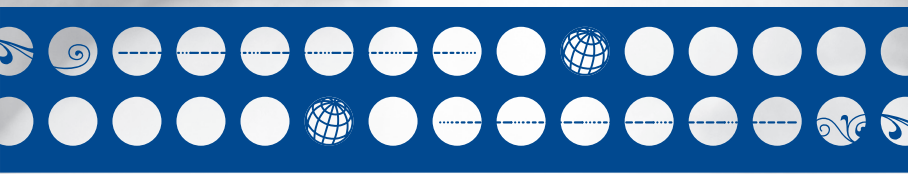


The PIH Guide to the
**Medical Management
of Multidrug-Resistant
Tuberculosis**

2nd Edition



USAID
FROM THE AMERICAN PEOPLE

TB CARE I

TB CARE II

**The PIH Guide to the
Medical Management
of Multidrug-Resistant
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2nd Edition

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Notice

This guide is intended to be a resource for physicians and other health care professionals who provide care and treatment to patients with drug-resistant tuberculosis. Every effort possible has been made to ensure that the material presented here is accurate, reliable, and in accord with current standards. However, as new research and experience expand our knowledge, recommendations for care and treatment change. It is, therefore, the responsibility of the individual physician or other health care professional to use his/her best medical judgment in determining appropriate patient care or treatment.

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Foreword to the Second Edition

Over the last several years, the policy to prevent and treat drug-resistant TB has improved substantially—so much so that most TB programs have introduced modern molecular diagnosis and the programmatic treatment of MDR-TB. Yet while the landscape on policy has changed dramatically, most drug-resistant patients go undiagnosed and untreated.

The goal of this pocket guide is to provide practitioners useful information for the clinical management of MDR-TB patients. We have drawn from WHO international guidelines whenever possible. Where WHO guidelines do not cover a specific topic, we have provided recommendations based on our interpretation of cohort studies, clinical trials, case reports, and personal experience.

The pocket guide is a revision of *The PIH Guide to the Medical Management of MDR-TB* (2003). This second edition has further grown out of our familiarity in treating drug-resistant TB in many different regions of the world—Eastern Europe, South America, North America, Asia, and Africa—where it is clear that successful prevention and treatment of MDR-TB can be achieved. The guide has added material and experiences from a host of institutions that form the coalition of TB CARE I and II. It is hoped that all national TB programs implementing MDR-TB care can benefit from this guide, as well as individual providers.

Countries are free to use this guide as is or to adjust it to better reflect their specific environment. This work may be copied, reproduced, or adapted, provided that subsequent distribution is not for commercial gain and that PIH is credited as the source. PIH would like for you to share with us any adaptation of this work. Please contact us at the address below.

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We dedicate this edition to the patients afflicted with MDR-TB and to the many who have partnered together to manage this disease. This includes the community health workers who deliver daily accompaniment to the patients, as well as the doctors, nurses, social workers, pharmacists, and other health care providers who focus on drug-resistant TB as a specialty. We thank them for their continued teaching of us how to be better at what we do.

Contents

Abbreviations	13
I Diagnosis of MDR-TB	16
1.1 Types of drug resistance	16
1.2 Types of drug susceptibility testing (DST)	17
1.3 Diagnosis of MDR-TB	19
1.4 Collection and transport of sputum specimens for DST	20
1.5 Xpert MTB/RIF	21
1.6 Line probe assay (LPA)	22
1.7 Using Xpert MTB/RIF to diagnose MDR-TB	23
1.8 Presumptive diagnosis of MDR-TB	25
1.9 Diagnosis of XDR-TB	27
1.10 Diagnosis of extrapulmonary MDR-TB	28
1.11 Diagnosis of MDR-TB in children	31
1.12 Diagnosis of MDR-TB in people living with HIV	32
2 Drugs and adjunctive therapies	35
2.1 Standard codes for writing TB treatment regimens	35
2.2 Anti-TB drugs and their side effects	36
2.3 Dosing of anti-TB drugs in adolescents and adults	45
2.4 Cross-resistance	48
3 Treatment of MDR-TB	50
3.1 Review of treatment of drug-susceptible TB	50
3.2 Treatment regimens for mono- and polyresistant TB	52
3.3 Suggested regimens for common patterns of mono- and polyresistant TB	54
3.4 Principles of MDR-TB treatment	56
3.5 Choice of anti-TB drugs used to treat MDR-TB	58
3.6 Building a MDR-TB treatment regimen	61
3.7 Duration of MDR-TB treatment	63
3.8 Treatment recommendations for XDR-TB	64
3.9 Extrapulmonary MDR-TB	66
3.10 Surgery for MDR-TB	68
3.11 Nutritional support	70
3.12 Corticosteroids	71

4	Treatment of MDR-TB in special conditions and situations	74
4.1	Pregnant women	74
4.2	Breast-feeding women	77
4.3	Patients with liver disease	78
4.4	Patients with chronic kidney disease	79
4.5	Patients with diabetes	83
4.6	Patients with seizure disorders	85
4.7	Patients with psychiatric disorders	86
4.8	Patients with substance abuse	87
5	Treatment of MDR-TB in children	89
5.1	Regimen design	89
5.2	Dosing of anti-TB drugs in children	90
5.3	Nutrition in children with MDR-TB	97
6	Treatment of MDR-TB/HIV coinfection	100
6.1	MDR-TB in HIV-positive compared to HIV-negative patients	100
6.2	ART in MDR-TB/HIV coinfection	101
6.3	Drug-drug interactions between anti-TB drugs and antiretroviral therapy	103
6.4	Adherence support and clinical monitoring in patients on MDR-TB/HIV cotreatment	106
6.5	Immune reconstitution inflammatory syndrome (IRIS)	108
7	Initial evaluation of MDR-TB patients	110
7.1	Pretreatment evaluation and screening	110
7.2	Educating and preparing the patient for treatment	111
7.3	Family planning	112
8	Monitoring of MDR-TB treatment	113
8.1	Monitoring treatment progress	113
8.2	Screening for adverse effects	115
8.3	Schedule of clinical and laboratory follow-up	118
9	Management of adverse drug effects	121
9.1	General considerations	121
9.2	Allergy: Anaphylaxis	123
9.3	Allergy: Rash	124

9.4	Gastrointestinal: Nausea and vomiting	126
9.5	Gastrointestinal: Gastritis and abdominal pain	128
9.6	Gastrointestinal: Diarrhea	130
9.7	Gastrointestinal: Hepatitis	131
9.8	Gastrointestinal: Pancreatitis	132
9.9	Musculoskeletal: Arthralgias	133
9.10	Musculoskeletal: Tendonitis and tendon rupture	134
9.11	Renal: Electrolyte abnormalities	135
9.12	Renal: Nephrotoxicity (acute renal failure)	139
9.13	Neurological: Ototoxicity (hearing loss or vestibulopathy)	141
9.14	Neurological: Peripheral neuropathy	144
9.15	Neurological: Depression	146
9.16	Neurological: Headache	148
9.17	Neurological: Psychosis	149
9.18	Neurological: Seizures	151
9.19	Neurological: Optic neuritis	153
9.20	Neurological: Dysgeusia (metallic taste)	154
9.21	Endocrine: Hypothyroidism	155
9.22	Endocrine: Gynecomastia	157
9.23	Endocrine: Alopecia	158
9.24	Endocrine: Dysglycemia and hyperglycemia	159
9.25	Endocrine: Lipodystrophy	160
9.26	Endocrine: Hyperlipidemia	161
9.27	Skin: Superficial fungal infections and oral thrush	162
9.28	Metabolic: Lactic acidosis	163
9.29	Cardiovascular: QT prolongation	164
9.30	Hematologic: Anemia or pancytopenia	165
9.31	Commonly used ancillary drugs for the management of adverse effects	167

10 Management of complications of MDR-TB 174

10.1	Respiratory insufficiency	174
10.2	Hemoptysis	176
10.3	Hematemesis or melena	177
10.4	Pleural effusion and empyema	178

I 1 Adherence to treatment	179
11.1 Monitoring adherence	179
11.2 Common adherence problems and their solutions	180
11.3 Reinitiating treatment after an interruption	181
I 2 Management of patients in whom MDR-TB treatment has failed	184
12.1 Assessment of patients at risk for failure	184
12.2 Identifying MDR-TB treatment failure in patients where it has been determined that all treatment options have been exhausted	186
12.3 Palliative care for patients in whom all the possibilities of treatment have failed	187
I 3 Community care for MDR-TB	190
13.1 Treatment delivery models	190
13.2 The DR-TB Supporter	192
13.3 DOT at home	194
13.4 Supervision of the DR-TB Supporter	195
13.5 Socioeconomic interventions (incentives and enablers)	196
13.6 Psychosocial and emotional support	197
I 4 Infection control for MDR-TB	199
14.1 Administrative controls	199
14.2 Environmental controls	200
14.3 Personal protection	202
14.4 FAST infection control strategy	204
14.5 Infection control in the community	207
I 5 MDR-TB workplace safety programs	209
15.1 Pre-employment evaluation	209
15.2 BCG vaccination	210
15.3 Screening and preventive therapy for health care providers with regular exposure to MDR-TB	211

16 Contact investigation and management of latent MDR-TB infection	213
16.1 Why do household contact investigation?	213
16.2 Diagnostic workup of household contacts of MDR-TB patients	215
16.3 Treatment of active TB in household contacts of MDR-TB patients	216
16.4 Treatment of latent infection in household contacts of MDR-TB patients	218
17 Recording and reporting	222
17.1 Registration of cases	222
17.2 The six mutually exclusive outcome definitions	226
17.3 Interim indicators for MDR-TB program monitoring	228
17.4 Final outcome indicators	229
18 Compassionate use and expanded access programs for new anti-TB drugs	231
18.1 New drugs and therapy	231
18.2 Definition of compassionate use/expanded access	232
18.3 Program issues	233
19 Procedures	235
19.1 Fine needle aspiration	235
19.2 Sputum induction	236
19.3 Gastric aspiration	240
20 Forms	242
20.1 Enrollment form	242
20.2 Follow-up form	247

Abbreviations

ADA	Adenosine deaminase
AFB	Acid-fast bacilli
AIDS	Acquired immunodeficiency syndrome
Am	Amikacin
Amx/Clv	Amoxicillin/clavulanic acid
ART	Antiretroviral therapy
ARV	Antiretroviral
BCG	Bacillus Calmette-Guérin
Bdq	Bedaquiline
CBC	Complete blood count
Cfz	Clofazimine
Clr	Clarithromycin
Clv	Clavulanic acid
Cm	Capreomycin
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CPC	Cetylpyridinium chloride
Cs	Cycloserine
CSF	Cerebrospinal fluid
CT	Computerized tomography
DOT	Directly observed therapy
DR	Drug resistance
DR-TB	Drug-resistant tuberculosis
DST	Drug susceptibility test
E	Ethambutol
EPTB	Extrapulmonary tuberculosis
Eto	Ethionamide
FDC	Fixed-dose combination
GFR	Glomerular filtration rate
Gfx	Gatifloxacin
H	Isoniazid
HIV	Human immunodeficiency virus
HPF	High-power field
IGRA	Interferon gamma release assay
IM	Intramuscular
Imp/Cln	Imipenem/cilastatin
IPT	Isoniazid preventive therapy

IV	Intravenous
Km	Kanamycin
LFT	Liver function test
Lfx	Levofloxacin
LPA	Line probe assays
LTBI	Latent TB infection
Lzd	Linezolid
MAC	<i>Mycobacterium avium</i> complex
MDR	Multidrug resistance
MDR-TB	Multidrug-resistant tuberculosis
Mfx	Moxifloxacin
MODS	Microscopic observation of drug susceptibility
Mpm	Meropenem
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NTM	Nontuberculous mycobacteria
NTP	National TB Program
Ofx	Ofloxacin
PAS	Para-aminosalicylic acid
PCR	Polymerase chain reaction
PI	Protease inhibitor
PIH	Partners In Health
PO	“Per os”; by mouth
PRN	“Pro re nata”; as needed
Pto	Prothionamide
R	Rifampicin
Rfb	Rifabutin
RR	Rifampicin resistance
S	Streptomycin
TB	Tuberculosis
Thz	Thioacetazone
TLA	Thin layer agar
TSH	Thyroid-stimulating hormone
TST	Tuberculin skin test
UVGI	Ultraviolet germicidal irradiation
WHO	World Health Organization
XDR	Extensive drug resistance
XDR-TB	Extensively drug-resistant tuberculosis
Z	Pyrazinamide

Abbreviations for commonly used antiretroviral drugs

Drug class	Name	Abbreviation
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz	EFV
	Nevirapine	NVP
Nucleoside reverse transcriptase inhibitors (NRTIs)	Zidovudine	AZT
	Stavudine	d4T
	Lamivudine	3TC
	Emtricitabine	FTC
	Abacavir	ABC
	Didanosine	ddI
	Tenofovir	TDF*
Protease inhibitors (PIs)	Indinavir	IDV
	Ritonavir	RTV
	Saquinavir	SQV
	Nelfinavir	NFV
	Lopinavir/ritonavir	LPV/r
	Atazanavir/ritonavir	ATZ/r

*TDF is a nucleotide reverse transcriptase inhibitor but is typically grouped with this class.

I Diagnosis of MDR-TB

I.1 Types of drug resistance

What is drug-resistant tuberculosis (DR-TB)?

- A type of tuberculosis (TB) caused by a bacterium (*Mycobacterium tuberculosis*) that has developed a genetic mutation(s) such that a particular drug (or drugs) is no longer effective against the bacteria.

Types of drug resistance

- **Drug-susceptible:** No resistance to any first-line anti-TB drugs.
- **Monoresistance:** Resistance to one first-line anti-TB drug.
- **Polyresistance:** Resistance to more than one first-line anti-TB drug other than isoniazid and rifampicin.
- **Multidrug resistance (MDR):** Resistance to at least isoniazid and rifampicin, the two most potent anti-TB drugs.
- **Rifampicin resistance (RR):** Resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, including monoresistance, MDR, and polyresistance.
- **Extensive drug resistance (XDR):** MDR plus resistance to at least one of the fluoroquinolones, and at least one of three injectable second-line drugs (capreomycin, kanamycin, and amikacin).

Other terminology

- “Pre-XDR” TB refers to an isolate that is resistant to either a fluoroquinolone or a second-line injectable, but not both. It is a commonly used designation but not officially accepted terminology by WHO or the global TB community.
- Totally drug-resistant (TDR) TB refers to an isolate that is resistant to all testable anti-TB drugs. Similar to pre-XDR TB, this term is not officially accepted by WHO or the global TB community, and there is no consensus on a precise definition.
- “DOTS-Plus” or “Category IV” are terms that are no longer used for DR- or MDR-TB patients.

1.2 Types of drug susceptibility testing (DST)

Phenotypic (or culture-based) DST

- Determines if an isolate is resistant to an anti-TB drug by evaluating the growth (or metabolic activity) in the presence of the drug.
- Usually done on Löwenstein-Jensen (LJ) solid medium or in the automated MGIT™ system (a liquid culture system).
- Other systems include microscopic observation of drug susceptibility (MODS), colorimetric redox indicator methods, thin layer agar (TLA), and the nitrate reductase assay, all of which have shown initial promise as rapid, inexpensive methods.
- Accuracy varies from one drug to another.
 - Very reliable for rifampicin and isoniazid but less so for pyrazinamide and much less for ethambutol.
 - Relatively good reliability for aminoglycosides, capreomycin, and fluoroquinolones.
 - Much less reliable for PAS, ethionamide, and cycloserine.

