Management of Multidrug-Resistant Tuberculosis in Children: A Field Guide

Photo: Justin Ide

Sentinel Project

Third Edition: November, 2016

This handbook was developed and written by The Sentinel Project for Pediatric Drug-Resistant Tuberculosis (http://sentinel-project.org/).

Preferred citation: Management of Drug-Resistant Tuberculosis in Children: A Field Guide. Boston, USA: The Sentinel Project for Pediatric Drug-Resistant Tuberculosis; November 2016, Third edition

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The Sentinel Project on Pediatric Drug-Resistant Tuberculosis is a global partnership of researchers, caregivers, and advocates aiming to develop and deploy evidence-based strategies to prevent child deaths from this treatable disease. We are a learning network committed to generating and disseminating knowledge and data for immediate action.

The third edition of this handbook is based on the Management of Multidrug-Resistant Tuberculosis in Children: A Field Guide, First Edition, November 2012, and Second Edition, March 2015, a resource developed by the Sentinel Project on Pediatric Drug-Resistant Tuberculosis.

Acknowledgements

The main writing committee for this handbook was: Jennifer Furin, James Seddon, and Carlos Perez-Velez.

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Editorial comments were provided by Agnes Gebhard, Maria Insua, Ieva Leimane, and Kwonjune Seung.

The authors of this handbook are thankful to countless people for the time, expertise, and generosity which led to the first and second editions of the manual. First and foremost, we are mindful of the children and their families who face this disease on a daily basis. Their bravery inspires us, and it is for them that we aspire to zero childhood deaths from TB. We are thankful to the leadership of the Sentinel Project for making this work possible. For funding and moral support, we thank the Stop TB Partnership, most notably Lucica Ditiu who makes us believe zero can be achieved. Finally, we thank the men and women who care for children facing health problems around the world. May we all come to know a day when all children have the hope of happy and healthy lives.

Table of Contents

Photo courtesy of Jennifer Furin

Introduction

Multidrug-resistant tuberculosis (MDR-TB) is a growing global health crisis; MDR-TB is defined as strains of TB with in vitro resistance to at least isoniazid and rifampin, and it is estimated there are more than five million people infected and sick with drug-resistant forms of TB in the world today (World Health Organization, 2011). Children represent a significant proportion of these cases yet they lack the same access to diagnosis and treatment as their adult counterparts. A recent meta-analysis of treatment for MDR-TB among children showed that more than 80% had positive outcomes when treated for MDR-TB and that pediatric patients tolerated second-line medications well (Ettehad, D. *et al.*, 2012). However, only 351 patients were included in this analysis, reflective of how few children in the world are diagnosed with and treated for MDR-TB.

Urgent action is needed to address this gap in care. Based on experiences with pediatric HIV, equitable access for children with MDR-TB will only occur once systematic approaches to diagnosing and treating children are developed and once access to pediatric formulations of second-line medications is widespread. This field guide is meant to serve as a tool for practitioners working with children at risk of infection or being sick with MDR-TB. Following the example set by Médecins Sans Frontières (MSF) in their publication "Treating drug resistant tuberculosis: what does it take," this guide focuses on issues relevant in clinical and programmatic practices and does not offer extensive background materials on management of MDR-TB, which can be found in multiple other guidelines (MSF, 2011). This field guide should be considered complementary to existing recommendations.

In general, a guide such as this should be developed using evidence-based research. Sadly, there are few empiric studies of MDR-TB in children. At the same time, practitioners in most countries are seeing children at risk for or sick with MDR-TB, who require immediate access to care. This field guide was developed by a team of experts who jointly have treated hundreds of children with MDR-TB over the last two decades in every region of the world. We hope it will be used as a tool to rapidly increase the number of children receiving care for MDR-TB. Case examples are included throughout the guide to show how these recommendations can be put into practice.

Whenever possible, management of children with MDR-TB should take place within the activities of a National TB Control Program (NTP). There are multiple advantages to doing this, including a contextual approach, integration with other health initiatives, and health systems strengthening. If activities occur outside the auspices of an NTP, all efforts should be made to report standardized outcomes and to collaborate with the NTP whenever possible.

Finally, we recognize that the term "children" encompasses a broad range of individuals and ages with widely different needs. A 2-year-old child requires a different approach to a 12-year-old, and the treatment of children with MDR-TB will never be a "one size fits all" approach. In essence, children older than 12 years of age can be managed as adults, although the specific emotional needs of adolescent children and their caregivers should be considered. We focus mainly on the care of younger children, which is most problematic and hope to offer a compendium of practical experience that can be useful for programs and providers caring for children with possible MDR-TB. We trust that this initial attempt will be greatly expanded and improved as the world gains and documents more experience with this neglected population in the coming years.

Section 1: Diagnosis of MDR-TB in Children

A diagnosis of TB in children can be made on clinical and radiological grounds in the majority of cases, even though bacteriological confirmation may not be possible. Furthermore, most children over the age of 7 years can provide sputum for bacteriologic confirmation and drug susceptibility testing (DST). Since children may have paucibacillary disease or extrapulmonary disease, and since sputum samples may be difficult to obtain in younger children, a bacteriologically confirmed TB diagnosis may be difficult to make, and testing for drug resistance may not be possible. Thus, a high index of clinical suspicion is needed, as well as the readiness to initiate MDR-TB treatment even in the absence of bacteriologically confirmed disease. Systematic approaches to the management of pediatric contacts of MDR-TB patients are needed. This section will discuss:

- Diagnosis of pediatric MDR-TB
- Diagnostic specimens, preparation, and testing
- Contact management

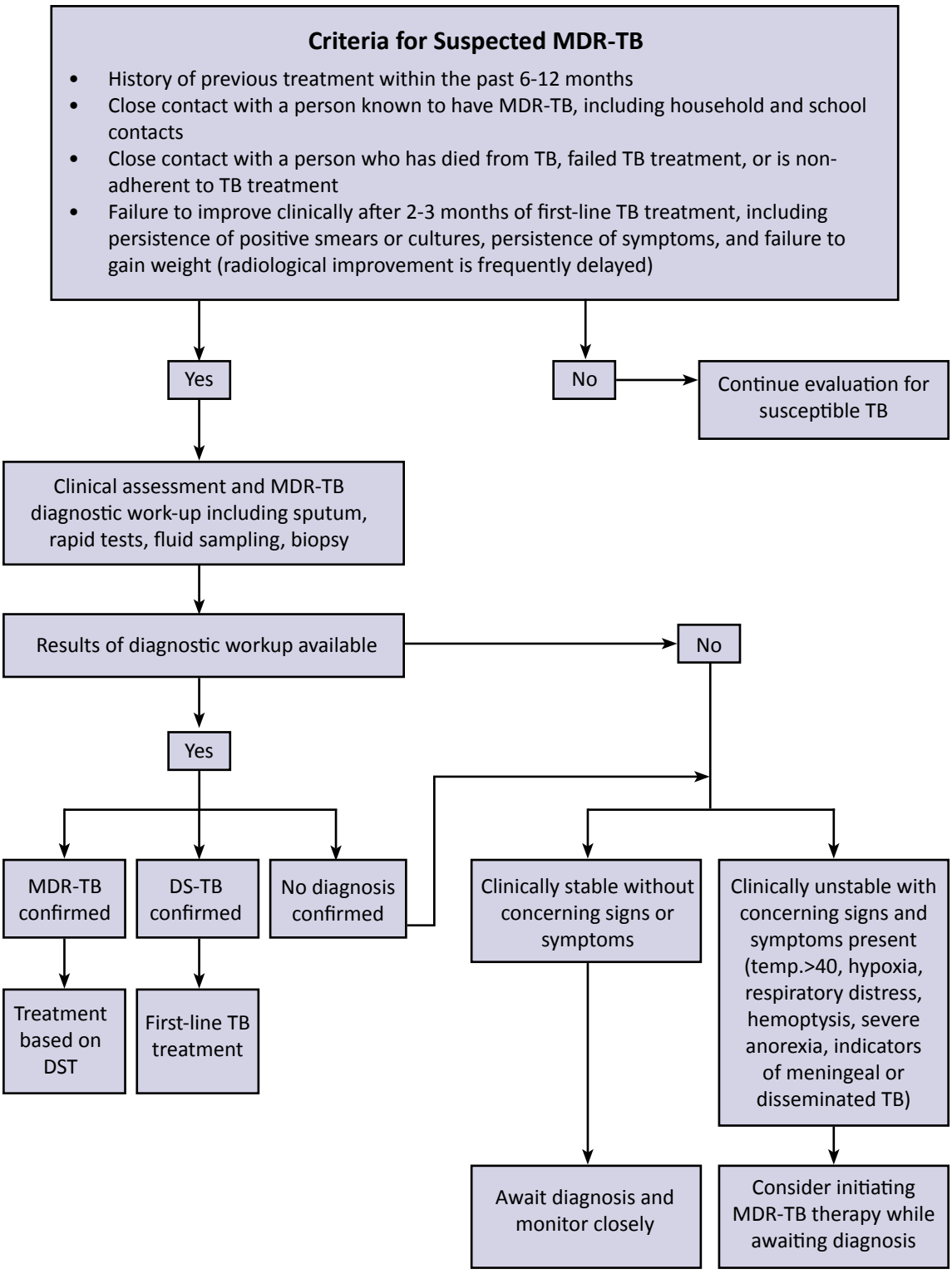
Recognition and Initial Management of a Child with Suspected MDR-TB

TB should be included in the differential diagnosis list of any child with a persistent non-remitting cough or fever, weight loss, or focal findings that are suggestive of TB, such as lymphadenitis, spinal deformities, ascites, and joint effusions. Diagnosis of MDR-TB among children is challenging and requires a high index of suspicion. The algorithm on the next page suggests a diagnostic strategy for determining risk factors for MDR-TB among children who have confirmed or suspected TB.

Abbreviations for drugs used in this handbook

INH	isoniazid	THA	ethionamide
RIF	rifampicin	PTO	protionamide
EMB	ethambutol	LVX	levofloxacin
PZA	pyrazinamide	MFX	moxifloxacin
SM	streptomycin	OFX	ofloxacin
CM	capreomycin	CS	cycloserine
KM	kanamycin	TZD	terizidone
AMK	amikacin	PAS	para-aminosalicylic acid
BDQ	bedaquiline	DLM	delamanid

Algorithm for Suspected MDR-TB in a Child



Case Examples: Suspected MDR-TB in a Child

Colombia

Antonio is a 7-year-old boy who presents to the clinic with 3 weeks of fever, cough, and a swollen right knee. His father notes that the boy has been "sleepy" at school and is no longer interested in playing football with his friends. When asked how he is doing, Antonio says his "leg hurts" but reports no other complaints. His father also tells you that Antonio's mother died last month. "They say it was from TB, but I do not know. She took her TB medication every single day with the nurse watching her." There are no other known TB exposures, and prior to this episode, Antonio has been healthy, growing well, and has received all his recommended vaccinations.

On examination, Antonio is pale and listless. His temperature is 39.6˚C and his weight is only 16 kg, which is below the fifth percentile for him and a drop from his growth curve, where he had previously been at the fifteenth percentile. He has cervical lymphadenopathy, right upper lobe crackles on pulmonary exam, and examination of the right knee shows a large effusion.

You suspect TB and are concerned about the possibility of MDR-TB, given that his mother died of TB while on first-line DOT. Antonio is clinically stable with no immediate indication to start MDR-TB treatment. He provides sputum for smear and culture, and a sample of his knee fluid is sent to the lab for analysis as well. You inquire about the use of a rapid genotypic test (GeneXpert) at the National Lab. His chest radiograph shows a patchy right upper lobe infiltrate. All sample results are negative when his father brings him back to the clinic with a temperature of 40.5˚C and in respiratory distress. Given his clinical instability and risk factors for MDR-TB, you start him on an MDR-TB regimen in the absence of bacteriologic confirmation. MDR-TB is never confirmed.

