials are underway or planned to evaluate MDR-TB infection treatment. Tuberculosis Child and Adolescent Multidrug-Resistant Preventive Therapy (TB-CHAMP) compares levofloxacin to placebo in children younger than 5 years of age, in South Africa, exposed in their home to MDR-TB. V-QUIN also compares levofloxacin to placebo, but in all household contacts, in Vietnam. Protecting Households on Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis patients (PHOENIx) is a multisite trial that will compare delamanid with isoniazid in household MDR-TB contacts, providing treatment to children younger than 5 years of age and to those with HIV and a positive test of infection. The results of these trials will not be available for a number of years.

CONCLUSIONS

After the exclusion of TB disease by symptom screening and, whenever possible, by CXR, some children exposed to an MDR-TB source case may be candidates for treatment. Fluoroquinolone-based regimens have been found to be safe and effective in multiple observational cohorts. While optimal treatment is being investigated, results will not be available for a number of years. The data published to date show that children tolerate MDR-TB infection treatment with fewer AEs than adults and that failure to treat will result in potentially preventable cases of disease. Dissemination of studies on programmatic implementation, including observational evidence from low- and high-burden settings, can facilitate larger-scale roll-out of MDR-TB infection treatment.

REFERENCES

1. Dodd PJ, Sismanidis C, Seddon JA. Global burden of drug-resistant tuberculosis in children: a mathematical modelling study. *Lancet Infect Dis*. 2016;16:1193–1201.
2. Marais BJ, Gie RP, Schaaf HS, et al. The natural history of childhood intra-thoracic tuberculosis: a

critical review of literature from the pre-chemotherapy era. *Int J Tuberc Lung Dis*. 2004;8:392–402.

3. Graham SM. The management of infection with Mycobacterium tuberculosis in young children post-2015: an opportunity to close the policy-practice gap. *Expert Rev Respir Med*. 2017;11:41–49.
4. Seddon JA, Fred F, Amanullah F, et al. Center for Global Health Delivery – Dubai. Policy brief: post-exposure management of multidrug-resistant tuberculosis contacts: evidence-based recommendations. Available at: http://sentinel-project.org/wp-content/uploads/2015/11/Harvard-Policy-Brief_revised-10Nov2015.pdf. Accessed October 3, 2017.
5. Mandalakas AM, Kirchner HL, Lombard C, et al. Well-quantified tuberculosis exposure is a reliable surrogate measure of tuberculosis infection. *Int J Tuberc Lung Dis*. 2012;16:1033–1039.
6. Mandalakas AM, Hesseling AC, Gie RP, et al. Modelling the cost-effectiveness of strategies to prevent tuberculosis in child contacts in a high-burden setting. *Thorax*. 2013;68:247–255.
7. Turkova A, Tebruegge M, Brinkmann F, et al. Management of child MDR-TB contacts across countries in the WHO European Region: a survey of current practice. *Int J Tuberc Lung Dis*. 2017;21:774–777.
8. Sneag DB, Schaaf HS, Cotton MF, et al. Failure of chemoprophylaxis with standard antituberculosis agents in child contacts of multidrug-resistant tuberculosis cases. *Pediatr Infect Dis J*. 2007;26:1142–1146.
9. Bamrah S, Brostrom R, Dorina F, et al. Treatment for LTBI in contacts of MDR-TB patients, Federated States of Micronesia, 2009-2012. *Int J Tuberc Lung Dis*. 2014;18:912–918.
10. Seddon JA, Hesseling AC, Finlayson H, et al. Preventive therapy for child contacts of multidrug-resistant tuberculosis: a prospective cohort study. *Clin Infect Dis*. 2013;57:1676–1684.
11. Balcells ME, Thomas SL, Godfrey-Faussett P, et al. Isoniazid preventive therapy and risk for resistant tuberculosis. *Emerg Infect Dis*. 2006;12:744–751.
12. Marks SM, Mase SR, Morris SB. Systematic review, meta-analysis, and cost-effectiveness of treatment of latent tuberculosis to reduce progression to multidrug-resistant tuberculosis. *Clin Infect Dis*. 2017;64:1670–1677.