Genotypic (or molecular) DST

- Detects the genetic mutation in the TB bacterium responsible for or associated with the resistance.
- In addition to detection of resistance mutations, can also simultaneously detect and identify *M. tuberculosis* in the sputum specimen.
- Examples include GeneXpert® System (Xpert MTB/RIF, Cepheid, USA), GenoType® MTBDR_{plus} and MTBDR_{sl} assays (Hain Lifescience GmbH, Germany), and INNO-LiPA Rif.TB line probe assay (Fujirebio Europe, Belgium; previously Innogenetics).

Sensitivity and turnaround time for different DST diagnostic methods*

	Sensitivity for <i>M. tuberculosis</i>	Turnaround time for detection of <i>M. tuberculosis</i>	Turnaround time for DST
Smear microscopy (light, fluorescent)	Low	Two hours	
Solid culture medium (LJ standard medium, 7H10 and 7H11)	High	16 days (smear +) 29 days (smear -)	Six weeks
Liquid culture medium (BACTEC™, MGIT™)	High	Eight days (smear +) 16 days (smear -)	Four weeks
Culture microcolonies (TLA, MODS)	High	14 days	14 days (H and R)
Line probe assay (MTBDRplus Assay, INNO-LiPA)	Moderate†		One day (on smear-positive sputum) 21 days (on a positive culture)
Automated real-time PCR (Xpert MTB/RIF)	High	Two hours	Two hours (R only)

*Adapted from *Tuberculosis: Practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries* (MSF/PIH).

†Generally done on smear-positive sputum. More sensitive assays are under development.

1.3 Diagnosis of MDR-TB

Countries are increasingly moving toward a “universal DST” strategy: Testing all patients with active TB disease for drug resistance at the start of therapy.

- New technologies for rapid molecular DST (e.g., Xpert MTB/RIF) have made this strategy more feasible.
- A WHO-sponsored analysis has determined this is both a lifesaving and cost-effective strategy for most countries (with greater than 1 percent MDR-TB in new patients).
- When resources are not yet available, patients with medium to high risk can be triaged for more efficient use of DST.
- WHO already recommends that all patients with HIV infection and active TB should have DST because undetected resistance carries a very high mortality, and in many high HIV-prevalence settings this may be the majority of TB patients.

Medium- and high-risk categories for MDR-TB

Medium risk

- Smear-positive after month two of first-line treatment.*
- Relapse after treatment with first-line anti-TB drugs.
- Return after being lost to follow-up from treatment with first-line anti-TB drugs.
- Household contact of a patient who died during TB treatment.
- Patients with new TB coming from high MDR-TB prevalent areas.†
- Health workers with new TB who come into contact with a variety of TB patients.

High risk

- Household contacts of MDR-TB patients.
- Failure of treatment with first-line anti-TB drugs.
- History of treatment with second-line anti-TB drugs.

*Smear-positive after two months and clinically deteriorating should be considered high risk.

†There is no firm cutoff for a “high MDR-TB prevalent area.” Many countries are moving toward a universal DST policy for all TB patients. Settings with greater than 3 percent of MDR-TB in new TB cases should mobilize resources for DST in all patients.

1.4 Collection and transport of sputum specimens for DST

Collection of sputum specimens

- Sputum specimens should be collected in well-ventilated spaces where air movement will protect against infection of others.
- Sputum specimens should not be collected in laboratories, toilets, waiting rooms, reception rooms, or any other enclosed space not specifically designed for that purpose.
- Sputum specimens should be collected in wide-mouthed containers that are sterile, clear, and leak-proof and that have a screw lid.
- Patient information should be written on the container (not on the lid).

Transport of sputum specimens

- It is better to transport specimens rather than have the patient travel long distances to provide a specimen.
- Prior to transport, specimens should be kept in a cool place, preferably a refrigerator at 4°C. If travel time is greater than one hour, cold boxes should be used during the transportation.
- If it is likely that storage and transit time will be more than three days in total or if the specimen is likely to be exposed to room temperatures for extended periods of time, a transport medium can be used, such as cetylpyridinium chloride (CPC).
 - CPC is not permitted for liquid culture methods (e.g., MGIT).
 - CPC can crystallize at low temperatures (it should not be refrigerated or frozen).
 - CPC specimens can be used with Xpert MTB/RIF.

1.5 Xpert MTB/RIF

What is Xpert MTB/RIF?

- At present, the rapid DST of choice in individuals suspected of MDR-TB is the Xpert MTB/RIF as it is the only platform that is quick, simple, and robust enough to be used outside reference laboratories. It can be used in peripheral laboratories and does not require sophisticated equipment and highly skilled personnel.
- The GeneXpert® System consists of an instrument, personal computer, bar code scanner, and preloaded software, and uses single-use disposable cartridges containing lyophilized reagents, buffers, and washes.
- The test is based on real-time polymerase chain reaction (PCR) technology targeting specific nucleic acid sequences in the *M. tuberculosis* complex genome, while simultaneously providing information about the most common mutations related to rifampicin resistance.
- The GeneXpert® System and the Xpert MTB/RIF assay are currently the only mature technology representing a new generation of automated diagnostic platforms. There are others in the prototype stage.

Sensitivity and specificity

- For TB detection, Xpert MTB/RIF is substantially more sensitive than microscopy.
 - Sensitivity is close to 100 percent in smear-positive tuberculosis.
 - Sensitivity is greater than 70 percent in smear-negative, culture-positive tuberculosis. Sensitivity is higher if the test is repeated.
- For rifampicin resistance, the sensitivity compared with conventional DST on culture is greater than 95 percent. The test has a high negative predictive value, therefore rifampicin-susceptible results can be considered to be true susceptible.
- Xpert MTB/RIF does not eliminate the need for conventional microscopy, culture, and DST, which are required to monitor treatment progress and to detect resistance to drugs other than rifampicin.
- Xpert MTB/RIF is not currently recommended for monitoring of response to TB treatment.

1.6 Line probe assay (LPA)

Description

- After extraction and PCR amplification of the resistance-determining region of DNA, mutations are detected by the presence or absence of binding to “probes,” indicated by the presence or absence of colored bands on a strip.
- “Direct testing” can be done on smear-positive sputum specimens and gives results in a few hours. Newer generation LPAs that can be directly tested on smear-negative sputum are under review.
- “Indirect testing” is done on a culture that is grown from the patient’s sputum. The test still takes hours, but since the culture takes weeks or months, the total time required is much longer than for direct testing.
- LPA tests are performed in reference-level facilities as they need dedicated rooms for DNA preparation and amplification, and a Biosafety Level 2 laboratory for processing sputum or a Biosafety Level 3 laboratory if manipulation of culture is required.

The GenoType® MTBDR*plus* assay (Hain Lifescience GmbH, Germany)

- Has been shown to have high sensitivity and specificity for detection of rifampicin and isoniazid resistance among smear-positive patients.
- Can identify if isoniazid resistance is due to mutations on the *katG* or *inhA* genes:
 - *KatG* mutation corresponds to resistance to high-dose isoniazid.
 - *InhA* mutation corresponds to resistance to both isoniazid and ethionamide, but not to high-dose isoniazid.
 - The correspondence between the genetic mutations for isoniazid and ethionamide resistance is not 100 percent (i.e. some *katG* mutations could be susceptible to high dose isoniazid; some *inhA* mutations could be susceptible to ethionamide).

INNO-LiPA Rif.TB line probe assay (Fujirebio Europe)

- Produces results only for common mutations in the *rpoB* gene that are associated with rifampicin resistance (similar to Xpert MTB/RIF).

1.7 Using Xpert MTB/RIF to diagnose MDR-TB

Xpert MTB/RIF rather than conventional microscopy, culture, and DST should be used as the initial diagnostic test in individuals suspected of having MDR-TB

- Rifampicin is the most important first-line anti-TB drug, and in most countries greater than 90 percent of rifampicin-resistant strains are also resistant to isoniazid.
- A positive result for rifampicin is an indicator that a patient may have MDR-TB, while a negative result in a sample identified as *M. tuberculosis*-positive makes a final diagnosis of MDR-TB highly unlikely.

A positive result for rifampicin resistance is an indicator that a patient may have MDR-TB, but like any test, false positives are possible

- If the patient is from a population that has more than a 10 percent prevalence of MDR-TB, the patient is considered to be highly likely to have MDR-TB. These patients should be treated with an MDR regimen. For example:
 - New TB patient in high MDR prevalence countries such as Russia or Eastern Europe.
 - Failure of treatment with first-line anti-TB drugs in most countries.
 - Relapse after successful treatment with first-line anti-TB drugs in some countries.
- If the patient is from a population that has between 2 percent and 10 percent prevalence of MDR-TB, a false positive should be considered possible. These patients should be treated with an MDR regimen until confirmatory DST results are available. For example:
 - New TB patient in high MDR prevalence countries such as China, South Africa, or South Korea.
 - Relapse after successful treatment with first-line anti-TB drugs in some countries.
- If the patient is from a population that has less than 2 percent prevalence of MDR-TB, a false positive should be considered likely. These patients may be started on a first-line anti-TB regimen until confirmatory DST results are available, as long as the patient is clinically stable.
 - Even in a low MDR prevalence area, a new TB patient with HIV infection may be considered for enrollment on

an MDR regimen especially if confirmation testing can not be performed in a timely fashion (preferably within seven days).

Confirmatory testing after an Xpert MTB/RIF result that is positive for rifampicin resistance

- Xpert MTB/RIF can be repeated if a sampling labeling mix-up or similar problem is suspected. This is not considered a confirmatory test, which should be a different method.
- A confirmatory test should have a quick turnaround and test at least isoniazid and rifampicin. Commonly LPA or MGIT is used.
- At the current time, confirmatory DST is required by most national guidelines after a positive test for rifampicin resistance by Xpert MTB/RIF. Even if there is no question about the diagnosis of MDR, knowing the susceptibility of other drugs besides rifampicin can help to guide therapy.
- Even if the confirmatory DST is pan-susceptible, the treatment regimen should not be automatically changed back to a first-line anti-TB regimen. There is limited experience with patients with discordance between genotypic and phenotypic tests. These patients should be reviewed carefully.

What to do with an Xpert MTB/RIF result that is positive for rifampicin resistance

If MDR prevalence in the population is:	Then:
Greater than 10 percent	Start MDR regimen.
2 percent to 10 percent	Start MDR regimen and consider switching to first-line regimen depending on results of confirmatory DST.
Less than 2 percent	<p>Start first-line anti-TB regimen if patient is clinically stable and consider switching to MDR regimen depending on results of confirmatory DST or if patient is clinically deteriorating.</p> <p>Consider starting an empiric MDR regimen if the patient is HIV-positive and a long delay in confirmation DST is anticipated.</p>

1.8 Presumptive diagnosis of MDR-TB

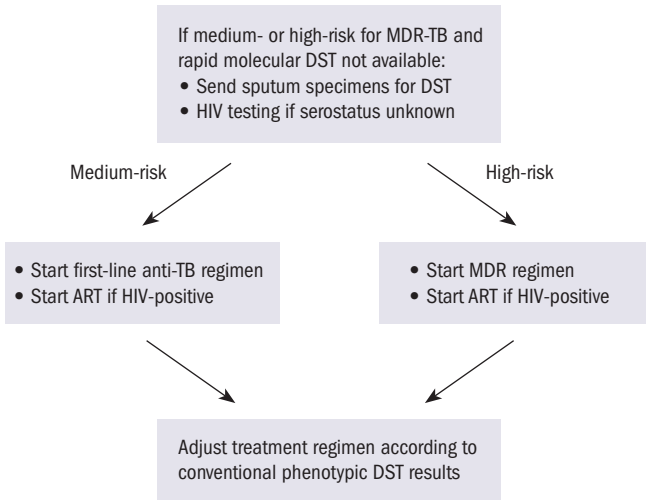
Presumptive MDR-TB is a diagnosis given to patients with a high risk of MDR-TB and a clinical decision has been made to start MDR-TB treatment before DST results are available

- This scenario should be rare but can happen when rapid DST is not available, and while culture-based DST is pending. This is particularly important when the patient's clinical status is poor.
- Empiric treatment with an MDR regimen may be adjusted when the result of culture-based DST is available.
- If the culture-based DST is not available for any reason (e.g., contaminated), the empiric MDR-TB regimen should continue for the full length of treatment.

Patients eligible for the presumptive diagnosis of MDR-TB and direct enrollment into treatment with an MDR regimen include:

- Failures of retreatment regimens with first-line drugs (formerly known as Category II regimens).
- Household contacts of documented MDR-TB patients that develop active TB disease.
- Household contacts of some patients with presumptive MDR-TB (patients who have died during treatment with first-line anti-TB drugs without DST) in high MDR prevalence settings.
- Failures of new regimens with first-line anti-TB drugs (formerly known as Category I regimens) in some situations. The prevalence of MDR-TB in these patients varies, but in many settings, these patients usually have MDR-TB.

Decision tree for presumptive diagnosis of MDR-TB



Adapted from *Management of MDR-TB: A field guide* (WHO/HTM/TB/2008.402a).

1.9 Diagnosis of XDR-TB

Who should be tested for resistance to second-line anti-TB drugs?

- In programs where capacity of DST to second-line drugs exists, all patients diagnosed with MDR-TB should be tested for XDR-TB.
- In areas where second-line DST is very limited, XDR-TB testing may be reserved for patients with risk factors for XDR-TB:
 - Persistently positive smears or cultures after eight months of MDR-TB treatment.
 - Close contact with an individual with documented XDR-TB.
 - Close contact with an individual for whom MDR-TB treatment is failing or has failed.
 - Chronic TB patients with unclear history of use of second-line anti-TB drugs (e.g., patients with a history of multiple courses of treatment with first-line regimens).

Testing for XDR-TB

- Diagnosing XDR-TB is done through conventional phenotypic DST for the injectable drugs (kanamycin/amikacin and capreomycin) and a fluoroquinolone.
- Commercially available LPA (e.g., GenoType® MTBDRsl) is starting to incorporate resistance mutations for second-line anti-TB drugs. However, the reliability of LPA for second-line DST has not been fully determined, and this cannot yet replace conventional phenotypic second-line DST.
 - LPA for second-line DST can be used as an initial test on smear-positive specimens to guide the initial treatment in XDR-TB suspects while awaiting confirmatory results from conventional phenotypic testing.
 - LPA that indicates genetic mutations associated with second-line drug resistance may be used to guide choice of second-line anti-TB drugs.
 - LPA negative for second-line drug resistance does not rule out resistance. If suspicion is high, the strain should be assumed to have second-line resistance until confirmatory second-line DST results are known.

1.10 Diagnosis of extrapulmonary MDR-TB

General considerations

- Extrapulmonary TB is underdiagnosed because it is very difficult to isolate *M. tuberculosis* from extrapulmonary specimens.
- Nonbacteriological tests, including X-ray and biochemical analysis of specimens, are important in the diagnosis of extrapulmonary TB since definitive bacteriological evidence may be lacking.
- Extrapulmonary TB can be especially confusing in HIV-positive patients as it may share similar characteristics of other opportunistic infections.