Kenya

Shamba is a 7-year-old boy who is brought to the health center by his mother after she notices "lumps" in his neck and that the child is "coughing all the time." Shamba says he feels tired and "sweaty all the time." He begins to cry and tells you he misses his father, who died last year. Upon further questioning, Shamba's mother reports in a whisper that her husband died of TB last year, even though he took his medications every day.

On examination, Shamba is noted to be cachectic. He is febrile to 39°C and tachycardic with a heart rate of 137. On exam, he has multiple cervical lymph nodes, which are cool to the touch but feel round and rubbery. His cardiac exam reveals a 2/6 systolic ejection murmur. His pulmonary exam reveals chest wall retractions with minimal expansion of the right hemithorax. The right side of the chest is dull to percussion, and no breath sounds can be heard.

Shamba is critically ill and undergoes an emergency thoracentesis with removal of 600 cc of straw-colored fluid. He is able to give a sputum sample, which is sent for smear, culture, and rapid DST. Because he is so ill, and given the fact that his father died of TB while in treatment, Shamba is started on treatment for MDR-TB. Two days later, the results from his rapid DST show resistance to RIF, and his final culture comes back with resistance to INH, RIF, EMB, and SM. Because he was started on treatment quickly, Shamba is able to fully recover and remains an active, playful 9-year-old (having completed 2 years of treatment when he was seven) at the top of his class in school.

Kazakhstan

Aizhan is an 11-year-old girl who presents to her health center with fever, weight loss, cough, and hemoptysis. Aizhan is in her fourth month of TB treatment and is currently on the INH/RIF continuation phase of treatment given through her National TB Program using DOTS.

Aizhan was originally diagnosed 4 months ago when she presented with the same symptoms and was found to have a positive acid-fast bacilli (AFB) smear. She was started on INH, RIF, PZA and EMB and received daily supervised therapy at a TB dispensary in her community. She has not missed a single dose of therapy. In her first month of treatment, she had a negative smear and reported feeling "better" with resolution of her cough and fever. During her second month of treatment, however, she began to cough again and developed drenching night sweats. Her month two smear was negative, and she was put on INH and RIF after the second month of therapy. Her symptoms worsened, and she began to have daily fevers. She presented to her clinic, and her month three smear showed "rare AFB," which was felt to be a "contamination" by her providers when a repeat smear was negative. She continued on INH and RIF. Her daily compliance with therapy was confirmed.

She now presents to the health center after having coughed "two cups" of blood. She also notes a 6 kg weight loss, daily fevers, severe cough, and shortness of breath. On exam she is ill-appearing, cachectic, and tachycardic, and her lungs have diffuse crackles and wheezes throughout all fields. Her sputum is streaked with blood, but a smear is done which shows AFB. A repeat history is taken, and Aizhan and her mother deny any contacts with other TB patients and specifically state that they have no known MDR-TB contacts or risk factors. A rapid HIV test is negative.

Aizhan is deemed to be at high risk for MDR-TB, as she is failing a first-line regimen given under strict DOT. Her sputum is sent for culture and DST. In the meantime, she is started on a regimen of KM, LVX, THA, CS, PAS, EMB, and PZA. She is hospitalized for the first 2 weeks of therapy and then returns to her home community. She receives her daily injection and other medications under strict DOT at the dispensary in her community. Her symptoms improve, and 2 months later, her smear is negative. Her DST returns and shows resistance to INH, RIF, EMB, and SM. She is continued on a regimen of KM, LVX, THA, CS, PAS and PZA, and monitored closely for compliance and adverse events.

Key Points:

- A high index of clinical suspicion is needed for timely diagnosis of MDR-TB in children.
- Risk factors include a history of previous treatment, failure to improve on first-line TB treatment, known MDR-TB contact, contact with a patient who died on TB treatment or failed TB treatment.
- Treatment in the absense of bacteriologic confirmation should be considered based on the DST of the contact or based on DST results from the child's own specimens (if available).
- Early initiation of appropriate treatment is essential to ensure good outcomes.

Diagnostic Specimen Management

There are multiple specimen types that can be taken from children to diagnose MDR-TB, and these can be sent for a variety of tests, including smear, liquid medium culture (i.e. MGIT), solid medium culture, pathology, or rapid diagnostic testing with the GeneXpert® or GenoType® MTBDRplus line probe assay. All relevant and available tests should be considered; performing multiple tests on one or more samples of a variety of specimen types significantly increases the diagnostic yield. The principles of specimen collection and management are described below. See Appendix A for a sample specimen collection form.

Infection Control Precautions

Any child with pulmonary TB might be able to transmit infection if he/she is coughing. As some procedures inherently induce cough, additional respiratory precautions should be taken, including collecting sputum outside or using a well-ventilated room. Sputum should always be collected outside when possible. If induced sputum collection is performed, the health care worker performing the procedure should wear an N95 mask, and all equipment must be adequately cleaned (sterilized) before reuse.

General Concepts for Specimen Collection

The proper collection of a specimen for microbiological studies (especially cultures) is the most important step in the detection of *Mycobacterium tuberculosis*. A poorly collected specimen may lead to failure in detecting *M. tuberculosis* and/or result in the recovery of contaminating organisms (including nontuberculous mycobacteria). For proper specimen collection:

- Avoid contamination from adjacent secretions or tissues.
- Collect the specimen at optimal times (e.g., early morning fasting gastric aspirate, before mobilization; induced sputum after fasting 2-4 hrs; expectorated sputum early morning).
- Always try to collect an optimal quantity of sample, which varies by specimen type. The recommended minimum volumes are just that; larger volumes (up to a point) generally provide higher bacteriological yields.
- Use appropriate collection devices (i.e., sterile, leak-proof specimen containers). If specimens (e.g., sputa) will require centrifugation, they should preferably be collected directly into 50-mL centrifuge (Falcon) tubes to avoid the need for their transfer from one container to another.
- Use appropriate transport media. Avoid saline or other solutions that may contain antimycobacterial preservatives, do not place biopsy samples in formaldehyde, and neutralize stomach acid if gastric aspirate.
- Collect specimens prior to administration of antituberculosis medications.
- Properly label each specimen (complete names; exact type of specimen source; date & time collected). Ensure that the label is on the container, not the lid.
- Minimize transport time.
- Maintain an appropriate environment (cool temperature, ideally between 5-15˚C) between collection of specimens and delivery to the laboratory.
- If a delay in transport is anticipated place specimen in refrigerator (ideally between 1-5˚C); freeze specimens for molecular (PCR) analysis.
- Package each specimen separately in a sealed transport bag.

Standard Operating Procedures for some of the samples are supplied in Appendix D.

Types of Specimens

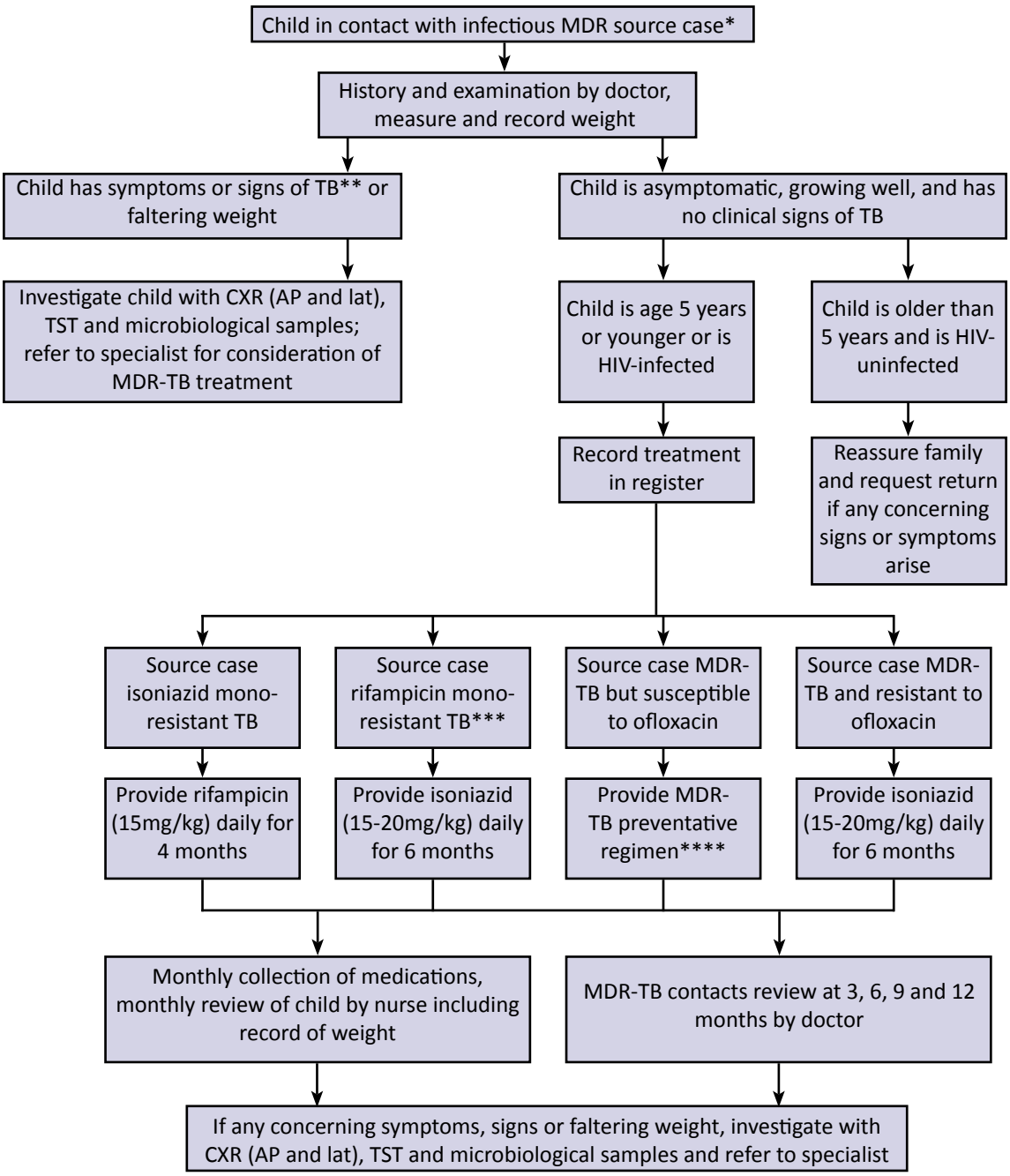
Specimen	Brief description of sample collection procedure	Recommended age group	Recommended *minimum* volume for studies*	Optimal collection time	Comments/ tips
Spontaneous sputum	Expectoration of sputum without prior saline nebulization	>7 y.o.	3 mL	Early morning	If child is unable to produce sputum of sufficient quantity and quality, consider sputum induction.
Induced sputum/ laryngopharyngeal aspirate	Expectoration of sputum preceded by hypertonic saline nebulization	Any age	3 mL	Early morning	If child is unable to expectorate, consider laryngo-pharyngeal suctioning.
Gastric aspirate (GA)	Nasogastric aspiration of gastric juice containing swallowed sputum	<7 y.o.	5 mL	Early morning before child gets out of bed	Upon awakening and sitting and standing, peristalsis begins, and stomach gradually empties, consequently compromising volume.
Gastric lavage (GL)	Nasogastric instillation of solution to "wash off" and recover sputum adhered to walls of stomach	<7 y.o.	10 mL	Early morning	Recommended only when 3 mL of gastric aspirate cannot be obtained.
String test	Esophagogastroduodenal nylon yarn that can absorb swallowed sputum	>4 y.o.	N/A	Unknown, but probably more a factor of duration in which it is left in place	Consider when good quality or quantity sputum and aspirates are not obtainable.
Nasopharyngeal aspirate	Nasopharyngeal suctioning of the nasopharynx to collect secretions from URT, but may also collect secretions from LRT if cough reflex is stimulated	≤5 y.o.	2 mL	Unknown, but probably higher yield in morning	The bacteriologic yield of nasopharyngeal aspirate tends to be similar to or lower than that of induced sputum or GA/GL.