Bacteriological testing

- Sputum samples should also be sent for smear, culture, and Xpert MTB/RIF, even if there is no evidence of parenchymal disease on X-ray. Pulmonary TB often accompanies extrapulmonary TB even if it is not apparent clinically.
- Biopsies (including needle aspirations of purulent collection) have the highest yield with smear, culture, or Xpert MTB/RIF. The procedure for fine needle aspiration of a lymph node is explained in Section 19.1.
- Fluid aspirates (e.g., pleural) may be sent for smear, culture, and Xpert MTB/RIF, but the yield is often low. A negative result should not be considered definitive evidence that the patient does not have extrapulmonary TB.
- The sensitivity of smear, culture, and Xpert MTB/RIF in biopsies and fluid aspirates is usually higher in HIV-positive patients.
- Just as in sputum specimens, the sensitivity of Xpert MTB/RIF in extrapulmonary specimens is higher than smear microscopy, but lower than culture.

Empiric treatment of extrapulmonary MDR-TB

- New extrapulmonary TB in household contacts of MDR-TB patients should be treated with an MDR-TB regimen based on DST profile of the index case. For example, a household contact of an MDR-TB patient who presents with new pleural TB should be treated with an MDR-TB regimen.
- New extrapulmonary manifestations (new pleural effusion, new ascites, etc.) during first-line TB treatment may be due to treatment failure and a sign of drug resistance. Empiric MDR-TB treatment may be considered in these patients.

Characteristics of common forms of extrapulmonary TB

Extrapulmonary TB Site Clinical and radiological signs

Analysis of fluid

Bacteriological testing

Lymph node TB (tuberculous lymphadenitis)

Cervical lymphadenopathy (scrofula) is the most common type. Purulent drainage or bacterial superinfection can occur in chronic or inadequately treated cases.

Granulomatous tissue may be seen on cytology

Smear, culture, or molecular testing of lymph node aspirates are often positive (see Section 19.1 for instructions on lymph node aspiration).

Pleural TB (pleurisy)

Symptoms are nonspecific: Dyspnea, chest pain, and cough. Chest X-ray may show a unilateral free-flowing pleural effusion.

Exudative pleural effusion: Protein/serum protein > 0.5; pleural fluid LDH/serum LDH > 0.6; or pleural fluid LDH > two-thirds upper limit normal for serum LDH. Elevated white blood cell count with lymphocytic predominance. Elevated adenosine deaminase (ADA).

Pleural biopsy has a higher culture yield than pleural fluid. If pleural fluid is sent for culture, sensitivity is higher if a large volume (50 cc) is sent. Culture and molecular testing of pleural fluid aspirate are often negative.

Spinal TB (Pott's disease)

Symptoms include chronic back pain (usually thoracic spine), neurological symptoms (from cord or nerve involvement), or spinal deformities (gibbus). Draining sinus tracts may form in chronic cases. Bone destruction or abscess formation on X-ray or CT.

Biopsy and fluid aspiration often not done in resource-constrained areas.

Smear, culture, or molecular testing of bone biopsy or aspiration of fluid collections are usually positive.

Extrapulmonary TB Site	Clinical and radiological signs	Analysis of fluid	Bacteriological testing
Joint TB (articular tuberculosis)	Subacute or chronic onset of joint pain, warmth, and swelling (usually a single large joint such as hip, knee, or ankle).	Inflammatory synovial fluid (turbid, elevated white blood cell count).	Synovial fluid aspiration may be positive for smear, culture, or molecular testing. Sensitivity of these tests in synovial tissue biopsy is higher.
Cerebrospinal fluid (CSF) TB (TB meningitis, intracranial tuberculoma)	Subacute or chronic onset of headache, nuchal rigidity, and fever.	CSF has low glucose, high protein, and white blood cell count < 1,000 cells/mm ³ with lymphocytic predominance (similar to cryptococcal meningitis in HIV-positive patients).	Culture and molecular testing of the CSF is often negative.
Genitourinary TB	Dysuria, hematuria, flank pain, fever. X-ray may show calcification of kidneys or ureter.	Pyuria, hematuria.	Culture and molecular testing of the urine are often positive.
Peritoneal TB	Subacute or chronic onset of ascites, fever, abdominal pain. CT may have varied presentation but shows diffuse involvement and enlarged lymph nodes.	Exudative peritoneal fluid: Serum ascites-albumin gradient < 1.1 g/dL. Elevated white blood cell count with lymphocytic predominance. Elevated adenosine deaminase.	Laparoscopy or laparotomy shows diffuse peritoneal involvement with studding. Culture and molecular testing of peritoneal biopsies are often positive. Peritoneal fluid is often negative for culture and molecular testing.

1.11 Diagnosis of MDR-TB in children

General considerations

- Obtaining a culture and DST in children is often difficult because young children may not be able to produce a sputum sample. Children are also more likely to have extrapulmonary TB or pulmonary TB with low bacillary loads.
- Most children over 6 years of age can be coached into producing a sputum sample.
- Procedures for gastric aspiration and sputum induction are explained in Chapter 19.

Presumptive diagnosis of MDR-TB in household contacts of MDR-TB patients

- Any young child diagnosed with active TB disease in a household with an MDR-TB patient should be considered to have presumptive MDR-TB until there is bacteriological evidence to the contrary (see Chapter 5 for MDR-TB treatment in children).
- Every effort should be made to obtain a sputum sample from the child that can be sent for DST (culture and Xpert MTB/RIF). Even though children of MDR-TB patients almost always have MDR-TB, there may be differences in the resistance pattern that affect the treatment regimen.
- Other family members should also be screened for active TB; DST obtained from these family members may inform the treatment regimen for the child.

Presumptive diagnosis of MDR-TB in children who fail first-line TB treatment

- Laboratory confirmation of drug resistance is often difficult, so clinicians need to be comfortable with starting MDR-TB treatment based on clinical or radiological failure of first-line TB treatment.
- Older children, especially adolescents, are notoriously non-compliant with treatment, so a trial of improving the adherence of the patient may be considered before declaring the patient a failure of first-line treatment. This often consists of frank and nonjudgmental conversations with the adolescent and adding measures to ensure the treatment is given under 100 percent directly observed therapy (DOT).

1.12 Diagnosis of MDR-TB in people living with HIV

Xpert MTB/RIF is the recommended test for drug resistance in every case of HIV-associated TB

- Untreated MDR-TB in an HIV-positive patient carries a high mortality. Many deaths from MDR-TB in HIV-positive patients occur before the diagnosis of MDR-TB.
- In high HIV prevalence settings such as sub-Saharan Africa this means the majority of TB patients should be tested with Xpert MTB/RIF.

Presumptive diagnosis of MDR-TB in HIV-positive patients

- Laboratory confirmation of MDR-TB may be difficult or impossible (e.g., extrapulmonary TB) for many coinfecting patients, so empiric MDR-TB treatment is important.
- Due to the high mortality of untreated MDR-TB in HIV-positive patients, empiric treatment with second-line drugs should be considered in patients who have a high risk for MDR-TB.
- HIV-positive household contacts of known MDR-TB patients should be treated empirically for MDR-TB if they develop active TB. This is the same recommendation for all household contacts, but it is more urgent if the contact is HIV-positive.
- Patients who meet the programmatic definition of failure to a standard first-line regimen (e.g., smear-positive at five months) should be started immediately on an MDR-TB regimen.

MDR-TB is often confused for IRIS in patients being treated for presumed drug-susceptible TB

- Immune reconstitution inflammatory syndrome (IRIS) is an exaggerated immune response to a previously undiagnosed opportunistic infection (unmasking IRIS) or an exacerbation of a partially or successfully treated opportunistic infection (paradoxical IRIS).
- TB-IRIS may present as fever, enlarging lymph nodes, worsening pulmonary infiltrates, respiratory distress, or new extrapulmonary manifestations.
- Mild to moderate TB-IRIS is relatively common, especially in severely immunosuppressed patients (CD4 count < 50 cells/mm³), but rare in its severe forms.

- TB-IRIS can be indistinguishable from the unmasking of undiagnosed and untreated MDR-TB in a patient who is assumed to have drug-susceptible TB.
- Patients suspected of TB-IRIS should have a diagnostic work-up for other possible opportunistic infections, as well as diagnostic tests such as Xpert MTB/RIF to rule out MDR-TB.

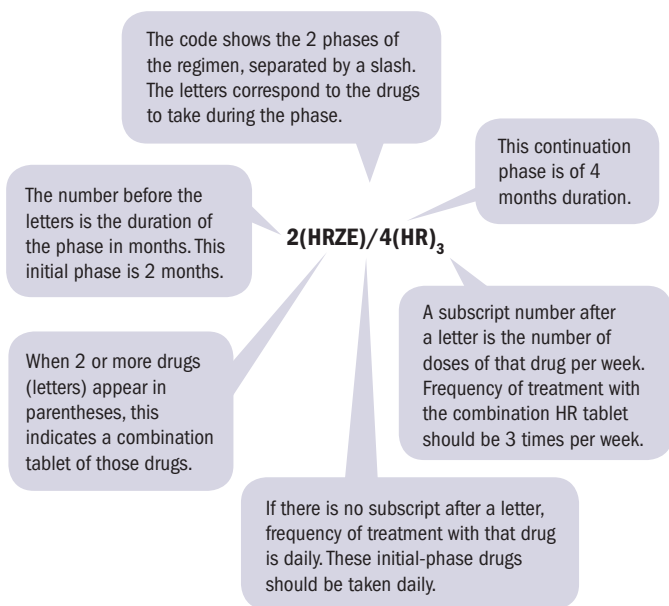
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2 Drugs and adjunctive therapies

2.1 Standard codes for writing TB treatment regimens

Example 1: A commonly used first-line anti-TB regimen is written:



Adapted from *Tuberculosis care with TB-HIV co-management* (WHO/HTM/HIV/2007.01).

Example 2: A commonly used MDR-TB regimen is written:

8K_{m6}-Lfx₇-Eto₇-Cs₇-Z₇/12Lfx₇-Eto₇-Cs₇-Z₇

- The injectable phase is eight months and includes an injectable given six days a week and four oral drugs given seven days a week.
- The continuation phase is 12 months and includes four oral drugs given seven days a week.

Description of anti-TB drugs, their side effects, and monitoring requirements

Drug name (abbreviation)	Description and adult dose	Side effects	Monitoring requirements and comments
Isoniazid (H)	Description: Bactericidal; inhibits mycolic acid synthesis most effectively in dividing cells; hepatically metabolized. Dose: 300 mg daily or 900 mg twice or thrice weekly.	Common: Hepatitis (10 percent to 20 percent have elevated transaminases), peripheral neuropathy (dose-related; increased risk with malnutrition, alcoholism, diabetes, concurrent use of aminoglycosides, or Eto). Less common: Gynecomastia, rash, psychosis, seizure.	Monitoring: Consider baseline and monthly liver enzymes, especially if age greater than 50 years. Comments: Give with pyridoxine 50 mg/day if using large dose or if patient is at risk for peripheral neuropathy (diabetes, alcoholism, HIV, etc.).
RIFAMYCINS Rifampicin (R) Rifabutin (Rfb)	Description: Bactericidal; inhibits protein synthesis by blocking mRNA transcription and synthesis; hepatically metabolized. Dose: R: 600 mg/day; Rfb: 300 mg/day.	Common: Orange-colored bodily secretions, transient transaminitis, hepatitis, GI distress. Less common: Cholestatic jaundice.	Monitoring: Consider baseline liver enzymes, repeat if symptoms (jaundice, fatigue, anorexia, weakness, or nausea and vomiting) appear.
Pyrazinamide (Z)	Description: Bactericidal; mechanism unclear; effective in acidic milieu (e.g., cavity disease, intracellular organisms); hepatically metabolized, renally excreted. Dose: 15-40 mg/kg daily.	Common: Arthritis/arthralgias, hepatotoxicity, hyperuricemia, abdominal distress. Less common: Impaired diabetic control, rash.	Monitoring: Baseline liver enzymes; uric acid can be measured if arthralgias, arthritis, or symptoms of gout are present. Comments: Usually given once daily, but can split dose initially to improve tolerance.

2.2 Anti-TB drugs and their side effects

Drug name (abbreviation)	Description and adult dose	Side effects	Monitoring requirements and comments
Ethambutol (E)	<p>Description: Bacteriostatic at conventional dosing (15 mg/kg); inhibits lipid and cell wall metabolism; renally excreted.</p> <p>Dose: 15-25 mg/kg.</p>	<p>Common: Generally well-tolerated.</p> <p>Less common: Optic neuritis, GI distress, arthritis/arthralgia.</p>	<p>Monitoring: Baseline and monthly visual acuity and red/green color vision test when dosed at greater than 15 mg/kg daily (more than 10 percent loss is considered significant); regularly question patient about visual symptoms.</p>
AMINOGLYCOSIDES	<p>Description: Bactericidal; aminoglycosides inhibit protein synthesis through disruption of ribosomal function; less effective in acidic, intracellular environments; polypeptides appear to inhibit translocation of the peptidyl-tRNA and the initiation of protein synthesis; renally excreted.</p>	<p>Common: Pain at injection site; proteinuria; electrolyte wasting (more common with Cm); cochlear ototoxicity (hearing loss, dose-related to cumulative and peak concentrations, increased risk with renal insufficiency, may be irreversible).</p> <p>Less common: Nephrotoxicity (dose-related to cumulative and peak concentrations, increased risk with renal insufficiency, often irreversible); peripheral neuropathy; rash; vestibular toxicity (nausea, vomiting, vertigo, ataxia, nystagmus); eosinophilia; ototoxicity potentiated by certain diuretics, especially loop diuretics.</p>	<p>Monitoring: Baseline and then monthly creatinine, urea, and serum potassium; more frequently in high-risk patients; if potassium is low, check magnesium and calcium; baseline audiometry and monthly monitoring in high-risk patients (high-risk patients: elderly, diabetic, or HIV-positive patients, or patients with renal insufficiency).</p> <p>Comments: Increase dosing interval or reduce dose and monitor serum drug concentrations as needed to control side effects.</p>
POLYPEPTIDES	<p>Capreomycin (Cm)</p>		

FLUOROQUINOLONES

Description: Bactericidal; DNA-gyrase inhibitor; renally excreted.

Dose: Ofx: 800 mg/day; Lfx: 750–1,000 mg/day; Mfx: 400 mg/day.

Ofloxacin (Ofx)
Levofloxacin (Lfx)
Moxifloxacin (Mfx)

Common: Generally well-tolerated, well-absorbed.

Less common: Diarrhea, dizziness, GI distress, headache, insomnia, photosensitivity, rash, vaginitis, tendonitis, psychosis, seizure (CNS effects seen almost exclusively in elderly).

Monitoring: No laboratory monitoring requirements.

Comments: Do not administer with antacids, sucralfate, iron, zinc, calcium, or oral potassium and magnesium replacements; Lfx, Mfx have the most activity against *M. tuberculosis*.

Cycloserine (Cs)

Description: Bacteriostatic; alanine analogue; interferes with cell-wall peptoglycan synthesis; renally excreted.

Dose: 500–1,000 mg/day.

Common: Neurologic and psychiatric disturbances, including headaches, irritability, sleep disturbances, aggression, and tremors.

Less common: Psychosis, peripheral neuropathy, seizures (increased risk of CNS effects with concurrent use of ethanol, H, Eto, or other centrally acting medications), hypersensitivity.

Monitoring: Consider serum drug monitoring to establish optimal dosing.

Comments: Give 50 mg of pyridoxine for every 250 mg of Cs (to lessen neurologic adverse effects).

THIAMIDES

Ethionamide (Eto)

Prothionamide

(Pto)

Description: May be bactericidal or bacteriostatic depending on susceptibility and concentrations attained at the infection site; the carbothioamide group, also found on Thz, and the pyridine ring, also found on H, appear essential for activity; hepatically metabolized, renally excreted.

Dose: 500–1,000 mg/day.

Common: GI distress (nausea, vomiting, diarrhea, abdominal pain, loss of appetite); dysgeusia (metallic taste); hypothyroidism (especially when taken with PAS).

Less common: Arthralgias, dermatitis, gynecomastia, hepatitis, impotence, peripheral neuropathy, photosensitivity.

Monitoring: Consider baseline liver enzymes.

Comments: May split dose or give at bedtime to improve tolerability; Eto and Pto efficacies are considered similar; Pto may cause fewer GI adverse effects.

Drug name (abbreviation)	Description and adult dose	Side effects	Monitoring requirements and comments
Para-aminosalicylic acid (PAS)	<p>Description: Bacteriostatic; disrupts folic acid metabolism (thought to inhibit the biosynthesis of coenzyme F in the folic acid pathway); hepatic acetylation, renally excreted.</p> <p>Dose: Depends on specific formulation.</p>	<p>Common: GI distress (nausea, vomiting, diarrhea); hypersensitivity; hypothyroidism (especially when taken with EtO).</p> <p>Less common: Hepatitis, electrolyte abnormalities.</p> <p>Drug interactions: Decreased H acetylation; decreased R absorption in nongranular preparation; decreased vitamin B12 uptake.</p>	<p>Monitoring: No laboratory monitoring requirements.</p> <p>Comments: PASER[®] consists of enteric coated granules that need to be administered with an acidic food or beverage (e.g., yogurt or acidic juice); PASER is stable for up to eight weeks at 40°C and 75 percent 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 eight weeks is needed, refrigeration below 15°C is required.</p>

Bedaquiline (Bdq)

Description: A diarylquinoline antimycobacterial drug that inhibits ATP synthesis.

Dose: 400 mg once daily for two weeks, followed by 200 mg three times per week for 22 weeks with food; the drug has a 5.5-month half-life.

Common: GI distress (nausea, vomiting, abdominal pain, loss of appetite); joint pain; headache.

Less common: QT prolongation, hyperuricemia, phospholipidosis (the accumulation of phospholipids in the body's tissues), elevated aminotransferases, chest pain, hemoptysis (coughing up blood). Possibly an increased risk of pancreatitis.

Drug Interactions: All CYP3A4 inhibitors or inducers. Rifampicin (a CYP3A4 inducer) reduces bedaquiline in blood by half; drugs that prolong the QT interval (e.g., dofazimine, moxifloxacin, antifungals, and many others) may result in additive cardiac toxicity—their use is only indicated when there are no other alternatives; more frequent ECG monitoring is required.

Monitoring: Monitor QT interval with ECG at baseline, 2 weeks, 12 weeks, and 24 weeks (more often if risk of QT prolongation is present); discontinue if significant ventricular arrhythmia or a QTcF interval > 500 ms develops; monitor liver enzymes every month.

Comments: A significant imbalance in fatalities was noted in Trial C208 Stage 2, with a higher number of deaths in the bedaquiline group (10 vs. 2 in the placebo group; RR=5.1; P=.017). There was no sudden death reported in the study. There was no discernible pattern for cause of deaths, and the reason for the imbalance in deaths is not clear.

Drug name (abbreviation)	Description and adult dose	Side effects	Monitoring requirements and comments
Linezolid (Lzd)	<p>Description: Oxazolidinone; inhibits protein synthesis; increasingly used for treatment of XDR-TB.</p> <p>Dose: 600 mg/day (reduce to 300 mg/day if serious side effects or intolerance develops).</p>	<p>Common: Diarrhea and nausea.</p> <p>Less common: Myelosuppression (decreased level of white blood cells, and/or anemia); lactic acidosis; optic and peripheral neuropathy (may be irreversible, and linezolid should be considered for suspension weighed against the risk of permanent blindness or disabling permanent neuropathy).</p>	<p>Monitoring: Monitor for peripheral neuropathy and optic neuritis. Monitor with a complete blood count (CBC) weekly during the initial period, then monthly. If symptoms of lactic acidosis develop, a medical evaluation including a lactic acid blood test should be done.</p> <p>Comments: All patients should receive pyridoxine while receiving linezolid (child: 5 to 10 mg/day; adult: 50 mg/day); do not use with patients taking serotonergic drugs, such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs, e.g., fluoxetine, sertraline, paroxetine), lithium, etc., as it may cause serotonin syndrome; avoid or monitor closely with tricyclic antidepressants.</p>

Clofazimine (Cfz)

Description: Riminophenazine; has activity *in vitro* but limited clinical evidence of efficacy.
Dose: 100 to 200 mg/day (oral) has been used. A regimen of 200 mg/day for two months, followed by 100 mg/day has been used.

Common: Orange/red discoloration of skin, conjunctiva, cornea, and body fluids; dry skin, pruritus, rash, ichthyosis, xerosis; gastrointestinal intolerance; photosensitivity.
Less common: Retinopathy, severe abdominal symptoms, bleeding, and bowel obstruction; QT prolongation.

Monitoring: Symptomatic monitoring only.

Comments: Discolors skin and body secretions orange, red, or brownish-black; this should go away after stopping the medicine, but may take a long time; avoid sun; use strong sunscreens.

Amoxicillin/clavulanic acid (Amx/Clv)

Description: Penicillin/beta-lactam inhibitor; very limited clinical evidence of efficacy.
Dose: 80 mg/kg daily in two divided doses.

Common: Diarrhea and abdominal discomfort are most common; nausea and vomiting.
Less common: Hypersensitivity and rash; rare side effects have been reported in other organ systems.

Monitoring: Symptomatic monitoring only.

Comments: Best tolerated and well absorbed when taken at the start of a standard meal.

Imipenem/cilastatin (Ipm/Cln)

Description: Beta-lactam/carbapenem (related to the penicillin/cephalosporin family of antibiotics but classified as belonging to the carbapenem class); very limited clinical experience. Given that imipenem is rapidly degraded by renal proximal tubule dipeptidases, it is used in combination with the dipeptidase inhibitor cilastatin.

Dose: 1,000 mg IV every 12 hours.

Common: Diarrhea, nausea, or vomiting.
Less common: Seizure (noted with CNS infection), palpitations, pseudomembranous colitis.

Monitoring: Symptomatic monitoring only.

Comments: Meropenem is preferred in children as fewer seizures have been associated with it; consider adding clavulanate (available as Amx/Clv) 125 mg every 8 to 12 hours.

Drug name (abbreviation)	Description and adult dose	Side effects	Monitoring requirements and comments
Meropenem (Mpm)	<p>Description: Beta-lactam/carbapenem (related to the penicillin/cephalosporin family of antibiotics but classified as belonging to the carbapenem class); very limited clinical experience.</p> <p>Dose: 1,000 mg IV every eight hours.</p>	<p>Common: Diarrhea, nausea, or vomiting.</p> <p>Less common: Seizure (but less is seen than with imipenem), palpitations, pseudomembranous colitis.</p>	<p>Monitoring: Symptomatic monitoring only.</p> <p>Comments: Consider adding clavulanate (available as Amx/Clv) 500/125 mg every 8 to 12 hours.</p>
High-dose isoniazid (high-dose H)	<p>Description: May be bactericidal or bacteriostatic depending on susceptibility and concentrations attained at the infection site; the carbothioamide group, also found on Thz, and the pyridine ring, also found on H, appear essential for activity; hepatically metabolized, renally excreted.</p> <p>Dose: 500–1,000 mg/day.</p>	<p>Common: GI distress (nausea, vomiting, diarrhea, abdominal pain, loss of appetite); dysgeusia (metallic taste); hypothyroidism (especially when taken with PAS).</p> <p>Less common: Arthralgias, dermatitis, gynecomastia, hepatitis, impotence, peripheral neuropathy, photosensitivity.</p>	<p>Monitoring: Consider baseline and monthly liver enzymes, especially if age greater than 50 years.</p> <p>Comments: Give with pyridoxine 50 mg/day.</p>

Clarithromycin (Clr)

Description: More active against nontuberculous mycobacteria, especially MAC, but some isolates of TB are susceptible *in vitro*; does not have proven value for the treatment of TB in humans, and *in vitro* data are not particularly encouraging (*M. tuberculosis* is intrinsically resistant to macrolides, a characteristic associated with expression of the *ermB* gene).

Dose: 500 mg twice daily.

Common: Diarrhea, nausea, abnormal taste, dyspepsia, abdominal pain/discomfort, headache, rare allergic skin reactions, liver toxicity, QT prolongation, pseudomembranous colitis, hearing loss.

Monitoring: No routine laboratory monitoring is indicated.

Comments: This medication may be taken with or without food; contraindicated in patients taking cisapride, pimozide, astemizole, terfenadine, ergotamine, or dihydroergotamine.

Thioacetazone (Thz)

Description: Known to be active against TB (by inhibiting cyclopropanation of cell wall mycolic acids in mycobacteria), but its role in MDR-TB treatment is not well-established; cross-resistance with some of the other anti-TB drugs (H, Eto/Pto, PAS) and overall is a weakly bacteriostatic drug; prevents the emergence of resistance when used with other first-line drugs.

Dose: 150 mg once daily.

Common: Nausea, vomiting, diarrhea, loss of appetite, skin rashes, aching joints and muscles, neuropathy.

Rare: Severe cutaneous hypersensitivity (including Stevens-Johnson syndrome), seizures, mood changes, hepatitis, bone marrow suppression.

Monitoring: No routine laboratory monitoring is indicated.

Comments: Contraindicated in HIV-infected individuals due to a risk of serious adverse reactions (Stevens-Johnson syndrome and death); persons of Asian descent also have a higher incidence of Stevens-Johnson syndrome; rarely used in MDR-TB treatment.

Adapted from *Tuberculosis: The Essentials*, Fourth Edition (Chapter 7, Table 2) and *Tuberculosis Drug Information Guide*, Second Edition.

2.3 Dosing of anti-TB drugs in adolescents and adults

Dosing of anti-TB drugs by weight class

Medication (abbreviation, common presentation)	Weight class			
	< 33 kg	33–50 kg	51–70 kg	> 70 kg (also maxi- mum dose)
GROUP 1: FIRST-LINE ORAL ANTI-TB DRUGS				
Isoniazid (H) (100, 300 mg)	4–6 mg/kg daily	200–300 mg daily	300 mg daily	300 mg daily
Rifampicin (R) (150, 300 mg)	10–20 mg/ kg daily	450–600 mg	600 mg	600 mg
Ethambutol (E) (100, 400 mg)	25 mg/kg daily	800–1,200 mg	1,200– 1,600 mg	1,600– 2,000 mg
Pyrazinamide (Z) (500 mg)	30–40 mg/ kg daily	1,000– 1,750 mg	1,750– 2,000 mg	2,000– 2,500 mg
GROUP 2: INJECTABLE ANTI-TB DRUGS				
Streptomycin (S) (1-g vial)	15–20 mg/ kg daily	500–750 mg	1,000 mg	1,000 mg
Kanamycin (Km) (1-g vial)	15–20 mg/ kg daily	500–750 mg	1,000 mg	1,000 mg
Amikacin (Am) (1-g vial)	15–20 mg/ kg daily	500–750 mg	1,000 mg	1,000 mg
Capreomycin (Cm) (1-g vial)	15–20 mg/ kg daily	500–750 mg	1,000 mg	1,000 mg
GROUP 3: FLUOROQUINOLONES				
Ofloxacin (Ofx) (200, 300, 400 mg)	Usual adult dose is 800 mg	800 mg	800 mg	800–1,000 mg
Levofloxacin (Lfx) (250, 500 mg)	Usual adult dose ranges from 750 to 1,000 mg	750 mg	1,000 mg	1,000 mg
Moxifloxacin (Mfx) (400 mg)	Usual adult dose is 400 mg	400 mg	400 mg	400 mg
Gatifloxacin (Gfx) (400 mg)	Usual adult dose is 400 mg	400 mg	400 mg	400 mg

GROUP 4: ORAL BACTERIOSTATIC SECOND-LINE ANTI-TB DRUGS

Ethionamide (Eto) (250 mg)	15–20 mg/ kg daily	500 mg	750–1,000 mg	1,000 mg
Prothionamide (Pto) (250 mg)	15–20 mg/ kg daily	500 mg	750–1,000 mg	1,000 mg
Cycloserine (Cs) (250 mg)	15–20 mg/ kg daily	500 mg	750 mg	750–1,000 mg
P-aminosalicylic acid (PASER®) (4-g sachets)	150 mg/kg daily	8 g	8 g	8–12 g

Sodium PAS Dosing can vary with manufacturer and preparation. Check dose recommended by the manufacturer in the drug insert.

GROUP 5: ANTI-TB DRUGS WITH LIMITED DATA ON EFFICACY OR LONG-TERM SAFETY

Bedaquiline (Bdq) The dosage in adult is 400 mg once daily for 2 weeks, followed by 200 mg 3 times per week for 22 weeks.

Linezolid (Lzd) 600 mg once a day for adults. May need to stop after a few months of therapy due to adverse effects.

Clofazimine (Cfz) 5 mg/kg or 200 mg daily for two months then 100 mg daily (limited data).

Amoxicillin/clavulanic acid (Amx/Clv) Dose for MDR-TB not well-defined. Some clinicians use 1,000/250 mg three times a day.

Imipenem/cilastatin (Imp/Cln) Usual adult dose is 1,000 mg IV every 12 hours.

Meropenem (Mpm) Usual adult dose is 1,000 mg IV every eight hours.

High-dose isoniazid (High-dose H) 16–20 mg/kg daily.

Clarithromycin (Clr) Usual adult dose is 500 mg twice daily. Its role in treatment of MDR-TB not clear; generally not used.

Thioacetazone (Thz) Usual adult dose is 150 mg daily. Its role in treatment of MDR-TB not clear; generally not used. Contraindicated in patients with HIV.

Adapted from *Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008* (WHO/HTM/TB/2008.402).

Notes

- Dosing of anti-TB drugs is based on the weight of the patient.
- Monthly monitoring of patient body weight is important. When adults gain weight or move into a higher weight class, their medication dose should be adjusted as well.
- Once-daily dosing is mandatory for anti-TB drugs from Groups 1, 2, and 3, as this is thought to improve the peak-dependent killing.
- Twice-daily dosing is an excellent strategy to reduce adverse effects of Group 4 drugs. Many patients can tolerate a full dose of ethionamide and cycloserine once daily, and once-daily dosing is allowed for Group 4 drugs. There are no studies comparing once-daily to twice-daily dosing for Group 4 drugs in terms of efficacy. Traditionally they have been given twice daily to reduce adverse effects.