* These values are the minimum recommended amount; larger volumes tend to have higher bacteriological yields.

Specimen	Brief description of sample collection procedure	Recommended age group	Recommended *minimum* volume for studies*	Optimal collection time	Comments/ tips
Stool	Sampling of random stool uncontaminated by urine or toilet bowl	Any age	1 table-spoon (5 g)	Any time	Bacteriologic yield of stool has so far been lower than that of sputum and GA/GL.
Broncho-alveolar lavage (BAL)	Bronchoscopy	Any age	3 mL	Any time	Bacteriologic yield of one BAL sample is not superior to that of serial induced sputum or GA/GL.
Cerebrospinal fluid	Lumbar puncture	Any age	2 mL	Any time	Submit the 3rd or 4th tube for culture to reduce the possibility of contamination due to skin flora.
Serosal fluids and tissues**	Serosal fluid aspirate followed by serosal tissue biopsy	Any age	1 mL	Any time	Bacteriologic yield of tissue is significantly higher than that of fluid. Biochemical markers useful in all fluids.
Urine	Clean-catch, midstream urine	Any age	2 mL	First micturition of the morning	Bacteriologic yield low except in urinary tract TB. Detection of lipoarabinomannan antigen has high sensitivity in severely immuno-compromised HIV-infected patients.
Blood	Phlebotomy	Any age	5 mL	Any time	Bacteriologic yield very low; use in severely ill HIV-infected patients.
Fine needle aspirate	Fine needle aspiration and/or biopsy, depending on type of tissue and clinical situation	Any age	Based on type	Any time	Also useful because histopathologic features consistent with TB can be diagnostic.

** Serosal fluids include pleura, pericardium, peritoneum, and synovium.

Management Algorithm for Child Contacts of MDR-TB Cases



* Infectious is defined as smear or culture-positive pulmonary TB

** Cough, reduced playfulness, fever, lethargy, abnormal bones or joints, faltering weight

*** If diagnosed by GeneXpert, consider MDR until confirmation by line probe assay (LPA) or DST

**** The composition of the preventive regimen will depend on the national program, but could be: (1) a fluoroquinolone and high dose INH, (2) a fluoroquinolone, high dose INH and EMB, (3) a fluoroquinolone and EMB, (4) high dose INH alone, or (5) a fluoroquinolone alone. Additional studies are underway to provide a strong evidence base for preventive therapy recommendations. In the largest observation cohort of children given prophlyaxis for MDR-TB, a regimen of INH (15-20 mg/kg/day), EMB (20-25mg/kg/day) and OFX (15-20mg/kg/day) for a total of 6 months was given (Seddon, J. et al. Clin Infect Dis, 2013)

See Appendix C for Contact Management Form

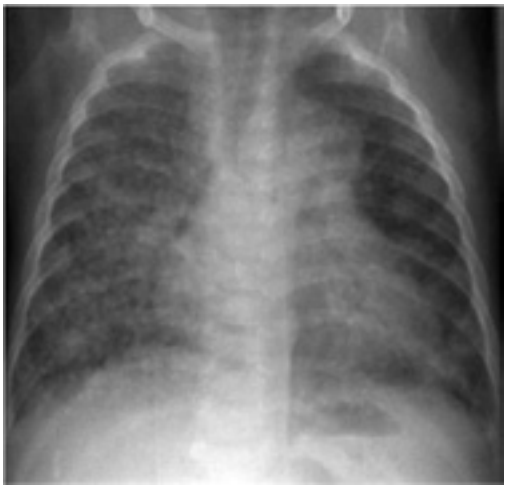
Case Example: Contact

South Africa

Lelethu is a 2½-year-old girl who has been referred to your clinic, as she is a known contact of someone with MDR-TB. The person with MDR-TB is her uncle who lives in the same house as her but sleeps in a separate room. He had been treated with first-line therapy for 5 months before being diagnosed with MDR-TB and has been coughing for months. He spends most days with Lelethu because both her parents work during the day, and he is her main caregiver. He has now been on MDR-TB treatment for 2 months and is feeling much better. He is still getting injections daily from the clinic. Lelethu's mother does not know much about his TB, so you ring the laboratory to get his results. You see that he had 3+ sputum smear-positive microscopy, and his TB is resistant to INH and RIF but susceptible to OFX, AMK and THA.

Lelethu is very well, and during the consultation she rushes around the clinic room playing with everything, and she appears very happy. Her mother tells you that she is not coughing and has no fever or sweating. You measure her weight, height and mid-upper arm circumference (MUAC) and then ask to look at her road-to-health card. She seems to be growing very well along the 25th percentile. Clinical examination is completely normal.

You decide that she should receive some MDR-TB preventive treatment. In a pilot program in the Western Cape of South Africa, the program advises giving INH at high dose (15-20mg/kg), EMB (20-25mg/kg), and OFX (15-20mg) daily for 6 months. You also arrange an HIV test, even though her mother says that she was tested in pregnancy and was found to be negative. The test is negative. Lelethu is reviewed by the nurse every month to measure her weight, check how she is getting on with the medications, and to ask if there are any problems. Every 3 months Lelethu comes back to your clinic to be seen by a nurse and a physician. She takes her prophylactic medications for 6 months, and at the twelfth month, she is still fit and well. Her weight and height have increased. She is then discharged.



X-ray showing miliary tuberculosis in a child.

Photo courtesy of Jeffrey Starke

Section 2: Regimen Design

The basic principles of treatment regimen design for children are the same as those for adults with MDR-TB. One major difference for children is that they often will not have bacteriologic confirmation of disease and thus their treatment regimen is based on the drug susceptibility pattern of source cases. The medications used for the treatment of children with MDR-TB are similar. However, most second-line drug formulations are not child-friendly, and preparation can be labor intensive. Pharmacokinetic and pharmacodynamic testing of second-line TB drugs has not been done in children. Current dosing recommendations are based on adult mg/kg doses. This section will discuss:

- Principles of regimen design in children
- Dosing recommendations for second-line TB drugs in children

Pictures of the commonly used first- and second-line drugs are included in Appendix B.

Principles of Regimen Design: Pediatric Considerations

Children with MDR-TB should be managed according to the same principles that guide adult therapy. These include:

- Use of any first-line medication to which susceptibility is documented or likely (pilot studies suggest that given the low risk of adverse events and potential benefit, high dose INH could be included routinely, unless high level INH resistance or Kat-G mutation is documented).
- Use of at least 4 second-line drugs to which the strain is likely to be sensitive; one of these agents should be an injectable, one a fluoroquinolone (preferably a later generation quinolone if available), and PZA should be continued.
- Use high-end dosing when possible.
- All doses should be given using DOT.
- 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.

Treatment is usually recommended based on the resistance pattern of the contact, although we know that close contacts do not always share the same resistance pattern as the source case (Cohen, T. *et al.*, 2011). The following are recommended as pragmatic guidance:

- Consider the use of INH and RIF for 6 months if there is evidence they may still be effective (i.e., no prior exposure to these medications, and contact with documented susceptibility), unless the child has previously received these medications. These are the two most powerful antituberculous agents, and if there is no prior exposure, sensitivity should be considered. It should be noted, however, that RIF can cause multiple drug-drug interactions and be problematic to use in children who are on ART. Risks and benefits should be carefully weighed. An overwhelming pill burden may make inclusion of these agents difficult, and adherence should be closely monitored if INH and RIF are to be used.
- A strong regimen consisting of at least four new second-line medications to which the strain is likely to be susceptible should be used in therapy in the absence of bacteriologically confirmed disease. If needed, it can be tailored back based on DST or the development of adverse events.
- Balance must be achieved between an effective MDR regimen and the development of adverse events (see Section 3), whereby weighing the morbidity and mortality of under-treated TB with the morbidity and mortality of various adverse events is taken into consideration.
- Some of the newer antituberculous agents, such as delaminid and bedaquiline, have not yet been evaluated in children but could be considered in cases of extreme resistance or severe adverse events.

Finally, children on MDR-TB therapy should have weight gain and height gain; these should be monitored monthly, and medication adjustments made accordingly.

Case Examples: Regimen Design

Bangladesh

Rami is a 3-year-old boy who presents to the clinic with swollen "lumps" in his neck. His mother reports he has been sick for several weeks. He is not playing normally and is not eating well. She also reports him having high fevers and a cough. She tells you that his auntie—who shares a bed with him—has TB and is being treated through a special program for people with resistant TB. Rami's physical examination and chest X-ray are consistent with TB. His rapid HIV test is negative. He is unable to cough sputum, even with induction, and two gastric aspirates are performed and sent for smear and culture. There is no bronchoscopy available where Rami lives. He is started on a short course of amoxicillin and told to return in 2 weeks, even though global guidelines would recommend starting Rami on MDR-TB treatment without bacteriologic confirmation.

Upon return to clinic, Rami has clinically worsened. He has lost 1 kg and his mother reports he sleeps all day. His smears were negative and cultures are pending. He is barely arousable. A lumbar puncture is performed which shows 15 nucleated cells of which 80% are lymphocytes. No AFB are seen in the spinal fluid.

You received results from his auntie's physicians, which show that she has resistance to INH, RIF, EMB, and SM.

Rami is diagnosed with TB meningitis and disseminated disease. Given his critical condition, he needs to start treatment immediately. He was likely infected by his auntie with whom he shares a bed, and she has documented resistance to HRES. However, studies have shown that children may not always share the resistance pattern of their contact, depending on their degree of interaction. Thus there is a possibility that Rami could have susceptible TB, and given his clinical status, he should not be denied access to INH and RIF, the two most powerful antituberculous medications. Rami is not on HIV treatment and has no contraindications to starting RIF.

Rami is started on INH and RIF. In addition to this, he is given five new medications based on the drug-resistance pattern of his contact, including PZA, LVX, KM, THA and CS. He is also started on prednisone as corticosteroids are indicated in cases of TB meningitis.

His gastric aspirates and CSF never grow. Rami improves and after 6 months, his INH, RIF and KM are discontinued, and he is continued on a regimen of PZA, LVX, THA, and CS for an additional 18 months. He clinically improves and is eventually declared cured after 24 months of total therapy, based on his clinical improvement, resolution of CXR findings, resolution of lymphadenopathy, and weight gain of 5 kg.

Haiti

Angelie is a 12-year-old girl who is referred to the central hospital having failed a first-line anti-TB regimen. Angelie took her medications daily under DOT. She had a positive sputum smear result at diagnosis, converted her sputum smear at month two, but had another positive sputum smear at month six. Under program conditions, samples were not sent for culture.

She reports feeling ill with cough, shortness of breath, and fevers. She is also losing weight. She reports that during the first month of treatment she felt "a little better" but overall feels worse now than she has since her diagnosis. She mentions that her father died of TB and that he had been in prison at the time. She was very close to him and visited him monthly.

Her clinical exam and X-ray are consistent with TB, and she has right upper lobe cavitary lesions. Her sputum is AFB smear positive. It is sent for culture and for rapid GeneXpert® testing. The GeneXpert® result is positive for *M. tuberculosis* and also has detected RIF resistance. Her HIV rapid test is negative.

Angelie returns to the clinic 5 days later and now reports hemoptysis and wheezing. Her culture is pending, but given her contact history, her clinical worsening, and her GeneXpert® result, she is started on treatment for MDR-TB. Her father never had drug-susceptibility testing done. She was exposed to INH, RIF, PZA, and EMB.