2.4 Cross-resistance

Cross-resistance between anti-TB drugs

Drugs	Cross-resistance
Rifamycins	Rifampicin and rifabutin have high levels of cross-resistance.
Isoniazid	Ethionamide/prothionamide can have cross-resistance to isoniazid if the <i>inhA</i> mutation is present.
Aminoglycosides and polypeptides	Amikacin and kanamycin have very high cross-resistance. Kanamycin/amikacin and capreomycin have moderate cross-resistance. Streptomycin has low cross-resistance with kanamycin/amikacin.
Fluoroquinolones	Fluoroquinolones have variable cross-resistance. There is cross-resistance between early generation fluoroquinolones (ofloxacin, ciprofloxacin) and later-generation fluoroquinolones (moxifloxacin, gatifloxacin). Levofloxacin is the biologically active enantiomer of ofloxacin; mutations that reduce susceptibility to ofloxacin will therefore reduce susceptibility to levofloxacin. In vitro, strains resistant to early generation fluoroquinolones (e.g., ofloxacin) may retain some degree of susceptibility to later-generation fluoroquinolones (e.g., moxifloxacin), though the clinical significance of this finding is unknown.
Thioamides	Ethionamide and prothionamide have 100 percent cross-resistance.
Thioacetazone	Cross-resistance to isoniazid, ethionamide/prothionamide, and PAS has been reported but is generally considered low.

References

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- *Tuberculosis Care with TB-HIV Co-management: Integrated Management of Adolescent and Adult Illness* (IMAI). (WHO/HTM/HIV/2007.01, WHO/HTM/TB/2007.380). Geneva: World Health Organization; 2007.
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3 Treatment of MDR-TB

3.1 Review of treatment of drug-susceptible TB

Treatment of drug-susceptible TB

Type of drug-susceptible case	Regimen	Comments
New case	2HREZ/4HR	For all forms of pulmonary and extrapulmonary TB, except for TB meningitis and osteoarticular/spinal TB.
New case in setting of high rate of isoniazid resistance	2HREZ/4HRE	Used in some settings with high isoniazid resistance and where DST is not done before treatment.
Pregnant	Use oral first-line drugs only	All pregnant women should receive pyridoxine 10 mg/day to prevent peripheral neuropathy. Add phytomenadione (vitamin K) orally 10 mg/day for the 15 days prior to expected date of delivery. Give one dose of phytomenadione 1 mg to the newborn on the day of birth. Do not use streptomycin.
Central nervous system, osteoarticular, and spinal TB	2HREZ/10HR	Durations of treatment ranging from 6 to 12 months have been recommended by different guidelines. Given the severity of these forms of extrapulmonary TB, a longer duration is recommended here.
Previously treated TB patients (relapse, failures, and return after default)	2HREZ/4HR or 3HREZ/5HRE or 2SHREZ/1HREZ/5HRE	Previously treated patients with an Xpert MTB/RIF test indicating rifampicin susceptibility should have isoniazid resistance ruled out by rapid DST. Bacteriological failures of a first-line regimen, if seriously ill or with a history of excellent adherence, may be started on an empiric MDR regimen while waiting confirmatory DST.

Notes

- Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy.
- The choice of regimen in HIV-positive TB patients is the same as in HIV-negative TB patients, although rifabutin can be substituted to lessen the interaction with ART (e.g., nevirapine and protease inhibitors).
- Isoniazid peripheral neuropathy occurs more commonly in pregnant and breast-feeding women, and patients with HIV infection, alcohol dependency, malnutrition, diabetes, chronic liver disease, and renal impairment. Such patients should receive preventive treatment with pyridoxine PO (5 to 10 mg/day in children; 10 mg/day in adults) along with their anti-TB drugs.
- Rifampicin decreases the efficacy of oral contraceptives. Patients may choose an oral contraceptive containing a high dose of estrogen (50 μ g), medroxyprogesterone IM, or barrier methods (diaphragm, condom, intrauterine device (IUD)).

3.2 Treatment regimens for mono- and polyresistant TB

Drug resistance surveys have shown that mono- and polyresistant TB are actually more common than MDR-TB

- Monoresistant and polyresistant TB have often gone undiagnosed in resource-limited settings because DST has not been widely available.
- Both conventional and rapid DST are becoming more widely available, so clinicians should expect to see more cases of mono- and polyresistant TB in the future.

WHO standardized regimens are not designed for treatment of mono- and polyresistant TB

- In the absence of DST, undiagnosed mono- and polyresistant TB are likely to be treated with WHO standardized regimens of first-line anti-TB drugs, either the six-month regimen for new patients (2HREZ/4HR) or the eight-month regimen for previously treated patients (2SHREZ/1HREZ/5HRE).
- The few cohort studies of the outcomes of the eight-month WHO standard retreatment regimen (2SHREZ/1HREZ/5HRE) in the treatment of mono- or polyresistant TB have shown poor results (high failure rates in patients with isoniazid resistance).
- Under program conditions, treatment of mono- and polyresistance with WHO standardized regimens has been shown to increase the risk of treatment failure and even worse, amplification to MDR.

Xpert MTB/RIF cannot by itself diagnose mono- or polyresistant TB

- Because Xpert MTB/RIF tests only for rifampicin resistance, it is not possible to diagnose mono- or polyresistant TB with this test alone.
 - If there is rifampicin resistance, the patient should be treated as an MDR-TB patient.
 - If there is no rifampicin resistance, the patient should be treated as a pan-susceptible patient. Further DST is indicated if there is a high rate of mono- or polyresistance involving isoniazid in the population.

- If the patient is at high risk for drug resistance, full DST should be requested even if Xpert MTB/RIF is negative for rifampicin resistance.

Treatment regimens for mono- or polyresistant TB

- Very few randomized clinical trials have been performed to determine the best treatment for mono- or polyresistant TB. There is a great need for such trials, particularly for isoniazid mono-resistance, which is the most common type of drug-resistant TB.
- The general principles of treatment of MDR-TB should be followed when selecting a treatment regimen for mono- and polyresistant TB (see Section 3.4).
- A laboratory diagnosis of mono- or polyresistant TB should be an opportunity to do a careful clinical evaluation. The evaluation should revisit past medical history to verify the patient's TB treatment and assess the risk for amplification of resistance.
- Prescription errors for mono- or polyresistant TB are a common pathway to amplification of resistance and development of MDR-/XDR-TB.

3.3 Suggested regimens for common patterns of mono- and polyresistant TB

Treatment regimens for mono- and polyresistant TB

Resistance pattern	Suggested regimens	Comments
H (\pmS)	9REZ (or 9HREZ if fixed-dose combinations are only available).	If high probability that the effectiveness of R has been compromised, use MDR regimen plus R.
H and E	3Km-R-Z-Lfx/6R-Z-Lfx.	The choice of injectable should be guided by DST if available. If high probability that the effectiveness of R has been compromised, use MDR regimen plus R.
H, E, and S (\pmZ)	MDR regimen plus R.	
Any non-MDR resistance pattern including R	MDR regimen plus H.	

Notes

- All the drugs in a regimen being used for a mono- or poly-drug resistance pattern must have a high likelihood of being effective, meaning:
 1. The DST indicates susceptibility.
 2. There is no possibility that additional resistance to first-line drugs could have been acquired after the sample was collected for DST.
 3. The first-line drugs were never used in a failing regimen or in an ineffective regimen.
- If any of the first-line drugs are considered to have a high likelihood of being ineffective, then an MDR regimen plus either isoniazid or rifampicin should be used.

Evaluation of the possibility of amplification of resistance prior to the start of treatment

- Amplification of resistance should be suspected when the patient has been inadvertently treated with one to two drugs while other companion drugs in the regimen were ineffective because of resistance.

- Consider the possibility that resistance amplification has taken place since the collection of the specimen for DST. The DST reflects the bacterial population at the time the sputum was collected, not when the results arrive to the clinician.
- For rapid DST, where the results return in just a few days, amplification is unlikely. However, with culture-based DST the results often come back several months after sputum collection and amplification of resistance is common.

Monitor for amplification of resistance during treatment

- Use Xpert MTB/RIF at month 0, 2, and 3. If rifampicin resistance develops, switch to a full MDR-TB regimen.

3.4 Principles of MDR-TB treatment

Number of drugs in an effective regimen

- The intensive phase should include at least four core second-line anti-TB drugs likely to be effective, plus pyrazinamide.
- If a drug does not meet the criteria of “likely to be effective,” it should not be counted as one of the four core second-line anti-TB drugs, even if it used in the regimen.
- In the case of unclear evidence about the effectiveness of some drugs, the treatment regimen may include more than five drugs.
- A drug should not be used when patient is known to have a strong contraindication of usage (e.g., major drug-drug interactions, overlapping toxicities, history of severe allergic reaction, or pregnancy).

Five criteria necessary for an anti-TB drug to be considered “likely to be effective” (it is not always possible that all five criteria can be ascertained and clinical judgment is often necessary)

1. The drug has not been used in a regimen that failed for the individual patient. For example, if the patient previously used ethambutol or pyrazinamide as part of a failed first-line regimen, neither of these drugs would be considered likely to be effective.
2. DST performed on the patient’s strain indicates that the strain is susceptible.
 - Only DST for first-line anti-TB drugs, injectables, and fluoroquinolones is considered reliable. DST for all other drugs is considered not reliable or standardized enough to base individual patient management solely on the DST results.
 - Laboratory resistance to pyrazinamide, ethionamide, or PAS, combined with a history of use in a failing regimen, strongly suggests the drug is ineffective.
3. No known resistance to drugs with high cross-resistance.
4. No known close contacts with resistance to the drug.
5. In the absence of DST or for drugs in which individual DST is not reliable, drug resistance surveys demonstrate resistance is rare to the drug in patients with similar TB history.

Amplification of resistance

- Due to the long turnaround time necessary for some types of DST, the patient may have already received months of a treatment by the time DST results become available from the laboratory.
- The possibility of further acquired resistance during this time must be considered. If there is a high probability of acquired resistance to a drug after the specimen for DST was collected, this drug should not be counted as one of the four second-line anti-TB drugs in the core regimen, but can be included as an additional drug.

Programmatic considerations

- Each dose is given under DOT throughout the treatment. A treatment card is marked for each observed dose.
- Ambulatory DOT can be either facility-based or home-based (often referred to as community-based).
- Treatment is given six or seven days a week. Six days a week is common in some outpatient settings where health workers are not available every day.

Standardized vs. individualized treatment

- MDR-TB programs often use a combination of the standardized and individualized approaches. However, in situations where DST is unavailable or limited to only one or two first-line drugs, programs will most commonly use a purely standardized approach.
- The following are definitions of terms often used to describe treatment strategies:
 - **Standardized treatment or regimen:** All patients in a defined group receive the same regimen.
 - **Individualized treatment or regimen:** Each regimen is designed based on the patient's past history of TB treatment and individual DST results.

Empiric treatment

- Empiric refers to the initiation of treatment prior to determination of a firm diagnosis of DR-TB.
- Empiric regimens can be standardized or individualized.
- For example, an empiric XDR regimen refers to the use of a regimen designed to treat XDR-TB before the diagnosis of XDR-TB is made.

3.5 Choice of anti-TB drugs used to treat MDR-TB

Group 1: Oral first-line drugs (H, R, E, Z)

- Pyrazinamide is routinely added to first-line MDR regimens if susceptibility (DST) is documented or if DST is unknown.
 - If well-tolerated, pyrazinamide is generally used for the entire length of treatment, including the continuation phase. Some clinicians may choose to stop it at the end of the injectable phase if the patient has adverse effects or minimal lung disease.
 - Patients who have already failed one or more courses of MDR-TB treatment have likely received pyrazinamide for an extended period. Pyrazinamide is not routinely used in these patients unless DST shows susceptibility.
- Ethambutol is not routinely added to MDR regimens. It can be added if it meets the criteria of being likely effective. If used, it should be used for the entire length of treatment, including the continuation phase.
- The newer rifamycins, such as rifabutin, have very high cross-resistance to rifampicin and are not used in MDR-TB treatment.

Group 2: Injectable anti-TB drugs (Km, Am, Cm)

- All patients should receive an injectable if susceptibility is documented or the drug is considered likely to be effective.
- Given the high rates of resistance to streptomycin in patients with MDR-TB, streptomycin is generally not used in MDR-TB treatment regimens.
- Kanamycin, amikacin, and capreomycin are all acceptable choices for the injectable. Decisions about which injectable to use are based on cost, side effects, and common resistance patterns in the population. The results of second-line drug resistance surveillance may inform these decisions.

Group 3: Fluoroquinolones (Ofx, Lfx, Mfx)

- The most potent available fluoroquinolones, in descending order based on in vitro activity and animal studies, are moxifloxacin, levofloxacin, and ofloxacin.
- Ciprofloxacin should never be used to treat TB because of its low potency compared to other fluoroquinolones.
- Ofloxacin use is discouraged because of lower potency com-

pared to levofloxacin. Levofloxacin is the biologically active enantiomer of ofloxacin; levofloxacin essentially contains double the active enantiomer of an equivalent dose of ofloxacin. Ofloxacin should only be used if levofloxacin is not available.

- Mostly based on cost and availability, levofloxacin is commonly used to treat MDR-TB. The dosing of levofloxacin is higher in treatment of TB compared to treatment of bacterial pneumonia. See Section 2.3 for dosing of anti-TB drugs.
- Moxifloxacin is reserved for special cases (e.g., high resistance, extensive disease, renal failure).
- Although gatifloxacin is similar to moxifloxacin in efficacy against TB, it is associated with serious hypo-/hyperglycemia and new-onset diabetes, and its routine use is not recommended.
- Later-generation fluoroquinolones (moxifloxacin and gatifloxacin) may have some efficacy against ofloxacin-resistant strains.

Group 4: Oral bacteriostatic second-line anti-TB drugs (Eto/Pto, Cs, PAS)

- Ethionamide and prothionamide are considered the most potent Group 4 drugs.
 - These drugs do have some cross-resistance with isoniazid. Ethionamide and prothionamide can be included in the regimen if the *inhA* gene is detected but should not be counted as likely effective drugs.
- Cycloserine or PAS should be included in MDR-TB regimens. Both share no cross-resistance to other anti-TB drugs. Since the combination of ethionamide/prothionamide and PAS often causes a high incidence of gastrointestinal disturbances and hypothyroidism, these drugs are usually used together only when three Group 4 drugs are needed.
- Terizidone molecular structure is closely related to that of cycloserine. It is unknown whether this drug is equally effective as cycloserine, so cycloserine is currently recommended over terizidone.
- The drugs in Group 4 may be started at a low dose and escalated over one to two weeks to improve tolerance.

Group 5: Anti-TB drugs with limited data on efficacy or long-term safety in the treatment of DR-TB (Bdq, Lzd, Cfz, Amx/Clv, Imp/Cln, Mpm, Clr, Thz)

- Group 5 drugs are recommended in cases where adequate regimens are impossible to design with the medicines from Groups 1 to 4.
- Bedaquiline and linezolid are the only Group 5 drugs with proven efficacy against TB with a randomized placebo-controlled human trial.
 - Neither of these drugs should be added alone to a failing regimen.
 - Bedaquiline is recommended in the treatment of fluoroquinolone-resistant MDR-TB.
 - Bedaquiline is listed here in Group 5, although WHO has not yet placed it in any group.
- All Group 5 drugs are described in more detail in Section 2.2.

3.6 Building a MDR-TB treatment regimen

Building a MDR-TB treatment regimen

Step 1	Choose an injectable drug	Choose a drug based on DST and treatment history. Streptomycin is generally not used because of high rates of resistance in patients with MDR-TB.
	Group 2: Kanamycin (or amikacin) Capreomycin	
Step 2	Choose a fluoroquinolone	Add a later-generation fluoroquinolone. If Ofx resistance is suspected or documented, use Mfx.
	Group 3: Levofloxacin Moxifloxacin	
Step 3	Plus at least two Group 4 drugs	Add Group 4 drugs until the regimen has at least four second-line drugs likely to be effective (all three may be needed). Choice is based on treatment history and side effect profile. DST is not fully reliable for the drugs in this group.
	Group 4: Ethionamide (or prothionamide) Cycloserine Para-aminosalicylic acid	
Step 4	Add Group 1 drugs	Z is routinely added except if the patient is intolerant or if resistance is highly likely based on history and DST. If the criteria of being a “likely effective drug” for E are met, it can be added to the regimen (but not counted as a core drug in the regimen).
	Group 1: Pyrazinamide Ethambutol	
Step 5	Consider Group 5 drugs	If there is not four second-line anti-TB drugs that are likely to be effective from Groups 2 to 4, add at least two Group 5 drugs.
	Group 5: Bedaquiline Linezolid Clofazimine Amoxicillin/clavulanic acid High-dose isoniazid Imipenem/cilastatin	

Example: How to build an MDR-TB treatment regimen

- A patient receiving first-line treatment for new patients (2HRZE/4HR) continues to be smear-positive after three months with clinical symptoms, including weight loss, fever, shortness of breath, and cough. The patient feels the shortness of breath is worsening, and the patient spends more than 50 percent of the day in bed. No DST was performed at the start of treatment. An Xpert MTB/RIF test is done at month three and is positive for rifampicin resistance. What should be done?

Answer

- An Xpert MTB/RIF that shows rifampicin resistance in a patient with poor clinical response to a standardized regimen for new patients is likely to be a true positive. This patient should be started on MDR-TB therapy. If possible, full first-line DST should be done.
- Since this patient is failing treatment with a full first-line regimen, it is likely that he is resistant to many or all of the first-line drugs.
- If second-line drug resistance is uncommon in the community, a typical regimen for this type of patient would be Km-Lfx-Eto-Cs-E-Z.
- If second-line drug resistance is moderately common in the community, or if the level of resistance to second-line drugs is not known, a typical regimen might be Cm-Mfx-Eto-Cs-PAS-E-Z.
- Once DST results to other anti-TB drugs come back, the regimen can be adjusted.
- In this patient, full first-line DST later showed resistance to H-R-S and susceptibility to E-Km-Cm-Ofx; testing to Z was not done. Km-Lfx-Eto-CS-E-Z was continued.

3.7 Duration of MDR-TB treatment

Duration of the injectable phase of MDR-TB treatment

- The injectable should be continued for at least eight months and at least four months after the patient becomes culture-negative—whichever is longer.
- Clinicians may use an individualized approach that reviews the cultures, smears, X-rays, and clinical status to decide how long to continue the injectable.
- The injectable can be dosed intermittently in patients with toxicity. Many patients tolerate injectables better when given three times a week (e.g., Monday, Wednesday, and Friday) compared to daily. Some clinicians routinely choose to switch to an intermittent schedule after the patient becomes culture-negative even if there is no toxicity. The weight-based dosing table in Section 2.3 is still relevant; intermittent injections should contain the same dose as daily injections.

Total duration of MDR-TB treatment

- Treatment should continue for a minimum of 20 months and at least 18 months after the patient becomes culture-negative—whichever is longer.
- Chronic patients with extensive pulmonary disease may require MDR-TB treatment for 24 months or longer.

3.8 Treatment recommendations for XDR-TB

- Use any Group 1 drugs that may be effective. Pyrazinamide is routinely added except if the patient is intolerant or if resistance is highly likely based on history (e.g., used in an MDR-TB regimen that failed) and DST.
- Consider a longer duration of use for the injectable (12 months or possibly the whole treatment). If the patient's strain is resistant to all injectables, use an injectable the patient has never used before.
- Use a higher generation fluoroquinolone, such as moxifloxacin.
- Use all Group 4 drugs that have not been used extensively in a previous regimen or any that are likely to be effective.
- Use two or more drugs from Group 5, including bedaquiline and linezolid.
- Consider compassionate use of new drugs.
- Consider resective surgery if there is localized disease.
- Ensure strong infection control measures.
- Manage HIV coinfection.
- Provide comprehensive monitoring and full adherence support.

Example: How to build an XDR-TB regimen

- A patient in whom a standardized regimen of Z-Km-Ofx-Eto-Cs has failed remains sputum smear-positive after eight months of treatment. A DST from a specimen taken four months ago shows resistance to HRZE-Km-Cm-Ofx and susceptibility to Eto.

Answer

- It is highly likely the patient is now resistant to ethionamide, as the patient was on effective monotherapy (resistant to all other drugs in the regimen) for at least four months. Furthermore, the DST to ethionamide is not always reproducible or reliable.
- A later-generation fluoroquinolone may have some effect, even though ofloxacin has tested resistant.

- Treatment options are limited, and there is no expert consensus on what regimen would be the best for this patient.
- Of the Group 5 drugs, at least two of the following drugs—bedaquiline, linezolid, and clofazimine—should be considered for inclusion in the regimen.
- The following regimens would be considered acceptable:
 - Z-Bdq-Lfx-PAS-Lzd-Cfz-Amx/Clv.
 - Z-Mpm-Mfx-PAS-Lzd-Cfz (plus Clv).
 - Z-Cm-Mfx-PAS-Amx/Clv-Cfz-Lzd.

3.9 Extrapulmonary MDR-TB

MDR-TB lymphadenitis

- Lymph node aspiration or excisional biopsy followed by culture-based or molecular DST on the sample can be useful in guiding therapy.
- The length of therapy has not been clearly defined but should likely be the same length as treatment for pulmonary MDR-TB.

MDR-TB spondylitis

- Bone biopsy or sampling of paravertebral fluid collections should be attempted in order to obtain material for DST.
- Persistent or increasing fluid collections on CT despite treatment with first-line anti-TB drugs may be sufficient evidence for empiric MDR-TB treatment in some patients.
- Operative intervention, either through open debridement or percutaneous drainage of fluid collections, is often required in combination with drug therapy.
- Total length of MDR-TB treatment should be at least 24 months.

MDR-TB meningitis

- Very little is known about treatment of MDR-TB meningitis. In the medical literature, there are only a few case studies.
- Treatment of a patient with presumed MDR-TB meningitis is complicated because many second-line drugs do not have good penetration into the CSF.
 - The fluoroquinolones have variable CSF penetration, with moxifloxacin thought to have better penetration based on animal studies.
 - Linezolid is believed to penetrate the CNS, and it has been used in meningitis treatment.
 - Imipenem has good CNS penetration, but children with meningitis treated with imipenem may have high rates of seizures, so meropenem is preferred for meningitis in children.
- Corticosteroids are generally used at the beginning of treatment of drug-susceptible and MDR-TB meningitis.

Penetration of anti-TB drugs in cerebrospinal fluid

Good penetration	Isoniazid, rifampicin, pyrazinamide, ethionamide, prothionamide, cycloserine, linezolid, imipenem, meropenem.
Penetration only in the presence of meningeal inflammation	Aminoglycosides (streptomycin, kanamycin, amikacin), fluoroquinolones (moxifloxacin, levofloxacin, ofloxacin).
Poor or no penetration	Ethambutol, PAS.
No or little data	Capreomycin, clofazimine, clarithromycin.

3.10 Surgery for MDR-TB

Considerations

- Surgery as an adjunct to chemotherapy for patients with localized disease can significantly improve outcomes where skilled thoracic surgeons and excellent pre- and postoperative care are available.
- Specialized surgical facilities should have stringent infection control measures in place. Infectious aerosols are generated in large quantities during surgery, mechanical ventilation, and pulmonary hygiene manipulations in the post-operative period.
- Patients being considered for surgery should be fully informed about the risks of surgery and anesthesia.

Indications

- Failure to demonstrate clinical or bacteriologic response to chemotherapy after three to six months of treatment.
- Recurrence of positive cultures during MDR-TB treatment.
- Relapse following completion of MDR-TB treatment.
- High likelihood of failure or relapse, due to a high degree of resistance or extensive parenchymal involvement, regardless of smear and culture status. Extensive bilateral disease, however, is a contraindication to surgery.
- Life-threatening complications of parenchymal disease, including hemoptysis, bronchiectasis, pneumothorax, bronchopleural fistula, or empyema.

Preoperative workup

- Chest imaging with computerized tomography (CT) to provide detailed assessment of the extent of lung parenchyma involvement.
- Pulmonary function testing with predicted postoperative forced expiratory volume in one second (FEV1) to evaluate if the patient has sufficient pulmonary reserve to survive lung resection.
- Baseline laboratory evaluation (serum electrolytes, renal function, and CBC) and ECG.

Timing of surgery

- Resective surgery should ideally occur early in therapy, normally within the first few months of treatment following smear or culture conversion.

- If conversion is not possible, then at least three months of anti-TB treatment is recommended prior to surgery.

Length of treatment after surgery

- In patients who are smear- or culture-positive at the time of surgery, treatment is continued for minimum of 18 months of documented culture negativity, and generally includes an extended period of injectable.
- In patients who are smear- and culture-negative at the time of surgery, treatment should be continued for a minimum of 18 months after culture conversion and no less than six months after surgery.
 - If pathology reveals viable bacilli on culture, it may be reasonable to continue therapy for 18 months after the surgery rather than 18 months after the previous conversion of sputum.

3.11 Nutritional support

Nutritional support is particularly important for MDR-TB patients.

- MDR-TB patients often are extremely wasted and have poor nutritional status.
- Second-line drugs can also decrease appetite, making adequate nutrition a greater challenge.

Without nutritional support, patients, especially those already suffering from baseline hunger, can become enmeshed in a vicious cycle of malnutrition and disease.

- Regular nutritional support or cash transfers to ensure access to good nutrition are indicated in all patients with poor economic resources.
- Ready-to-use therapeutic food such as a fortified peanut paste is excellent for use in children and has no secondary cost to the family in terms of cooking fuel for its use.
- See Section 5.3 for more information on nutrition for children.

3.12 Corticosteroids

Uses of corticosteroids in MDR-TB patients

- Corticosteroids may be beneficial as an adjunctive therapy in MDR-TB patients with severe respiratory insufficiency, or central nervous system or pericardial involvement.
 - Prednisone is commonly used, starting at approximately 1 mg/kg and gradually decreasing the dose by 10 mg per week.
- Corticosteroids may also alleviate symptoms in MDR-TB patients with an exacerbation of obstructive pulmonary disease.
 - Prednisone may be tapered over one to two weeks, starting at approximately 1 mg/kg and decreasing the dose by 5 to 10 mg per day.
 - When a more immediate response is needed, injectable corticosteroids are often used.

Side effects of corticosteroids

- Increased appetite, weight gain, high blood pressure, anxiety, depression, difficulty sleeping, hypertension, icterus, erectile dysfunction, hypogonadism, hypothyroidism, amenorrhea, cataracts or glaucoma, water retention, swelling, gastritis, easy bruising, acne, lower resistance to infection, and osteoporosis.
- The mood swings, anxiety, and depression can be difficult to differentiate from the neurotoxicity of cycloserine.

Avoid corticosteroids in:

- Patients infected with HIV if they are not on ART.
- Pregnant patients; birth defects can occur in 1 of 1,000 births.

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4 Treatment of MDR-TB in special conditions and situations

4.1 Pregnant women

Considerations

- Pregnancy should be avoided while undergoing treatment for MDR-TB because some of the second-line anti-TB drugs may cause birth defects.
- Determination of the degree of TB disease severity in the pregnant woman is critical:
 - Severity of symptoms of active TB.
 - Degree of weight loss and ability to do normal daily activities.
 - Extent of disease on chest X-ray.
 - Bacteriological evaluation (e.g., sputum smear and culture).
- The decision to postpone the start of treatment should be agreed upon by the patient and doctor after discussion of the risks of untreated TB versus the benefits delaying exposure of the fetus to teratogens.
 - Untreated MDR-TB in pregnant women carries similar risks of morbidity and mortality compared to nonpregnant women.
 - The fetus can develop congenital TB or, more commonly, can be infected in the postnatal period and progress rapidly to disease.
 - The safety of many second-line anti-TB drugs is uncertain.

Management

- The risk of birth defects in MDR-TB treatment is highest in the first trimester of pregnancy. The gestational age of the fetus should be determined, either through calculation based on the last menstrual period or by dating using ultrasound.
- The benefit of treating MDR-TB in pregnancy in most circumstances outweighs the risks.
 - Most patients should start treatment as soon as the diagnosis is made.
 - Treatment can be deferred until the second trimester only if the patient is clinically stable with minimal disease.
- The initial MDR-TB regimen in pregnancy should be composed of three or four oral second-line anti-TB drugs. These

drugs should have demonstrated efficacy against the infecting strain.

- Avoid aminoglycosides during pregnancy due to the risk of toxicity to the developing fetal ear. Capreomycin may carry a lower risk of ototoxicity and is the drug of choice if an injectable cannot be avoided.
- Avoid ethionamide due to the increased risk of nausea and vomiting, as well as its potential teratogenicity.
- Levofloxacin, cycloserine, and PAS have limited data on safety and long-term use in pregnancy but are considered the drugs of choice for MDR-TB treatment in pregnancy.
- The regimen may be reinforced with an injectable and other drugs immediately postpartum.
- Total treatment duration is the same as in nonpregnant patients.

Safety of anti-TB drugs in pregnancy

Medication	Safety class*	Comments
First-line anti-TB drugs		
Isoniazid (H)	C	Experience in gravid patients suggests safety. Pyridoxine (vitamin B6) should be used during pregnancy.
Rifampin (R)	C	Experience in gravid patients suggests safety.
Ethambutol (E)	B	Experience in gravid patients suggests safety.
Pyrazinamide (Z)	C	Experience in gravid patients suggests safety; however, there is less data than other first-line anti-TB drugs. WHO recommends its routine use.
Streptomycin (S)	D	Documented toxicity to developing fetal ear. Risks and benefits must be carefully considered. Avoid use when possible.
Second-line anti-TB drugs		
Kanamycin (Km) Amikacin (Am)	D	Documented toxicity to developing fetal ear. Risks and benefits must be carefully considered. Avoid use when possible.

Capreomycin (Cm)	C	Avoidance strongly recommended. Less ototoxicity reported in adults with capreomycin than with aminoglycosides; unknown if these data can be extrapolated to the developing fetal ear. Generally, injectables are avoided in the gravid patient, but in life-threatening situations when an injectable is needed capreomycin could be considered. (Wavy ribs were reported in studies with rodents.)
Fluoroquinolones	C	Use with caution when essential. No teratogenic effects seen in humans when used for short periods of time (two to four weeks). Long-term use in gravid patients is limited, but given bactericidal activity, benefits may outweigh risks.
Ethionamide (Eto)	C	Avoid if possible. Teratogenic effects observed in animal studies; significantly worsens nausea associated with pregnancy.
Cycloserine (Cs)	C	No significant experience in gravid patients; animal studies have not documented toxicity.
PAS	C	Use with caution when essential. Not considered to be teratogenic.
Bedaquiline (Bdq)	B	Not recommended due to limited data. This drug should only be used in pregnancy when there are clearly no other options.
Linezolid (Lzd)	C	Not recommended due to limited data.
Clofazimine (Cfz)	C	Use with caution when essential; drug appears to be safe during pregnancy when used at lower doses for leprosy, but experience is limited.
Clarithromycin (Clr)	C	Avoid if possible. May be teratogenic.
Rifabutin (Rfb)	B	Experience in gravid patients suggests safety.
Amoxicillin/ Clavulanic acid (Amx/Clv)	B	Experience in gravid patients suggests safety.