She is started back on PZA and EMB, given the possibility of sensitivity. She is not started on INH, given that a majority of patients with RIF resistance also have INH resistance. She is also started on five new drugs to which she has not been previously exposed. Her regimen is PZA-EMB-LVX-KM-THA-PAS and CS. She is also started on an albuterol inhaler for her wheezing. She develops severe nausea and vomiting during the first 2 weeks of therapy, and her dose of THA is lowered and divided into morning and evening doses.

Four weeks later, her DST results are obtained, showing resistance to INH and RIF but sensitivity to all other first and second-line medications. She is continued on a regimen of EMB-PZA-KM-LVX and CS. After 6 months of negative cultures, her KM is discontinued, and she completes 18 months total of therapy with EMB-PZA-LVX and CS. She remains smear and culture negative, has gained weight, her symptoms have resolved, and after 18 months of therapy she is declared cured.

dosing guides that can be used in the field, with updates to the dosing from the 2012 version of this handbook based on the existing data from South Africa. Further updates will be provided as more data are analyzed from this large study. Programs should use this while recognizing that updated dosing recommendations will be available soon.

South Africa

JR is a 7-year-old child whose mother was diagnosed with extensively drug-resistant tuberculosis. When a post-exposure protocol is implemented and a nurse visits JR's home to see if anyone is sick there, she finds that JR has been coughing sputum for a month and has lost 3 kg. He also has fever and night sweats and no longer wants to play football with his teammates at school. He had an HIV test done 2 months ago which was negative.

On examination he is sweaty, pale, and warm to the touch. His weight is 26 kg. His conjunctiva are pale, he has no icterus, he has no lymphadenopathy, and his heart is normal. His lung exam reveals crackles and bronchial breath sounds at the right apex. His abdomen is normal as are his extremities. A chest radiograph shows a large right upper lobe cavitary lesion. His sputum is sent for Xpert MTB/RIF® and is positive for both *M. tuberculosis* and rifampin resistance. Because he has a known contact with XDR-TB, he is empirically started on an XDR-TB regimen while awaiting second-line DST.

He has a baseline ECG which reveals a QTc interval of 411msec. His albumin is 3.1 gm/dL. His initial regimen is PZA, DLM, CFZ, LZD, CS, HD-INH and THA. His DLM dose is 50mg twice a day as is recommended based on PK and safety studies. His THA is discontinued after his line-probe assay shows an inhA mutation and he is continued on the rest of his regimen. He does well, gains weight, and is back playing football one month after starting treatment.

Vietnam

DT is an 11 year-old-child who is found to be sick with signs and symptoms of TB after his mother died of the disease. His mother was found to have MDR-TB resistance only to INH and RIF, but she was unable to take her medications daily because she had no transport money to get to the clinic, and she had a sick child to take care of at home. DT is brought to the clinic by his father after he has an episode of coughing blood, and the doctors there collect a sputum as they think he has TB.

On exam he is found to be febrile to 39C, weighs 34 kg, and his pulmonary exam reveals crackles and wheezing throughout the left lung. His chest radiograph shows left sided ulceroinfiltrative disease with small nodules and cavities throughout the lung field. DT is started on TB treatment and 4 days later his sputum results come back positive for *M. tuberculosis* and rifampin resistance, but his second-line drugs susceptibility testing looking at ofloxacin and kanamcyin show no evidence of resistance.

Because he does not have documented resistance, DT is started on a novel, shortened regimen for the treatment of his MDR-TB. The regimen consists of HD-INH, EMB, PZA, KM, THA, MFX, CFZ, and after starting the regimen, DT quickly improves, becomes smear negative, and his fevers and cough abate.

DT is able to take his treatment daily with the support of a community health worker who comes to his home, and he is able to go back to school three weeks after starting treatment. He has multiple negative smears and cultures, and after 4 months on treatment, he is moved to the continuation phase of the regimen which consists of HD-INH, EMB, PZA, MFX, and CFZ. He continues to do well and is able to complete treatment after a total of ten months, cured of his MDR-TB.

Key Points:

- Follow basic principles of regimen design used in adults.
- Therapy in the absence of bacteriologic confirmation is more likely needed in children and should include a strong regimen that can be scaled back based on DST or development of adverse effects.
- Consider inclusion of INH and RIF unless the patient has received them in the past or has contraindications to their use.
- Corticosteroids should be used in cases of meningitis, pericarditis and disseminated disease.

Dosing of Second-Line Antituberculous Agents For Pediatrics

Proper dosing of second-line agents for children is key to ensure good outcomes and to prevent the development of additional resistance. Unfortunately, dosing recommendations for children can be somewhat complicated. This is due to the fact that there are limited pharmacokinetic data (i.e. the way the body metabolizes a drug) on most second-line drugs in children, and optimal doses are yet to be determined. An ongoing pharmacokinetic study in South Africa will provide data on all second-line drugs in children; results from the injectables, ethionamide, and the fluoroquinolones have been presented at the Union TB meetings in Kuala Lumpur (2012) and Paris (2013). The second problem is that there are not pediatric-friendly formulations of most of the drugs used to treat MDR-TB in children (with the exception of some of the fluoroquinolones and PAS); most programs split adult tablets, which can lead to inconsistent dosing.

There are emerging data on some of the second-line drugs in children based on a sample of children from Cape Town. In the meantime, children are being treated now, and there is a need for improved dosing recommendations. This manual provides dosing guides that can be used in the field, with updates to the dosing from the 2012 and 2015 versions of this handbook based on the existing data from South Africa. Further updates will be provided as more data are analyzed from this large study. Programs should use this while recognizing that updated dosing recommendations will be available soon.

Weight-Based Dosing in Children

Group A: Fluoroquinolones

Levofloxacin (15-20 mg/kg)		
kg	**250 mg tablet**	**25 mg/mL suspension**
1.0–2.9	not recommended	
3.0–4.9	0.25 tab	2.5 mL
5.0–8.9	0.5 tab	5 mL
9.0–11.9	0.75 tab	7.5 mL
12.0–16.9	1 tab	10 mL
17.0–24.9	1.5 tabs	15 mL
25.0–29.9	2 tabs	20 mL

Dosing tables courtesy of James Seddon, Karen Day, and Michael Rich

Moxifloxacin (7.5–10 mg/kg)		
kg	**400 mg tablet**	**20 mg/mL suspension**
1.0–2.9	not recommended	
3.0–3.9	not recommended	1.5 mL
4.0–4.9	not recommended	2 mL
5.0–7.9	not recommended	2.5 mL
8.0–13.9	not recommended	5 mL
14.0–14.9	0.5 tab	5 mL
15.0–19.9	0.5 tab	7.5 mL
20.0–26.9	0.5 tab	10 mL
27.0–29.9	0.5 tab	12.5 mL

The moxifloxacin suspension is not available commercially and must be prepared.

Group B: Second-line injectable agents

Drug	Daily dose	Maximum daily dose
Streptomycin	20-40 mg/kg once daily	1000 mg
Amikacin	15-20 mg/kg once daily	1000 mg
Kanamycin	15-20 mg/kg once daily	1000 mg
Capreomycin	15-20 mg/kg once daily	1000 mg

To illustrate dose calculation, take the example of a child that weighs 6.9 kg.

- Both the low and high doses for the child's weight are calculated.
  For kanamycin:
  Low dose: 15 mg/kg x 6.9 kg = 103 mg
  High dose: 20 mg/kg x 6.9 kg = 138 mg

- A convenient dosing is then chosen between the two numbers.
  Select a dose between the two numbers and towards the higher number. In this case, choose: 125 mg per day, single dose.

- Calculate the number of mL to draw up in the syringe based on the mg/mL concentration of the preparation.

Group C: Other core second-line agents

Prothionamide/Ethionamide (15–20 mg/kg)	
kg	**250 mg tablet**
1.0–2.9	not recommended
3.0–4.9	0.25 tab
5.0–8.9	0.5 tab
9.0–11.9	0.75 tab
12.0–16.9	1 tab
17.0–24.9	1.5 tabs
25.0–29.9	2 tabs

Cycloserine/Terizidone (15–20 mg/kg)		
kg	**250 mg capsule**	**1 capsule in 10 mL water**
1.0–2.9	not recommended	
3.0–4.9	0.25 cap	2.5 mL
5.0–8.9	0.5 cap	5 mL
9.0–11.9	0.75 cap	7.5 mL
12.0–16.9	1 cap	10 mL
17.0–24.9	1.5 caps	15 mL
25.0–29.9	2 caps	20 mL

For older children who cannot swallow capsules, the capsules can be opened and dissolved in 10 mL water to aid administration.

Drug	Daily dose	Maximum daily dose
Clofazimine	2–3 mg/kg once daily; if the child is <25 kg, give 100 mg every second day	200 mg
Linezolid	10 mg/kg/dose twice daily for children <10 years of age; 300 mg daily for children ≥10 years of age. Also give vitamin B6.	600 mg

Group D: Add on agents (not part of the core MDR-TB regimen)

D1

Pyrazinamide (30–40 mg/kg)		
kg	**400 mg tablet**	**500 mg tablet**
1.0–2.9	not recommended	
3.0–4.9	0.25 tab	0.25 tab
5.0–5.9	0.5 tab	0.25 tab
6.0–9.9	0.5 tab	0.5 tab
10.0–11.9	1 tab	0.5 tab
12.0–14.9	1 tab	1 tab
15.0–18.9	1.5 tabs	1 tab
19.0–20.9	1.5 tabs	1.5 tabs
21.0–25.9	2 tabs	1.5 tabs
26.0–26.9	2 tabs	2 tabs
27.0–29.9	2.5 tabs	2 tabs

Ethambutol (15–25 mg/kg)	
kg	**100 mg tablet**
1.0–2.9	not recommended
3.0–7.9	1 tab
8.0–12.9	2 tabs
13.0–15.9	3 tabs
16.0–26.9	4 tabs
27.0–29.9	5 tabs

Older children over 16 kg can use the adult 400 mg tablet in combination with the 100 mg tablet to reduce the pill count

Rifampicin (10–20 mg/kg)		
kg	**150 mg tablet**	**300 mg tablet**
1.0–2.9	not recommended	
3.0–3.9	0.5 tab	-
4.0–4.9	0.5 tab	-
5.0–7.9	1 tab	-
8.0–12.9	1.5 tabs	-
13.0–17.9	2 tabs	1 tab
18.0–25.9	3 tabs	1.5 tabs
26.0–29.9	4 tabs	2 tabs

High-dose isoniazid (15–20 mg/kg)	
kg	**100 mg tablet**
1.0–2.9	not recommended
3.0–4.9	0.5 tab
5.0–8.9	1 tab
9.0–12.9	2 tabs
13.0–20.9	3 tabs
21.0–26.9	4 tabs
27.0–29.9	5 tabs

Older children over 14 kg can use the adult 300 mg tablet in combination with the 100 mg tablet to reduce the pill count

D2

Bedaquiline		
kg	**Dose**	**Duration**
<20 kg	consult expert	
20–32 kg	Weeks 1-2 (14 days): 200 mg once daily Weeks 3-24 (22 weeks): 100 mg thrice weekly	24 weeks
>33 kg	Weeks 1-2 (14 days): 400 mg once daily Weeks 3-24 (22 weeks):200 mg thrice weekly	24 weeks

Delamanid		
kg	**Dose**	**Duration**
<20 kg	consult expert	
20–34 kg	50 mg twice daily	24 weeks
>35 kg	100 mg twice daily	24 weeks

According to recent WHO guidelines (November, 2016), delamanid is the drug of choice in children, but bedaquiline can be considered in settings in which there is limited access to DLM

D3

PAS (150–200 mg/kg)		
kg	**PASER granules (4g sachet)**	
	Daily	**Twice daily**
1.0–2.9	not recommended	
3.0–3.9	500 mg	250 mg
4.0–5.9	1000 mg	500 mg
6.0–8.9	1500 mg	750 mg
9.0–12.9	2000 mg	1000 mg
13.0–15.9	2500 mg	1250 mg
16.0–20.9	3000 mg	1500 mg
21.0–24.9	4000 mg	2000 mg
25.0–28.9	5000 mg	2500 mg
29.0–29.9	6000 mg	3000 mg

PASER® is stable for up to 8 weeks at 40˚C and 75% humidity, and therefore can be distributed to the patient on a monthly basis in most environments with no cold chain. If storage of longer than 8 weeks is needed, refrigeration below 15˚C is required.