*A=Safety established using human studies; B=Presumed safety based on animal studies; C=Uncertain safety, no human studies and animal studies show an adverse effect; D=Unsafe, evidence of risk that may be justifiable under certain clinical circumstances.

4.2 Breast-feeding women

Considerations

- Transmission of active TB can occur easily from mother to infant.
- Anti-TB drugs pass from the mother into breast milk in concentrations that would equal only a small fraction of the therapeutic dose used in infants.
- The effect of exposure to anti-TB drugs on infants through breast milk has not been established.

Management

- A breast-feeding mother with active MDR-TB should receive a full course of treatment, as timely and effective treatment is the best way to prevent transmission of MDR-TB to her baby.
- The mother and her baby should not be completely separated. If the mother is sputum smear-positive, a family member should be recruited to provide care for the infant until the mother becomes sputum smear-negative.
 - Common time between mother and infant should be spent in well-ventilated areas or outdoors.
 - The mother should wear a surgical mask during contact with the baby until she is smear-negative.
- Given the unknown risks of anti-TB drugs in breast milk, formula feeding should be considered as an alternative to breast-feeding when resources and training are available. Mothers who formula-feed should be provided with a supply of formula, fuel for boiling water, and the necessary apparatus (stove, heating pans, and bottles) for the entire time that the infant will formula-feed. The mother (or caregiver) should also be trained on how to prepare infant formula in a sanitary method.

4.3 Patients with liver disease

Considerations

- Patients with liver disease are at increased risk of hepatotoxicity due to anti-TB drugs.
- Of the first-line drugs, isoniazid, rifampicin, and pyrazinamide are associated with hepatotoxicity. Pyrazinamide carries the highest risk.
- Of the second-line drugs, ethionamide, prothionamide, and PAS can also be hepatotoxic, although less so than first-line drugs.

Management

- The presence of liver disease should be assessed prior to initiation of therapy. History and physical exam should specifically focus on evaluation of symptoms and signs of chronic disease, history of viral hepatitis, history of medication-induced hepatotoxicity, and degree of alcohol consumption.
- Patients with a history of liver disease should have liver function tests checked prior to treatment and monthly while on treatment.
- In general, patients with chronic liver disease should not receive pyrazinamide. All other drugs can be used with close laboratory monitoring of liver function. Stoppage of offending drugs should be considered if significant liver inflammation occurs.
- Uncommonly, a patient with TB may have concurrent acute hepatitis that is unrelated to TB or anti-TB treatment. In this case, clinical judgment should be used in determining whether treatment should proceed or be delayed until resolution of the hepatitis.
- Alcohol consumption should be discouraged while patients are on anti-TB therapy.

4.4 Patients with chronic kidney disease

Considerations

- Chronic kidney disease is common in MDR-TB patients. Etiologies include renal TB disease, damage due to previous injectable toxicity, diabetes mellitus, and HIV-associated nephropathy.
- Anti-TB drugs that are excreted by the kidney can accumulate to toxic levels in patients with renal dysfunction.

Management

- Renal function should be estimated by calculating the creatinine clearance in all patients receiving MDR-TB treatment.
- Anti-TB therapy should be adjusted in patients with decreased creatinine clearance.

$$\begin{aligned} & \text{Creatinine clearance (estimated glomerular filtration rate)} \\ & = \text{ideal body weight (kg)} \times (140 - \text{age}) \times \frac{\text{Constant}}{\text{Creatinine clearance } \left(\frac{\mu\text{mol}}{\text{L}} \right)} \end{aligned}$$

- The constant in the formula = 1.23 for men and 1.04 for women
- Ideal body weight:
 - Ideal body weight (men) = 50 kg + 1 kg per cm of height over 150 cm.
 - Ideal body weight (women) = 45 kg + 1 kg per cm of height over 150 cm.
- Normal values for serum creatinine:
 - For women: 45-90 $\mu\text{mol/L}$ (about 0.5 to 1.0 mg/dL).
 - For men: 60-110 $\mu\text{mol/L}$ (about 0.7 to 1.2 mg/dL).
 - If creatinine is reported in conventional units (mg/dL) from the laboratory, one can convert it to an SI unit ($\mu\text{mol/L}$) by multiplying by 88.4. For example, creatinine = 1.2 mg/dL is equivalent to $(88.4 \times 1.2) = 106.1 \mu\text{mol/L}$.

Example: Calculating the creatinine clearance

- A female patient has a serum creatinine = 212 $\mu\text{mol/L}$, age = 46, weight = 50 kg. What is the creatinine clearance?
 - Creatinine clearance = $50 \times (140 - 46) \times (1.04 \text{ for women}) / 212 = 23.0 \text{ mL/min}$.
 - Since the creatinine clearance is below 30, renally excreted drugs need to be dose-adjusted.
- Note: The above calculation is an estimate of creatinine clearance. More accurate measurement can be achieved through a more cumbersome process of timed urine collection and comparison of urine creatinine to serum creatinine.

Dosing of anti-TB drugs in patients with renal insufficiency

Drug(s)	Dose and frequency if creatinine clearance < 30 mL
Isoniazid (H)	No change
Rifampicin (R)	No change
Pyrazinamide (Z)	25-35 mg/kg three times per week (not daily)
Ethambutol (E)	15-25 mg/kg three times per week (not daily)
Rifabutin (Rfb)	2.5-5.0 mg/kg per day
Streptomycin (S)	12-15 mg/kg two or three times per week (not daily)
Kanamycin (Km)	12-15 mg/kg two or three times per week (not daily)
Amikacin (Am)	12-15 mg/kg two or three times per week (not daily)
Capreomycin (Cm)	12-15 mg/kg two or three times per week (not daily)
Levofloxacin (Lfx)	750-1,000 mg three times per week (not daily)
Moxifloxacin (Mfx)	No change
Ofloxacin (Ofx)	600-800 mg three times per week (not daily)
Ethionamide (Eto)	250-500 mg daily
Prothionamide (Pto)	250-500 mg daily

Cycloserine (Cs)	250 mg once daily or 500 mg three times per week
PAS	(PASER®) 8 g/day in two divided doses
Bedaquiline (Bdq)	No change in mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution)
Linezolid (Lzd)	No change
Clofazimine (Cfz)	No change
Amoxicillin/clavulanic acid (Amx/Clv)	1,000/250 mg twice daily for creatinine clearance 10-30 mL/min 1,000/250 mg once daily for creatinine clearance < 10 mL/min
Imipenem/cilastatin (Imp/Cln)	750 mg every 12 hours for creatinine clearance 20-40 mL/min 500 mg every 12 hours for creatinine clearance < 20 mL/min
Meropenem (Mpm)	750 mg every 12 hours for creatinine clearance 20-40 mL/min 500 mg every 12 hours for creatinine clearance < 20 mL/min

Adapted from *Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008* (WHO/HTM/TB/2008.402).

Notes

- To take advantage of the concentration-dependent bactericidal effect of many anti-TB drugs, standard doses are given unless there is intolerance.
- The appropriateness of a 250-mg daily dose of cycloserine has not been established. For MDR-TB patients with chronic renal insufficiency, there should be careful monitoring for neurotoxicity. Therapeutic drug monitoring may be helpful.
- Sodium salt formulations of PAS may result in an excessive sodium load and should be avoided in patients with renal insufficiency. Formulations of PAS that do not use sodium salt can be used without the hazard of sodium retention.
- Caution should be used with injectable drugs in patients with chronic renal insufficiency because of the increased risk of both ototoxicity and nephrotoxicity.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided in patients with acute or chronic renal insufficiency, as they may precipitate renal failure.

Dosing of commonly used drugs in patients with renal insufficiency

Drug	Dosage based on creatinine clearance (mL/min)
Antibiotics	
Amoxicillin (PO)	> 30: No change 10-30: Usual dose every 12 hours < 10: Usual dose once a day
Cotrimoxazole (PO)	> 30: No change 15-30: 50 percent of the usual dose < 15: Use not recommended
Fluconazole (PO or IV)	> 50: No change < 50: 50 percent of the usual dose once a day
Ancillary drugs for adverse effects	
Metoclopramide (PO or IV)	> 40: No change 10-40: 50 percent of the usual dose < 10: 25 percent of the usual dose
Ranitidine (PO or IV)	> 50: No change < 50: Usual dose once a day
Antiretrovirals	
AZT (PO)	> 10: No change < 10: 300 mg once a day
d4T (PO)	> 50: No change 25-50: 15 mg every 12 hours < 25: 15 mg once a day
TDF (PO)	> 50: No change 30-49: 300 mg every two days 10-29: 300 mg twice a week < 10: Use not recommended
3TC (PO)	> 50: No change 30-49: 150 mg once a day 15-29: 150 mg first dose, then 100 mg once a day 5-14: 150 mg first dose, then 50 mg once a day < 5: 50 mg first dose, then 25 mg once a day

Notes

- In chronic renal insufficiency, the dose of all renally excreted drugs, including drugs used for comorbidities and adverse effects, will need a dosing adjustment.
- This table includes only some of the most commonly used drugs and is not comprehensive. Check the manufacturer inserts for full information.

4.5 Patients with diabetes

Considerations

- Patients with diabetes are at increased risk for developing MDR-TB.
- TB can be more difficult to diagnose in patients with diabetes due to a higher occurrence of atypical chest X-ray findings and extrapulmonary TB.
- Patients with diabetes and MDR-TB are at increased risk for poor outcomes.
 - Patients with diabetes mellitus have impaired immunity compared to healthy individuals.
 - Elevated blood sugar can worsen the clinical course of TB; TB can worsen glycemic control in diabetics.
 - Sequelae of diabetes may potentiate the adverse effects of anti-TB drugs, especially renal dysfunction and peripheral neuropathy.

Management

- All patients with MDR-TB should be screened for diabetes as part of the initial clinical evaluation.
- Diabetes must be optimally managed throughout the treatment of MDR-TB. The physician responsible for MDR-TB treatment should be in close communication with the provider team managing the patient's diabetes. The responsibility for management of diabetes, however, often falls to the physician treating the patient for MDR-TB.
- Providers and patients should adhere closely to the foundations of diabetes management, including adoption of a diabetic diet, monitoring of symptoms of hypo- and hyperglycemia, and practicing good foot care.
- Patients with diabetes usually have some underlying chronic diabetic nephropathy. This increases the risk of injectable nephrotoxicity.
 - Creatinine and potassium levels should be monitored frequently—weekly for the first month and then at least monthly thereafter while receiving the injectable.
 - An ACE inhibitor should be considered in all patients with diabetes to prevent progression of diabetic nephropathy.

- Patients should have regular monitoring of blood glucose levels and other important markers of diabetes management.
 - Goal capillary blood glucose levels are 80-120 mg/dL before meals and 100-140 mg/dL before bedtime. Higher levels are appropriate if a patient has a history of hypoglycemia. Patients may need intensive glucose monitoring until these goals are met.
 - Goal hemoglobin A1c is < 7 percent. Levels should be checked every three months if treatment changes or patient is not meeting goals. Checks can be extended to every six months in stable clinical situations.
 - Patients with diabetes should undergo a yearly retinal exam.
 - Blood pressure should be checked monthly.
- Tight control of blood glucose can be achieved through pharmacologic therapy.
 - Oral hypoglycemic drugs can be used during the treatment of MDR-TB but may require adjusting the dosage due to drug-drug interactions.
 - Some experts recommend the use of insulin for tight blood glucose control in all patients with diabetes and tuberculosis.
 - Use of ethionamide or prothionamide may make it more difficult to control insulin levels.

4.6 Patients with seizure disorders

Considerations

- Second-line anti-TB drugs, specifically cycloserine and high-dose isoniazid, can cause seizures. The risk of seizure from these medications is higher in patients who have pre-existing seizure disorders.
- Isoniazid and rifampicin may have drug-drug interactions with many of the antiseizure medications.

Management

- Patients with pre-existing seizure disorders should be evaluated to determine whether the seizure disorder is under control and whether the patient is taking antiseizure medication. If the seizures are not under control, initiation or adjustment of antiseizure medication will be needed before the start of MDR-TB therapy. In addition, any other underlying conditions or causes of seizures should be corrected.
- Cycloserine should be avoided in patients with active seizure disorders that are not well-controlled with antiseizure medication. In cases where cycloserine is a crucial component of the treatment regimen, antiseizure medication should be adjusted as needed to control the seizure disorder prior to initiating cycloserine.
- High-dose isoniazid should be avoided in patients with seizure disorder.

4.7 Patients with psychiatric disorders

Considerations

- Patients with MDR-TB have high rates of depression and anxiety because of the chronicity of disease and socioeconomic stressors.
- Cycloserine can cause depression, anxiety, irritability, and psychosis. The risk of neurotoxicity is higher in patients who have pre-existing psychiatric disorders, but the benefits of using this drug may outweigh the risk of adverse effects.

Management

- Patients with psychiatric disorders should have a psychiatric evaluation prior to the start of MDR-TB treatment. If a mental health specialist is not available, the treating physician should conduct the psychiatric evaluation.
- The initial evaluation should establish the patient's baseline level of mental health, which can be used for comparison if new psychiatric symptoms develop while the patient is on treatment. Any psychiatric illness identified at the start of or during treatment should be optimally managed.
- Cycloserine should be used with caution in patients with psychiatric disease. Close monitoring of the patient's mental health is recommended.
- Family members should be educated about cycloserine toxicity and instructed to contact the medical team at the first sign of behavioral changes.
- Treatment with psychiatric medication and individual counseling may be necessary to manage the patient suffering from a psychiatric condition or neurotoxicity caused by MDR-TB treatment. The physician treating MDR-TB should be involved in all psychiatric management decisions.
- Group therapy has been very successful in providing a supportive environment for MDR-TB patients with or without psychiatric conditions.
- Healthcare providers treating MDR-TB should work closely with a mental health specialist and have an organized system for managing psychiatric emergencies, including psychosis, suicidal ideation, or any situation in which patients are a danger to themselves or others. Psychiatric hospitalization should be available 24 hours a day.

4.8 Patients with substance abuse

Considerations

- Alcohol or drug abuse is common among patients with MDR-TB in some settings.

Management

- Patients with substance dependence should be offered treatment for their addiction. Complete abstinence from alcohol or other substances should be strongly encouraged, although active consumption is not a contraindication for MDR-TB treatment. If the treatment is repeatedly interrupted because of substance abuse, treatment should be suspended until successful treatment of addiction or measures to ensure adherence have been established.
- Well-executed DOT gives the patient contact with and support from health care providers, which often allows patients with substance dependence to complete treatment.
- Cycloserine will have a higher incidence of adverse effects in patients dependent on alcohol or other substances, including a higher incidence of seizures. Cycloserine, however, should be used if it is considered important to the regimen. The patient should be closely observed for adverse effects in these situations.

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5 Treatment of MDR-TB in children

5.1 Regimen design

Considerations

- The basic principles of regimen design for children are the same as those for adults with MDR-TB.
- Most second-line drug formulations are not child-friendly, and preparation can be labor-intensive.
- Children generally tolerate second-line anti-TB drugs well.
- DST confirmation is not needed to start an MDR regimen in a child (see Section 1.11).