Drug	Daily dose	Maximum daily dose
Amoxicillin-clavulanate*	80 mg/kg in two divided doses based on the amoxicillin component	4000 mg amoxicillin and 500 mg clavulanate
Meropenem	20–40 mg/kg IV every 8 hours	6000 mg

*Amoxicillin-clavulanate should only be given in combination with meropenem or imipenem. It should be given 30 minutes prior to the IV infusion of meropenem or imipenem.

Section 3: Monitoring

Diagnosing children with MDR-TB and designing an appropriate treatment regimen can be major obstacles in the management of pediatric MDR-TB. Another challenge is maintaining the patient on therapy for 18-24 months and making sure that he or she is closely followed by physicians, nurses, health care workers, and caregivers. Children have been successfully treated for MDR-TB, but only with appropriate monitoring and follow-up. Monitoring is needed to evaluate therapeutic efficacy and to mitigate the development of adverse events. This section will discuss:

- Timing and types of monitoring
- Adverse events and management strategies
- Management of co-morbid conditions
- Adherence support
- Nutritional monitoring and support

Treatment monitoring schedule

All children	Baseline	Month										Ongoing
		1	2	3	4	5	6	9	12	15	18	
HIV status	•											
Toxicity (symptoms, signs)	•	•	•	•	•	•	•	•	•	•	•	•
Height and weight	•	•	•	•	•	•	•	•	•	•	•	•
Audiology[1]	•	•	•	•	•	•	•					
Color vision testing[2]	•	•	•	•	•	•	•	•	•	•	•	•
CXR[3]	•			•			•					
TB culture and DST[4]	•	•	•	•	•	•	•	•	•	•	•	
Creatinine and potassium[1]	•	•	•	•	•	•	•					
TSH, T_4[5]	•			•			•	•	•	•	•	•
Hematology (FBC, diff)[6]	•	•	•		•		•	•	•	•	•	•
LFTs				•			•	•	•	•	•	
ECG to assess QTc interval (for children on BDQ, CFZ, MFX, or DLM)	•	•	•	•	•	•						
HIV-infected children												
Cholesterol[7]	•						•				•	•
CD4 count and viral load	•						•				•	•

[1] Monthly while on injectable and at 6 months following termination of injectable
[2] If on ethambutol
[3] If any pulmonary involvement
[4] Monthly if old enough to expectorate; if unable to expectorate and initially smear or culture positive, monthly until culture-converted then every three months; if initially smear and culture negative, perform if clinically indicated
[5] If on ethionamide, prothionamide or PAS
[6] If on linezolid or HIV-infected
[7] For patients on ART, depending on the regimen

Identification and Management of Adverse Events

Type of adverse event	Likely culprit drugs	Identification	Management
Hepatotoxicity	INH, PZA, RIF, THA, Bedaquiline (BDQ), PAS, Clofazimine (CFZ), Delamanid (DLM)	Tender liver, visible jaundice	Stop all drugs; Wait for liver function to return to normal; Re-introduce drugs one-by-one sequentially, every 2 days with monitoring of liver function before introducing the next drug.
Visual problems	EMB, LZD	Regular testing with Ishihara Chart	Stop EMB or substitute for alternative drug.
Hearing problems	AMK, KM, CM	Identified through audiometry or problems in communication	Consider stopping the injectable drug, substituting for an alternative drug such as delamanid, reducing dose or increasing dose interval.
Thyroid dysfunction	THA, PAS	Regular blood testing, clinical hypothyroidism or goitre	Consider thyroxine supplementation (0.05mg daily) if (a) clinical hypothyroidism, or (b) raised TSH and decreased fT4; If raised TSH and normal fT4 repeat test in 1 month.
Renal impairment	AMK, KM, CM	Regular blood testing, symptoms of high potassium	If creatinine rises or potassium is elevated, stop injectable, substitute for alternative drug, dose three times a week or reduce dose.
Severe rash (SJS)	Any drug	Severe rash, peeling mucus membranes, child unwell	Stop all drugs; Wait until clinical condition has improved; Re-introduce drugs one-by-one sequentially, every 2 days, monitoring clinically.
Nausea and vomiting	THA, EMB, PAS	Clinically	Consider separating the dosing of THA from the other drugs by giving it in the evening; Consider reducing the dose of THA and building the dose up to full dose over 2 weeks.
Peripheral neuropathy	INH, LZD	Clinically	Give or increase pyridoxine; If persistent or severe, stop INH.

Type of adverse event	Likely culprit drugs	Identification	Management
Diarrhea	PAS	Clinically	Split dose of granules to give small doses throughout day; Reduce dose; Consider loperamide.
Neuropsychiatric problems	INH, OFX, LVX, MFX, TZD, CS	Seizures, headache, behaviour changes, sleep disturbances	Verify correct dosing; Stop likely culprit drug; If symptoms persist, reintroduce and stop next most likely drug; If symptoms severe or persistent, stop all likely drugs or reduce dose.
Joint problems	PZA, OFX, LVX, MFX	Clinically	Verify correct dosing; Consider reducing dose/stopping possible culprit drug; Consider trial of allopurinol.
Painful injection sites	AMK, KM, CM	Clinically	Add local anesthetic to drug in equal volumes; Vary site of injection on a daily basis; Consider stopping injection and adding DLM; If severe, consider splitting dose and giving half into two different sites.
QTc prolongation	BDQ, MFX, CFZ, DLM	Monthly assessment by ECG Fainting, racing heart, and severe chest pain A QTc interval is considered prolonged if it is > 500msec or if it is > 50msec and the patient has symptoms	Repeat the ECG; Check electrolytes, repeat as needed; Review ancillary drugs to see if any prolong the QTc interval; if so, stop likely culprit drug; Check thyroid; Discontinue MFX and reassess; if still prolonged, discontinue CFZ or BDQ.
Skin pigmentation/ discoloration	CFZ	Skin turns a darker brown or orange color while on the medication, and may also become very dry	Reassure patient that this will improve 2-3 months after treatment stops and skin will return to normal color

Co-Morbid Conditions

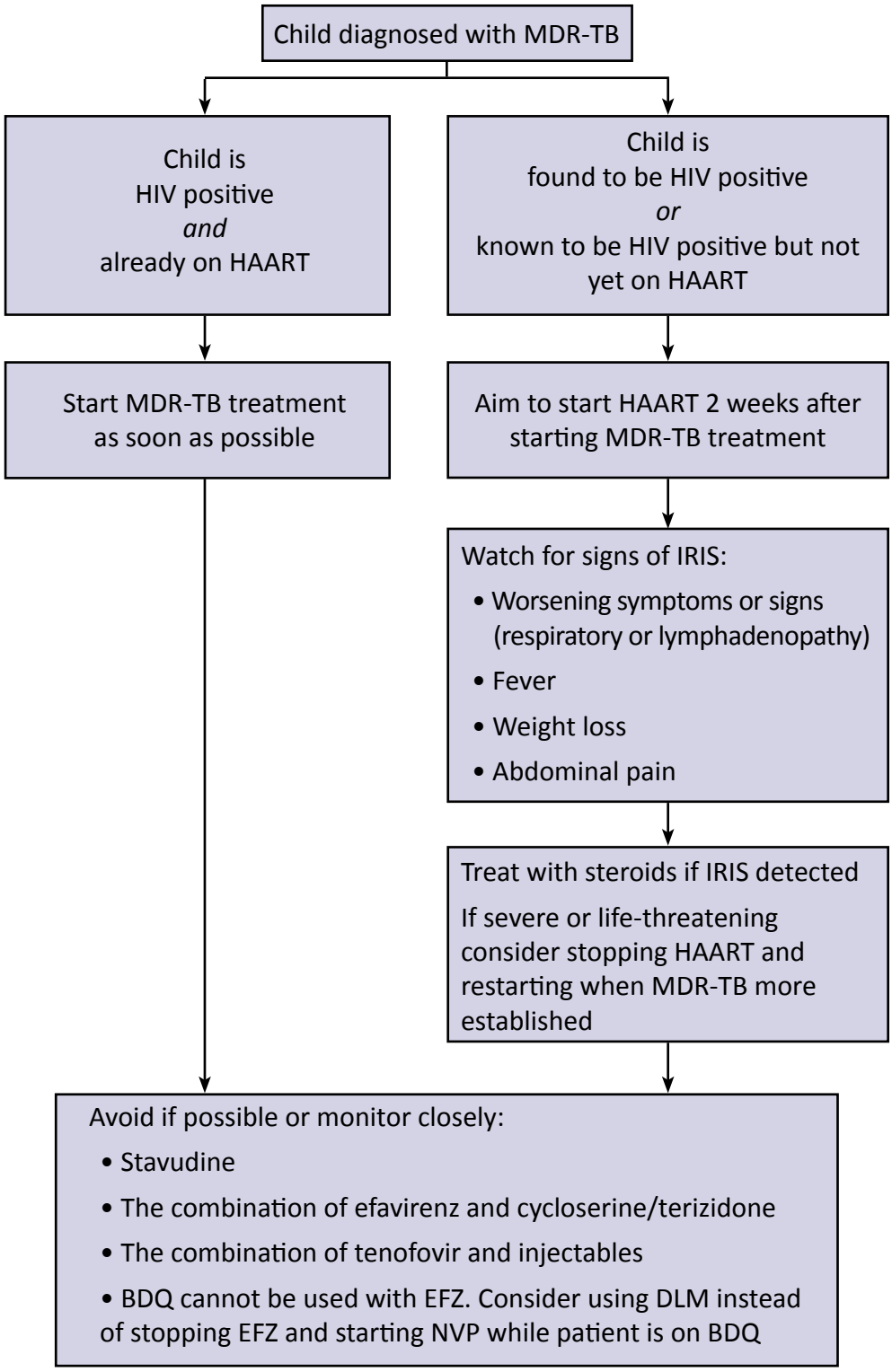
Children with MDR-TB often suffer from other conditions. These may be pre-existing, or develop as a result of their MDR-TB, or may be in conjunction with their MDR-TB. Common co-morbid conditions seen in children with MDR-TB include HIV, diabetes mellitus, orthopedic problems, and reactive airway disease. In each of these cases, children do better in terms of MDR-TB outcomes when their co-morbid conditions are also aggressively treated and controlled. Management of co-morbid conditions should follow these principles:

- Management should occur at the same time as treatment for MDR-TB; waiting for MDR-TB treatment to finish or move to a "continuous" phase puts the patient at risk for poor outcomes from both conditions.
- Management should be provided in an integrated setting making care easy for the patient and reducing the risk of MDR-TB in other clinical settings (i.e. diabetes clinic, asthma clinic).
- Care should be taken to avoid giving drugs with overlapping toxicities when possible.

A detailed algorithm on the management of children with co-morbid HIV is included in this field guide. For other co-morbid conditions, we recommend the following:

- Diabetes mellitus: Blood sugar results may fluctuate in the setting of acute MDR-TB, and thus, more frequent monitoring of blood sugars is necessary. In addition, common drugs used to treat TB may exacerbate glucose control problems and could have overlapping toxicities with both the disease itself (e.g. peripheral neuropathy) and with diabetes treatment regimens (e.g. oral antihyperglycemics). Patients may need to adjust their insulin dosing for tighter control, especially in the early stages of treatment. In addition, patients should be provided with adequate calories to ensure healthy weight gain.
- Reactive airway disease: Active MDR-TB can exacerbate existing reactive airway disease or cause reactive airway disease. Bronchodilators should be used for both maintenance and rescue situations. Inhaled corticosteroids **can** be safely used in children with MDR-TB.
- Orthopedic problems: Children may develop TB of the spine or joints, requiring the use of braces or other support devices. Children may also need physical therapy as part of their recoveries. When possible, local materials should be used for devices, and simple physical therapy regimens (e.g. chest clapping) that can be done at home should be designed.
- All children with MDR-TB should have a full complement of immunizations. It is important to verify immunizations at each appointment.

Algorithm for Management of Children on Treatment for MDR-TB and HIV



Adherence

Adherence to MDR-TB therapy is one of the cornerstones of treatment success. Hospitalization is not necessary for most children with MDR-TB and may actually decrease rates of adherence. As with adults, all children should be given treatment under DOT for each dose. Clinic-based DOT may place undue burdens on patients and their families, and where feasible, community-based DOT should be considered. If community-based DOT is not feasible, patients should be given incentives (e.g. food baskets) and enablers (e.g. transportation vouchers) to assist in treatment adherence.

Pediatric MDR-TB patients face special challenges with adherence. Very young children may not be able or willing to swallow tablets. Adolescent patients may use non-adherence as a way of asserting their independence. It is important to recognize that adherence strategies will need to be tailored to the individual patient and may change over time, even for the same patient. Some common principles should be followed in improving adherence among pediatric MDR-TB patients. These include:

- Age-appropriate patient education for the child and the caregiver. This is an extremely important part of adherence. The level of information given, and the manner in which it is delivered will need to be tailored according to the age of the child and where they are in their treatment course.
- Avoid the use of physical restraints and nasogastric tubes when possible. Avoidance may not be possible in all settings. Where restraints or nasogastric tubes are required, a daily assessment of ongoing need should be made.
- Adherence should be approached as a relationship, and pediatric patients offered some control over the process whenever possible (i.e. holding the medication spoon or dispenser with the provider; deciding the order in which to take the medications).
- It may be convenient to dose all medications at the same time, but this may be overwhelming for children. Twice or thrice daily dosing can be considered for some medications. Even with once daily dosing, half of the pills could be given in the morning and half in the evening, provided patients are not dosed the same medication more than once in 24 hours.
- Drug substitution to improve adherence (i.e. the changing of one effective medication for another in a successful treatment regimen to assist with adverse event management) can be considered, provided the substitution does not compromise the integrity of the regimen.
- Pediatric adherence depends on the caregivers. They should be involved at all stages and help make decisions about improving adherence.
- Incentives should be provided to children on a daily or weekly basis, depending on age. This could be as simple as a positive mark on a wall chart, singing a favorite song, or eating a special food. For adolescents, mobile phone minutes have been shown to be a powerful incentive. Incentives should also be provided to caregivers.

It is important to remember that children are often far more adherent than providers imagine them to be. Non-adherence may also be a sign of psychological or emotional distress, and social support should be given to both the child and the caregiver.

Case Examples: Adherence

Zimbabwe

Liswelicha is an 11-year-old boy diagnosed with MDR-TB. He is started on a regimen based on his DST which includes PZA-EMB-KM-LVX and PTO. He starts his medications in the hospital and initially does well, but after several episodes of vomiting, he refuses to take the "yellow one" (i.e PTO) because "it smells bad and makes my stomach hurt." He tries to run away from the hospital and once is found outside on the road looking for a taxi. He is adamant that the problem is the PTO, and he starts having anticipatory vomiting of all of his medications. Attempts are made to restrain and force him to swallow the PTO, but he continues to vomit and struggles strongly. A nasogastric tube is placed, but he removes it within an hour, even with both hands restrained.

A nurse talks with Liswelicha, and he again states that it is the "yellow pill" he has a problem with. He says he will take all of his other medications—"even the shot"—as long as he does not have to take the PTO. A review of his DST confirms sensitivity to CS, and the hospital has an adequate supply. His PTO is stopped, CS is started, and Liswelicha becomes adherent, and his behavioral problems resolve.

Liswelicha is discharged from the hospital and does well for 7 months, with 100% adherence documented. He travels to a local clinic daily to take his medication. The clinic calls in his tenth month of treatment and says he has not come in for the past week. A home visit is made, and his mother notes he has moved to a camp for boys looking for work in the city. Liswelicha is found on a visit to the camp and states that he no longer needs his medication because he feels well. He also notes that now that he is 12, he needs to work to earn money for his family. A meeting is held with Liswelicha and his mother, and he agrees to return home and finish his treatment. The clinic agrees to offer his family a monthly food basket for every month that Liswelicha remains on therapy. He completes 18 months of treatment then leaves to migrate to another country for work.

Georgia

Nino is a 2-year-old girl undergoing treatment for MDR-TB. Her father had confirmed MDR-TB and died while on therapy. Nino is in the hospital for her treatment, and she is started on PZA-KM-LVX-THA and TZD, as her father had resistance to INH, RIF and EMB. She is also given INH and RIF in case she has drug-susceptible TB, as she has no contraindications to receiving these medications. Nino is quite ill and has major problems with vomiting her medications. Because she is in the hospital, her nurses and caregivers are able to space out her medications throughout the day, as the volume of

the medications alone may be making her vomit. She has also developed "welts" at the site of her injection and screams in agony when the shot is given. Her mother is distraught and threatens to take Nino home.

An intravenous line is placed to allow Nino to receive her injection through the line for 7 days. A charity group brought some dolls to the hospital and Nino is besotted with a small baby doll. The nurses use the doll to soothe Nino when she cries, and she develops a game where she pretends to give the doll shots and medicine when she has to take hers. Another physician also recommends mixing some local anesthetic with the injection to ease her pain. After one week, her IV is removed, but a smaller needle is used to give the injections. A warm compress is also placed in the site of the injection to ease her pain. Nino still cries, but her doll provides a way for her to get comfort and to play act some of her fears. She completes 18 months of therapy, and both she and her doll are cured.

Key points:

- Children at different ages will have different adherence needs, and adherence needs change over time.
- Age-appropriate partnerships with children and their caregivers are key to improve adherence.
- Some adverse effects are very real, and if treatment modifications can be made without affecting regimen integrity, these should be considered.
- Family factors that affect pediatric adherence should be addressed.

Nutritional Monitoring for Children with MDR-TB

One of the key indicators for clinical monitoring in children being treated for MDR-TB is improvement in nutritional status. If a child does not have an improvement in nutritional status while being treated for MDR-TB, that child has little chance of having a successful treatment outcome.

There are several ways to monitor the nutritional status of a child undergoing treatment for MDR-TB. A baseline measure of weight, height, and mid-upper arm circumference (MUAC) should be made in all children with MDR-TB. The MUAC is an indicator of acute malnutrition; if such malnutrition is present, acute nutritional interventions are needed, according to local standards. At monthly follow-up, height and weight should be assessed. The weight-for-age and weight-for-height should be plotted for all children between 0 and 5 years, and body mass index (BMI) should be plotted for all children between 5 and 19 years. While there are many methods that can be used for assessing nutritional status, what is important in following MDR-TB

patients is that their percentiles improve over time and do not decrease at any point in time.

If a child does not demonstrate improved nutritional status, this is a sign that his or her MDR-TB is not being appropriately treated. Children with MDR-TB require a higher caloric intake than their well counterparts because of the active metabolism associated with MDR-TB. Failure to improve nutritional status is an early and clear indicator that the MDR-TB may not be under control.

In addition to active MDR-TB contributing to poor nutritional status, many children and their families with MDR-TB often live in poverty. Thus, families may not be able to meet their basic nutritional needs. Nutritional support for children and their families should be considered a routine part of clinical care for persons with MDR-TB. Physicians and nurses often counsel children and their parents that "the child needs to eat better." This advice, however, is often not followed because the family cannot access food. Nutritional counseling can still be given in this setting, and some practical advice is offered below.

Some programs try to improve nutritional status by prescribing vitamins for children with MDR-TB. These vitamins can be important sources of needed micronutrients, and vitamin B6 must be given to all children receiving therapy for MDR-TB. However, too many vitamins can increase the pill burden of the child and may not be well absorbed. It is always preferable to give the child vitamins combined with calories in the form of food. A program effort should be made to provide families with a food basket enough to feed the child and siblings to avoid excessive splitting of portions received by the MDR-TB patient alone.

Practical Nutritional Advice for Children and Families with MDR-TB

Children with MDR-TB and their families are often told that the child needs to "eat better." They are given little, if any, practical advice on how to do so, especially in settings where they are unable to afford foodstuffs. This section offers practical advice on nutritional counseling for children and their families with MDR-TB.

- Know the resources in the community that offer nutritional assistance. TB programs may offer assistance directly to patients and their families on MDR-TB treatment. In other cases, there are additional groups working to provide nutritional support, such as non-governmental organizations, faith-based organizations, and community groups. These groups may give monthly or quarterly food provisions to families. Additional groups—including popular kitchens, community food groups, and food pantries—can provide single or ongoing cooked meals.
- Know the resources of the patient and family. Instead of telling them to "eat better," ask them about the food they eat. Start by asking "how many meals do you eat a day?" Then proceed to ask about the composition of meals, who eats first in the family, and if there are any

foods they avoid. Specifically ask if the child is able to drink milk.

- Know the locally available staple foods and the general price ranges for these foods. This can be done by taking a small shopping trip in the neighborhood. Once food availability and costs are known, patients and families can be given practical nutritional advice. For example, instead of encouraging them to "eat more protein" or "eat more meat," recommend eggs (which contain protein but are often not as expensive as meat) or different cuts of meat (e.g. the liver or heart) which may cost less than other cuts. If the child is able to drink powdered milk, then the recommended recipe for making the milk could be "doubled" to increase caloric intake (i.e. add twice as much powder to the same amount of water). Nuts, legumes, and oil are all high protein foods that may be more affordable, depending on the setting. The same applies to leafy and green vegetables. Discourage families from buying expensive vitamin supplements and encourage them to invest instead in calorie-rich foods.
- Recommend to the family that the child eat several small meals during the day. It can be overwhelming to a sick child to sit down to a larger plate of food. Eating multiple small, high calorie meals may help the child gain weight. This can be especially helpful for children with nausea and vomiting, which is common in patients on second-line antituberculous therapy.

Photo courtesy of Jennifer Furin

Special populations

Neonates

Neonates are at high risk for both TB infection and disease, include MDR-TB, and there are little data or experience in managing MDR-TB in these vulnerable children. In general, if a woman has MDR-TB and is culture positive in the last month of pregnancy, it can be presumed that the neonate has been exposed to MDR-TB. The baby can become sick with the disease, acquired either congenitally in utero or postnatally via airborne spread. Although there are limited data on the management of MDR-TB during pregnancy, clinical experience suggests that women can be treated with most of the commonly used MDR-TB drugs. However the injectables should be avoided, if possible, especially during the first trimester due to their adverse effects on the developing fetal ear. Therapeutic decisions regarding MDR-TB treatment during pregnancy must weigh the risks of untreated MDR-TB — including death of the mother and transmission to the neonate — versus the risks of exposing the neonate to the toxicity of second-line drugs. Pyridoxine (vitamin B6) should be given to all pregnant women being treated for MDR-TB.

In terms of the management of babies born to women with MDR-TB, they should be evaluated for signs or symptoms of active disease at birth and then on a regular basis. The TST and IGRAs are of very limited utility in neonates. Complicating things, neonates are more likely to develop disseminated disease and exhibit non-classical TB symptoms, including irritability, poor feeding, splenomegaly, and hepatomegaly. To confirm a diagnosis of MDR-TB in a neonate whose mother had active MDR-TB during pregnancy, the placenta should be examined. Additional diagnostic studies in babies suspected of MDR-TB disease should include an immediate gastric aspirate and then 3 additional gastric aspirates, a lumbar puncture, blood samples, skin swabs and other relevant swabs/samples for mycobacteriologic assessment, with chest radiography or other imaging as indicated. If disease is suspected, treatment should be started as soon as possible and should be based on the DST of the mother. Dosing recommendations are the same as for older children.

Children born to women undergoing treatment for MDR-TB should be breast-fed if the mother is able to do so. Small concentrations of second-line drugs are present in the breast milk, so the neonate should be given pyridoxine (vitamin B6). Women who are still culture positive should wear a surgical mask when breastfeeding, and the baby should not share a bed with the mother. There is no need, however, to separate the mother-child pair as part of routine MDR-TB care. Sick and exposed neonates should be closely followed, preferably by a neonatologist or clinician with experience on MDR-TB in newborns.

Adolescents

Adolescents (defined by the WHO as persons between the ages of 10 and 19 years) are often a population that can be overlooked when discussing pediatric MDR-TB.

The clinical presentation of TB in this group and their ability to provide sputum for diagnostics often leads to them being thought of as adult patients. Data from multiple field sites, however, have shown that adolescents have worse treatment outcomes when compared with adults, especially those adolescents co-infected with HIV. While issues around adherence require special attention in this population with changing emotional and social needs, data show that adolescents may also have an increased death rate compared with adults. These deaths appear to occur early in the course of therapy, suggesting a delay in diagnosis. For these reasons, it is important to consider the needs of this special population in diagnosing MDR-TB and supporting adherence. The use of adolescent support clubs, such as those that have been used to support adolescents with HIV, could be of great utility in this population.

Section 4: Infection Control

Infection control is of paramount importance in the management of MDR-TB in children. Children should be protected from becoming infected with MDR-TB in both the health facility and home setting. Children with MDR-TB should be safely managed in a way that does not cause unnecessary psychosocial stress and avoids making them victims of stigma. Children with MDR-TB usually do better in a home setting and when they are able to resume normal activities, such as going to school. In most cases, as long as the child is on appropriate therapy for MDR-TB, the risk of transmitting MDR-TB is low. This section offers practical guidance on facility-based infection control and home/community-based infection control that acknowledges the need to reduce MDR-TB transmission risk while at the same time acknowledging the important developmental needs of a growing child. This section will discuss:

- All family members of children with MDR-TB should themselves be actively screened for TB by a trained provider
- Facility-based infection control
- Community-based infection control

Facility-Based Infection Control

Although negative pressure airflow isolation rooms and precautions are the gold standard in TB infection control, there are simple infection control measures that can be easily put into place to make nosocomial transmission of MDR-TB less likely. These include:

- Having patients wait outdoors
- Using windows for natural ventilation
- Having separate waiting areas for TB and MDR-TB patients with separate entrances and air supplies
- Considering separate waiting areas for patients with cough if space allows
- Separating waiting areas for HIV patients, who are exceptionally vulnerable to TB, when possible
- Avoiding scheduling patients for well visits on days when known MDR-TB patients are being seen
- Ensuring that appropriate therapy be given and maintained for all TB patients
- Having patients with active cough wear surgical masks to decrease transmission

- Avoiding unnecessary hospitalizations
- Discharging patients on treatment from the wards as quickly as possible once effective therapy has been started and can be maintained in the community. This can be within days to weeks of starting MDR-TB therapy.
- Taking special infection control measures during highly infectious diagnostic procedures such as induced sputum collection

Case Example: Infection Control

Rwanda

At a primary care clinic in rural Rwanda, the nurse notes that three patients have been diagnosed and are now being treated for MDR-TB. One of them is a 5-year-old child who was seen at the clinic 6 months ago with diarrhea. The nurse is very worried about TB transmission in her small, four-room clinic. She requests some benches from the government so that patients can wait outside, but she knows this will not work in the rainy season. She runs an antenatal clinic on Wednesday mornings and a vaccination clinic on both Wednesday and Thursday mornings. She asks all TB patients to come for sputum testing and DOT after 2 p.m. on Wednesdays and Thursdays, and she leaves the clinic windows open at night. She also arranges for home-based DOT for her MDR-TB patients and visits them in their homes monthly to perform follow-up visits and collect specimens. She also requests a small awning for the clinic, so that all sputum specimens can be collected outside, even in the rain.

Community-Based Infection Control

Patients with MDR-TB can be safely treated in the community setting, and the risk for ongoing transmission is low, once the patient is on appropriate MDR-TB therapy. Some community and household measures should be taken to decrease transmission in the household and community. These include:

- MDR-TB patients should ideally sleep in a separate room.
- Windows in the home of a MDR-TB patient should be kept open as often as possible.
- MDR-TB patients should spend as much time outside whenever possible, including visits with friends and family members.
- MDR-TB patients should be provided with social support to be able to stay on MDR-TB therapy.

Household and community members often fear becoming infected with MDR-TB when a child with MDR-TB is returned to the community. As long as the child is maintained on appropriate treatment for MDR-TB, his or her risk of infectiousness is low. Once his or her smear is negative, he or she should return to normal activities—including school and sporting teams—provided his or her clinical status allows. Education should be provided to family members and key community members (i.e. teachers, coaches, ministers). This will decrease stigma and discrimination. Specific points to address include:

- Once the child is on MDR-TB treatment, he or she is unlikely to transmit disease.
- If smear-negative, the child doesn't need to wear a mask in public.
- Children with MDR-TB can share bathrooms, utensils, balls, tools, crayons, etc.
- Children with MDR-TB feel better physically and psychologically when they can return to their usual environments and activities.

Case Example: Infection Control

Peru

Blanca is a 9-year-old girl who was diagnosed with MDR-TB 3 months ago. She is clinically improved and ready to return home. Her family and friends are glad she is coming back, but they are worried they might get sick from her. They begin to gossip in the neighborhood, and some people even threaten to block her from coming into her apartment building.

Worried, her mother speaks to the local priest who agrees to help her talk about MDR-TB with the community. He preaches a sermon the Sunday before Blanca comes home in which he gives the community facts about MDR-TB. He and Blanca's mother answer any questions people have. Blanca's apartment is small, and she cannot have her own sleeping area. However, the church donates a mattress to her mother, and Blanca returns home to sleep there. She returns to school a week after coming home. Her teacher sends a note home her second week back stating that Blanca was punished for borrowing another child's pencil. Blanca's mother arranges for the priest to speak with the school as well. Blanca receives her DOT from a community health worker prior to going to school every day. After 2 months, she is thriving in the community and playing on the girls' football team.

Selected References

This field guide is meant to provide practical advice for clinicians and programs managing children exposed to, infected with and sick with MDR forms of TB. Much of the material in this handbook comes from collected expert opinion. In addition to expert opinion, some key references were used in the development of this guide. These include:

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Appendix A: Sample Intake Form

PERSONAL DATA	
Name:	**Date of evaluation:**
Caregiver:	**Date of birth:**
Place of Residence:	**Age:**
	Sex:
	Medical record number:
Telephone:	
Address and mobile phone number (if different than above):	
Name of evaluator:	
Health establishment:	

TB HISTORY	
□ **Never diagnosed**	**Year first diagnosed with TB:**
Ever received BCG? □ Yes, year(s):_____ □ No □ Unknown	**Diagnosed by:** □ AFB □ Other (specify): □ Culture □ CXR
Suspect primary MDR-TB □ Yes □ No	
Check all risk factors that apply: □ Close contact with known MDR-TB □ Close contact with person who died of TB or failed TB treatment □ Previous treatment □ Failure to improve on current TB treatment	
Summary of previous antituberculous drug use (mark each drug patient has received for >1 month) □ INH □ SM □ FQ □ AMX-CLV □ RIF □ KM □ THA/PTO □ CFZ □ EMB □ AMK □ CS □ Other:_____ □ PZA □ CM □ PAS □ Other:_____	

IMMUNIZATION HISTORY	
Has the child been fully immunized for age: □ Yes □ No **If no, what vaccines are missing?**	**Has patient had BCG?** □ Yes □ No **Is BCG scar present?** □ Yes □ No

SOCIO-DEMOGRAPHIC DATA

Currently in school:
□ Yes
□ No
□ N/A

Who are the primary caregivers?

Number of household members:

Are the caregivers employed?
□ Yes
□ No

Number of household members when diagnosed with TB:

If yes, what is their work?

Number of household members when diagnosed with MDR-TB:

How far does patient live from health facility?

Have parent(s) been tested for HIV?
□ Yes
□ No

How did patient get to the health facility?

If yes, date and result:

How long does it take patient to get to the health facility?

REVIEW OF SYSTEMS

Check all that apply

□ Cough
□ Sputum
□ Poor appetite
□ Weight loss
□ Bronchospasm
□ Dyspnea at rest
□ Dyspnea on exertion
□ Tired, listless, not playing
□ Swelling or "lumps" in neck, arms or groin
□ Vertebral pain
□ Back pain
□ Other:_____

□ Hemoptysis
Largest quantity in mL:
Date of first episode of hemoptysis:

Most recent quantity in mL:
Date of most recent hemoptysis:

Current medications:

Allergies or adverse reactions:

PAST MEDICAL HISTORY

Diabetes
□ Yes □ No

Asthma
□ Yes □ No

Previous hospitalization(s)?
□ Yes □ No

Other:

Hospitalization(s) in pulmonary ward?
□ Yes □ No

Has patient been tested for HIV?
□ Yes
□ No
If yes, date and result:

Reason for hospitalization(s):

Name of hospital(s):

Prior transfusion(s)
□ Yes
□ No

Date of transfusion(s):
Indication for transfusion(s):

BIRTH HISTORY AND PAST SURGICAL HISTORY	
Was patient born at home? □ Yes □ No **Did the mother receive prenatal care?** □ Yes □ No **Were there any problems at birth?** □ Yes □ No **If yes, describe:**	**Prior sugery?** □ Yes □ No **Procedure(s):** **Date(s) of surgery:** **Complications:**

PHYSICAL EXAM			
Temp:	**BP:**	**HR:**	**RR:**
Weight:	**Height:**	**BMI:**	
General appearance			
HEENT Conjunctiva: Sclera: Oropharynx:	**Lymphadenopathy present?** JVD: Thyromegaly:	**Cor** Tachycardic? Murmurs? Extra heart sounds?	**Lungs** Wheezing? Crackles? Bronchial breathing sounds?
Abdomen Bowel sounds? Organomegaly? Tender?	**Extremities** Edema? Cyanosis? Pulses:	**Neuro** Mental status: Reflexes: Strength: Gait:	**Developmental** Describe development for age:

TEST RESULTS							
Drug susceptibility testing:							
	Sample number	Date of sample collection	Date of results	AFB results (**P**os, **N**eg, **U**nknown)	Laboratory	Resistant to	Susceptible to
1				P N U			
2				P N U			
3				P N U			
4				P N U			
5				P N U			
6				P N U			
Chest radiograph:							
Other lab results:							
Impression/plan:							

SUMMARY OF KNOWN TB CONTACTS									
Name of contact	**Relation to patient**	**Date of TB diagnosis**	**Lived in same household when contact had TB?**	**History of multiple treatments?**	**Died during treatment?**	**History of documented MDR-TB?**	**Current AFB status***	**Current status of TB contact****	**Resistant to which drugs?**
			Y N U	Y N U	Y N U	Y N U	P N U	C T S D U	
			Y N U	Y N U	Y N U	Y N U	P N U	C T S D U	
			Y N U	Y N U	Y N U	Y N U	P N U	C T S D U	
			Y N U	Y N U	Y N U	Y N U	P N U	C T S D U	

Unless stated otherwise, indicate **Y**es, **N**o or **U**nknown

* For AFB status, indicate **P**ositive, **N**egative or **U**nknown

** For current status, indicate **C**ured, in **T**reatment, **S**ymptomatic but not in treatment, **D**eceased, or **U**nknown

Appendix B: Medications Used to Treat MDR-TB

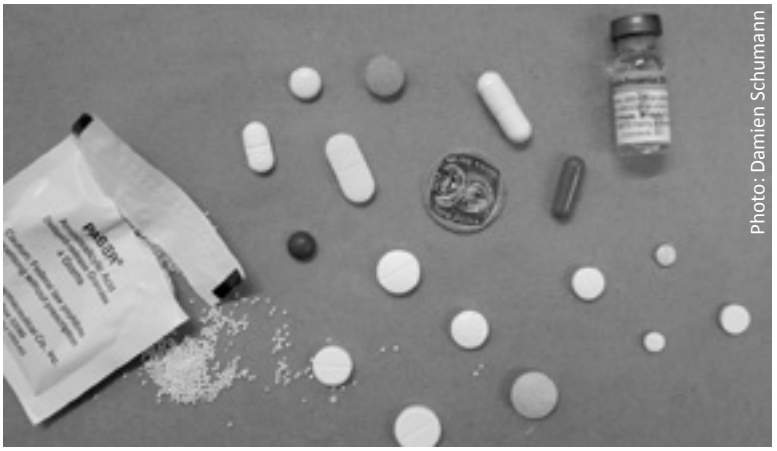


Photo: Damien Schumann

Clarithromycin (CLR)
Form: tablet
Dose: 500 mg

Prothionamide (PTO)
Form: tablet
Dose: 250 mg

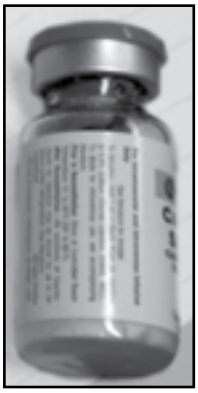
Amoxicillin-clavulanic acid (AMX-CLV)
Form: tablet
Dose: 500 mg

Moxifloxacin (MFX)
Form: tablet
Dose: 400 mg

Clofazimine (CFZ)
Form: soft gel
Dose: 100 mg

Cycloserine (CS)
Form: capsule
Dose: 250 mg

Kanamycin (KM)
Form: solution for injection
Dose: 500 mg



Capreomycin (CM)
Form: lyophilized powder
Dose: 1 g

Para-Aminosalicylic acid (PAS)
Form: granules
Dose: 4 g

Appendix C: Contact Management Form for Children Exposed to MDR-TB

CHILD PERSONAL INFORMATION	
Child name:	**Clinic name:**
Child date of birth:	**Clinic phone number:**
Child folder number:	**Clinic fax number:**
Child address:	

SOURCE CASE INFORMATION			
Source case name:		**Date of sample production:**	
Relationship to child:		**Sputum smear result:**	
DST results:			
	Resistant	**Susceptible**	**Not tested**
Isoniazid			
Rifampicin			
Ofloxacin			
Amikacin			
Ethionamide			

PHYSICAL EXAM			
Weight:	**HIV test date:**	**Mantoux test date:**	**CXR date:**
Height/length:	**HIV test result:**	**Mantoux test size (mm):**	**CXR impression:**

Symptoms:	**Management:**
□ Cough > 2 weeks	□ Fever
□ Losing weight	□ Reduced energy
□ Night sweating	□ Abnormal joints/spine
	□ Refer
	□ Prophylaxis
	□ Discharge/observe

PREVENTIVE TREATMENT			
	Date started	**Dose**	**Number of tablets**
Isoniazid			
Ofloxacin			
Ethambutol			
Other:			

MONITORING CHART			
Month	Weight	Height	Clinical review completed
1			
2			
3			
4			
6			
9			
12			

Appendix D: Protocols for Specimen Collection

Gastric Aspiration

Gastric aspiration can be used in children when sputa cannot be spontaneously expectorated nor induced using hypertonic saline. Since gastric aspiration is not an aerosol-generating procedure, it poses a low risk for transmission. Normal infection control measures should be in place, and staff should use respirators (as coughing in the patient can be accidently induced by the procedure), eye protection, and non-sterile gloves.

Procedures for gastric aspiration adapted from WHO guidelines, 2006. An instructive video on the procedure can be found at the following website: https://www.youtube.com/watch?v=IWl_TY_LbZk&feature=youtu.be

Contraindications

- Child not fasted for 4 hours
- Low platelet count or bleeding tendency

Material required

- Non sterile gloves
- Nasogastric tube (10F)
- Syringe 5-30 cc with appropriate connector for the nasogastric tube
- Litmus paper
- Specimen container
- Lab request forms
- Pen
- Sterile water or normal saline
- Sodium bicarbonate solution (8%)
- Alcohol/chlorhexidine

Procedure

- Position child on his/her back or side.
- Have an assistant to hold the child.
- Measure the distance between the nose and stomach to estimate the distance that will be required to insert the tube into the stomach.
- Attach a syringe to the nasogastric tube.
- Gently insert the nasogastric tube through the nose and advance it into the stomach.

- Withdraw gastric contents (2-5 mL) using the syringe attached to the nasogastric tube.
- To check that the position of the tube is correct, test the gastric contents with litmus paper: blue litmus turns red in response to acidic stomach contents. Tube position can also be checked by pushing 3-5 mL of air into the stomach and listening with a stethoscope over the stomach.
- If no fluid is aspirated, insert 5-10 mL of sterile water or normal saline and attempt to aspirate again. If still unsuccessful, attempt this again. Do not repeat more than three times.
- Withdraw gastric contents (ideally at least 5-10 mL).
- Transfer gastric fluid from the syringe into a sterile container.
- Add an equal volume of sodium bicarbonate to the specimen in order to neutralize the acidic gastric contents and prevent destruction of tubercle bacilli.

After the procedure

- Wipe the specimen container with alcohol/chlorhexidine to prevent cross-infection and label the container.
- Fill out the lab request forms.
- Transport the specimen in a cool box to the lab for processing as soon as possible (within 4 hours).
- Give the child his or her usual food.

Sputum Induction

Sputum induction (SI) is a useful procedure for obtaining sputum specimens in situations where suspected or known TB patients cannot self-expectorate, and where a bacteriological result is desired for diagnosis or follow up.

Practice points

- The procedure can be repeated twice on the same day, at least 4 hours apart, in order to obtain the specimens.
- Due to the risk of bronchospasm, only trained health staff must conduct the procedure, preferably a nurse.
- Sputum induction is an aerosol-generating procedure. Therefore, appropriate infection control measures must be taken. Specifically:
  - An appropriate site must be available. The minimum requirement is a small room with good ventilation.
  - Staff must use respirators, eye protection and non sterile gloves.

Material required

General

- Mask (respirator) for the operator and caregiver (if present)
- Eye protection and non sterile gloves for operator
- Oxygen (on standby in case of emergency)
- Pulse oximeter
- Request form

Preparation Pre-nebulization

- Spacer device (holding chamber) and mask
- Salbutamol metered dose inhaler

Nebulization

- Mask, chamber and tubing
- Antibacterial filter
- Nebulizer (Ultrasonic is the preferred type)
- Sterile solution of 3-6% sodium chloride, refrigerated if possible (more irritant)

Aspiration

Suction material usually required only for children under 5 years old.

- Suction catheter (7 or 8F)
- Mechanical suction device & mucus trap or 50 mL syringe if not available
- Sputum collection container
- Sterile solution of 0.9% sodium chloride

Infection control measures

Management of materials

- Spacer devices (holding chambers) should either be sterilized after each patient (preferred) or disinfected after each patient by soaking in hexanios for at least 15 minutes, then rinse, then soak again in a new bath of hexanios for 15 minutes. Rinse well and then wipe dry.
- All masks, tubing, suction catheters and syringes should be disinfected with 2% chlorine and then discarded.
- Antibacterial filters should be fitted and changed for each patient to protect the nebulizer, oxygen cylinder (if used), and any aspiration device (if used).

Management of the environment

The site must be left unused with the windows open or extraction fan on for at least 30 minutes after the procedure to allow adequate replacement of air in the room. No one should enter this room during the period without a respirator.

Contraindications

- Patient not fasted for 2 hours

- Severe respiratory distress
- Oxygen saturation less than 92% in room air
- Bleeding – low platelet count, nose bleeds or other bleeding source
- Reduced level of consciousness
- History of significant asthma or chronic obstructive airways disease

Procedure

Prior to nebulization

- Explain the procedure to the patient and the accompanying adult.
- Have the patient in a sitting position.
- Ask older children to rinse their mouth with water.
- Use pulse oximeter to obtain baseline oxygen saturation.
- Administer 2 puffs of salbutamol 10 seconds apart. Use a holding chamber for all children. Wait 5 minutes before starting nebulization.
- Prepare a sputum container.

Nebulization

- Fill the nebulizer with 5 mL 3-6% hypertonic saline solution.
- Put on an N95 or FFP2 respirator and provide one for any accompanying adult.
- Place the nebulizer mask over the patient's face.
- Leave the patient to inhale.
- Stop the procedure and obtain a sample as soon as the patient starts to cough productively. In young children careful attention, with suctioning at the right moment is critical to avoid the sample being swallowed. If sputum is not induced during the procedure, continue until the reservoir is empty (not longer than 15 minutes), then attempt sample collection.

The patient should be observed for respiratory distress and the procedure should be stopped at any time if severe cough or wheeze develops.

Nasopharyngeal suction (usually required for children < 5 years)

- Do 1 to 2 minutes of clapping on the chest.
- Lay the child flat on his or her side, facing away from the operator.
- If a mechanical suction device and mucus extractor are available, use these. If not:
  - Fit a suction catheter to a 50 mL syringe. Lubricate the end of the catheter.
  - Measure the distance from the tip of the nose to the tragus of the ear. Insert the suction catheter to that depth.
  - When inserting and withdrawing the tube, pull on the plunger of the syringe to create suction.
  - Once the syringe is filled with air and mucus, disconnect it from the suction catheter and purge the air (tip facing upward), so that only

mucus is left in the syringe.
  - To collect the mucus, draw 2 mL of 0.9% saline into the syringe to rinse, then empty contents into the sample container.

Note that sputum may sometimes not be produced until up to 24 hours later. Therefore if a good sputum sample is not immediately produced, older children can be given a collection container to take home.

All patients should be observed for at least 15 minutes after the procedure to ensure there are no signs of respiratory distress. Recheck the oxygen saturation post procedure. Give oxygen if saturation has dropped below 90%.

Possible adverse effects to anticipate

In all cases, try to obtain a specimen only if the patient condition permits. Do not repeat the procedure in the case of severe adverse effects.

- Coughing spells (~40%)

  If severe, stop the procedure and administer salbutamol. Oxygen should be available and can be administered in severe cases.

- Nosebleeds (~8%)

  Stop the procedure and apply constant pressure to the mid portion of the nose until the bleeding stops. Note that it is very common to see blood in the specimens collected from nasopharyngeal suction; this in itself is not an adverse effect.

- Wheezing (<1%)

  Monitor the child closely. Stop the procedure if wheeze increases. Administer salbutamol, and oxygen if severe.

- Vomiting (<1%)

  Stop the procedure and observe the child closely until the vomiting stops.

Protocols courtesy of Michael Rich

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