Children who are household contacts of a patient with MDR-TB

- The empiric MDR-TB regimen should be based on the DST pattern of the index case. This is the same recommendation for all household contacts, but it is more pertinent if the contact is a young child.
- If the index case has presumptive MDR-TB and is receiving an empiric MDR regimen, the child may also be given the same empiric regimen.
- A household contact of a patient who failed or died on first-line TB treatment and in whom DST is unknown should be considered for empiric MDR treatment.
- Every effort should be made to obtain a DST for the child (see Section 1.11).

Children who fail treatment with first-line TB regimens

- Children who fail to improve clinically on TB regimens often warrant empiric regimens for MDR-TB.
- Every effort should be made to obtain a DST from the child who is not responding to anti-TB drugs, including gastric aspirates and sputum induction in children with pulmonary TB.
- When no DST is available from a contact or child (or the DST is pending) and MDR-TB is likely, the design of an individualized treatment regimen should be based on past TB treatment history and local DST patterns.

5.2 Dosing of anti-TB drugs in children

General considerations

- Anti-TB drugs should be dosed according to weight and adjusted regularly as weight increases during treatment.
- When a liquid formulation is available, it should be used for patients less than 15 kg.
- Most second-line TB drugs do not have pediatric liquid or tablet formulations, so it may be necessary to cut pills in order to approximate the correct dose.
- It is difficult to split tablets into 0.75. It is suggested to split the tablet in half and then split a half tablet in half. Discard the smaller quarter tablet and give the child a half tablet plus the remaining quarter tablet.
- In patients below 5 kg the doses of most anti-TB drugs have not been established, but often the potential benefit outweighs the risks. In such patients, the child should be dosed as close to the middle of the mg/kg range as possible.

Weight-based dosing tables

Isoniazid (7–15 mg/kg for patients less than 30 kg; maximum dose 300 mg daily)			
kg	50 mg per 5 mL oral solution	100-mg tablet	300-mg tablet
5	5 mL	0.5 tab	-
6	6 mL	1.0 tab	-
7	7 mL	1.0 tab	-
8	8 mL	1.0 tab	-
9	9 mL	1.0 tab	-
10	10 mL	1.5 tab	-
11	11 mL	1.5 tab	-
12	12 mL	1.5 tab	-
13	13 mL	2.0 tab	-
14	14 mL	2.0 tab	-
15	15 mL	2.0 tab	-
16–20	-	2.0 tab	-
21–30	-	-	1.0 tab

Notes

- The table shows the “regular” dose for children, not high-dose isoniazid, which is rarely used in children.
- Children at risk for peripheral neuropathy (e.g., malnutrition or HIV coinfection) should also receive pyridoxine 5–10 mg/day.

Rifampicin (10-20 mg/kg for patients less than 30 kg; maximum dose 600 mg daily)			
kg	100 mg per 5 mL oral suspension	150-mg tablet	300-mg tablet
5	4 mL	0.5 tab	-
6	5 mL	0.5 tab	-
7	5 mL	0.5 tab	-
8	6 mL	1.0 tab	-
9	7 mL	1.0 tab	-
10	8 mL	1.0 tab	-
11	9 mL	1.0 tab	-
12	10 mL	1.0 tab	-
13	10 mL	1.5 tab	-
14	11 mL	1.5 tab	-
15	12 mL	1.5 tab	-
16-30	-	-	1.0 tab

Note

- Oral solution is preferred for patients less than 15 kg.

Ethambutol (15-25 mg/kg, maximum dose 1,200 mg daily)		
kg	100-mg tablet	400-mg tablet
5-7	1.0 tab	-
8-13	2.0 tab	-
14-17	3.0 tab	-
18-26	-	1.0 tab
27-30	-	1.5 tab

Note

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

Pyrazinamide (30-40 mg/kg for patients less than 30 kg; maximum dose 2,000 mg daily)		Pyrazinamide (30-40 mg/kg for patients less than 30 kg; maximum dose 2,000 mg daily)	
kg	400-mg tablet	kg	500-mg tablet
5-7	0.50 tab	5-6	0.25 tab
8-9	0.75 tab	7-9	0.50 tab
10-14	1.00 tab	10-11	0.75 tab
15-20	1.50 tab	12-18	1.00 tab
21-27	2.00 tab	19-25	1.50 tab
28-30	2.50 tab	26-30	2.00 tab

Notes

- Pyrazinamide comes in either 400-mg or 500-mg tablets.
- Tablets are big enough to split into quarters.

Injectable anti-TB drugs		
Drug	Daily dose	Maximum daily dose
Streptomycin	20-40 mg/kg once daily	1,000 mg
Amikacin	15-30 mg/kg once daily	1,000 mg
Kanamycin	15-30 mg/kg once daily	1,000 mg
Capreomycin	15-30 mg/kg once daily	1,000 mg

Example: Injectable dose calculation for a child that weighs 6.9 kg

- Calculate the low and high doses for the child's weight. For kanamycin:
 - Low dose: $15 \text{ mg/kg} \times 6.9 \text{ kg} = 103 \text{ mg}$
 - High dose: $30 \text{ mg/kg} \times 6.9 \text{ kg} = 207 \text{ mg}$
- Choose a convenient dose between the two numbers.
 - Select a dose between the two numbers and toward the higher number. In this case, 200 mg is a convenient dose.
- Calculate the number of mL to draw up in the syringe based on the mg/mL concentration of the preparation.

Levofloxacin

5 years and under: 15–20 mg/kg split into two doses (morning and evening)

Over 5 years: 10–15 mg/kg once daily

kg	Under 5 years (250-mg tablet)	More than 5 years (250-mg tablet)
10–15	0.50 tab twice daily	
16–23	0.75 tab twice daily	1.0 tab once daily
24–30	1.00 tab twice daily	1.5 tab once daily

Notes

- Levofloxacin is dosed twice daily for children 5 years of age and under (total daily dose: 15–20 mg/kg/day) and once daily for children over 5 years of age (total daily dose: 7.5–10 mg/kg/day). This is done because children under 5 years metabolize the levofloxacin faster than those older than 5 years.
- Levofloxacin is not recommended for children under 10 kg. It may be used by some clinicians in MDR-TB treatment if the potential benefit outweighs the risks. Such children should be dosed as close to the middle of the range as possible.
- Once-daily dosing at 15 mg/kg resulted in adequate serum concentrations for children less than 5 years in at least one program and can be used as an alternative if twice-daily dosing is not programmatically possible.

Moxifloxacin (7.5–10 mg/kg)

kg	400-mg tablet
10–17	0.25 tab
18–30	0.50 tab

Note

- Later-generation quinolones such as levofloxacin and moxifloxacin are recommended instead of ofloxacin as they are more potent. Dosing for ofloxacin is not provided in this guide.

Cycloserine (10–20 mg/kg)		
kg	250-mg capsule	1 capsule in 10 mL water
5	0.25 cap	2.5 mL
6–9	0.50 cap	5.0 mL
10–11	0.75 cap	7.5 mL
12–22	1.00 cap	10.0 mL
23–30	2.00 cap	-

Note

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

Prothionamide/ethionamide (15–20 mg/kg)	
kg	250-mg tablet
5–10	0.5 tab
11–18	1.0 tab
19–24	1.5 tab
25–29	2.0 tab

PAS (200–300 mg/kg for patients less than 30 kg)	
kg	PASER® Jacobus
5	500 mg twice daily
6–7	750 mg twice daily
8–10	1,000 mg twice daily
11–14	1,500 mg twice daily
15–18	2,000 mg twice daily
19–22	2,500 mg twice daily
23–26	3,000 mg twice daily
27–30	3,500 mg twice daily

PAS (200–300 mg/kg for patients less than 30 kg)	
kg	MonoPAS® 9.2 g Macleods
5–6	1.5 g twice daily
7–8	2.0 g twice daily
9–13	3.0 g twice daily
14–18	4.0 g twice daily
19–24	6.0 g twice daily
25–30	8.0 g twice daily

Notes

- PASER® is stable for up to eight weeks at 40°C and 75 percent 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 eight weeks is needed, refrigeration below 15°C is required.
- PASER® comes with a dosage scoop graduated in milligrams, and MonoPAS® 9.2 g comes with a measuring spoon graduated in grams.

Group 5 anti-TB drugs		
Drug	Daily dose	Maximum daily dose
Bedaquiline (Bdq)	Dose not yet determined in children	
Linezolid (Lzd)	10 mg/kg given two times daily (pyridoxine should also be given)	600 mg
Clofazimine (Cfz)	Limited data, but 1 mg/kg once daily has been given	200 mg
Amoxicillin/ clavulanic acid (Amx/Clv)	80 mg/kg (based on the amoxicillin component) in two divided doses	4,000 mg amoxicillin and 500 mg clavulanic acid
Meropenem (Mpn)	20-40 mg/kg IV every eight hours	6,000 mg
Imipenem/cilastatin (Imp/Cln)	Meropenem is preferred in children	

Note

- Most of the Group 5 drugs, except amoxicillin/clavulanic acid and linezolid, have limited experience with dosing in children. The data on long-term use of all the Group 5 drugs in children is also limited.

5.3 Nutrition in children with MDR-TB

Children with MDR-TB require a higher caloric intake than their well counterparts because of the active metabolism associated with MDR-TB.

- A baseline measure of weight, height, and mid-upper arm circumference should be made in all children with MDR-TB.
 - If baseline malnutrition is present, acute nutritional interventions are needed.
- Failure to improve nutritional status is an early and clear indicator that the MDR-TB may not be under control.
 - Weight-for-age and weight-for-height should be plotted on a chart for all children between 0 and 5 years.
 - Body mass index (BMI) should be plotted for all children between 5 and 19 years.

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.

- 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. There may be additional groups working to provide nutritional support, such as nongovernmental organizations, faith-based organizations, and community groups.
- Know the resources of the patient and family. Start by asking, “How many meals do you eat a day?” Then proceed to asking 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.
 - 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. Eating multiple, small, high-calorie meals may help the child gain weight. This can be especially helpful for children with nausea and vomiting due to treatment.

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6 Treatment of MDR-TB/HIV coinfection

6.1 MDR-TB in HIV-positive compared to HIV-negative patients

MDR-TB transmission and mortality in HIV-positive patients

- People with living with HIV are vulnerable to MDR-TB infection and are at high risk of developing active MDR-TB once infected.
- HIV-positive patients are more likely to die from MDR-TB than HIV-negative patients.
 - HIV-positive patients may experience delayed diagnosis of MDR-TB because they may more frequently be smear- or culture-negative at the outset.
 - HIV-positive patients often die while waiting for laboratory confirmation of MDR-TB and before starting effective therapy. This was best illustrated by the rapid and deadly spread of XDR-TB among HIV-positive patients in South Africa.
 - HIV-positive patients are more likely to die during MDR-TB treatment than HIV-negative patients, though mortality decreases once ART is started.

Adverse effects of MDR-TB treatment in HIV-positive patients

- More research is necessary, but some adverse effects of second-line anti-TB drugs seem to be more common in patients with HIV. These include:
 - Nephrotoxicity (acute renal failure).
 - Electrolyte wasting.
 - Hypothyroidism.
- HIV-positive patients have to take more drugs than HIV-negative patients, and these additional drugs may have adverse effects. Some adverse effects are common to both second-line anti-TB drugs and ART, which may result in added rates of adverse events. These include:
 - Anemia.
 - Rash or anaphylaxis.
 - Nausea and vomiting.
 - Psychiatric adverse effects.
- Treatment monitoring needs to be more intense in HIV-positive patients for both response to therapy and adverse effects.

6.2 ART in MDR-TB/HIV coinfection

ART improves survival in MDR-TB patients infected with HIV

- For drug-susceptible TB, it is now well-established that earlier initiation of ART is associated with a decrease in mortality, and this is particularly evident in very immunosuppressed patients.
- In the pre-ART era, mortality during MDR-TB treatment without ART was often greater than 90 percent.
- ART improves survival of HIV-infected patients with MDR-TB.

Start ART as soon as possible in MDR-TB patients

- MDR-TB patients who are already on ART should continue it.
- WHO recommends that MDR-TB patients who are not already on ART should start ART within the first eight weeks of starting effective MDR-TB treatment irrespective of CD4 count.
- Initiating ART with second-line anti-TB drugs may be challenging because of overlapping adverse effects and the high pill burden, but a well-trained clinical team can usually initiate ART within two weeks of starting MDR-TB treatment in stable patients.

Choice of first-line ART regimen

- Just as in HIV-positive patients without MDR-TB, a first-line ART regimen should include two nucleoside reverse-transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse-transcriptase inhibitor (NNRTI).
- In many countries, the preferred first-line ART regimen is TDF + 3TC + EFV. A similarly definitive recommendation cannot be made in patients co-infected with MDR-TB.
- The ART regimen should be chosen to avoid potential overlapping toxicities with second-line anti-TB drugs.
 - TDF is generally avoided because of the possibility of overlapping renal toxicity with the injectables, which can result in death. TDF is therefore reserved for cases of ART drug resistance or if other NRTIs are unsuitable because of

- severe adverse effects, such as anemia (AZT) and peripheral neuropathy (d4T).
- d4T is no longer recommended to be included in first-line ART regimens. In MDR-TB patients, it should generally not be used because of overlapping adverse effects, especially peripheral neuropathy, which is caused by many second-line anti-TB drugs.
 - AZT should not be started in patients with a hemoglobin value less than 7 g/dL, which is common in patients with MDR-TB. This is because AZT can cause hematological toxicity, including severe anemia.
 - NVP is generally avoided due to the risk of hepatotoxicity when used concurrently with pyrazinamide. EFV is the preferred drug in the setting of MDR-TB treatment with pyrazinamide-containing regimens.
- The most commonly used ART regimen for MDR-TB patients infected with HIV is AZT + 3TC + EFV.

6.3 Drug-drug interactions between anti-TB drugs and antiretroviral therapy

Rifamycin derivatives and ART

- While rifamycin derivatives are not routinely used in MDR-TB treatment, they are used in the treatment of rifampicin-sensitive poly- and mono-resistant TB.
- There are numerous interactions with antiretroviral therapy (ART) due to liver enzyme induction of the rifamycins.

Possible combinations of ARVs and rifamycins

	Rifampicin (R)	Rifabutin (Rfb)
NNRTIs		
Nevirapine (NVP)	Do not combine unless Rfb is not available and there are no other options. If NVP is used, dose ramping is not necessary.	May be combined without dose adjustment.
Efavirenz (EFV)	May be combined without dose adjustment.	May be combined without dose adjustment.
NRTIs		
Abacavir (ABC) Didanosine (ddl) Lamivudine (3TC) Stavudine (d4T) Zidovudine (AZT) Tenofovir (TDF)	May be combined without dose adjustment.	May be combined without dose adjustment.
PIs		
Indinavir (IDV)	Do not combine.	Rfb: 300 mg/day IDV: 1 g every eight hours.
Nelfinavir (NFV)	Do not combine.	May be combined without dose adjustment.

Lopinavir/ ritonavir (LPV/r)	May be combined if Rfb is not available. LPV/r: LPV super-boosted with ritonavir (400 mg/400 mg twice daily) or double dose of LPV/r (800 mg/200 mg twice daily). R: Usual dosage	Rfb: 150 mg/day. LPV/r: Usual dose.
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Atazanavir/ ritonavir (ATZ/r)	Do not combine.	Rfb: 150 mg three times a week. ATZ/r: Usual dose.
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Adapted from *Tuberculosis: Practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries* (MSF/PIH).

Quinolones and ddi

- Buffered ddi contains an aluminum/magnesium-based antacid and if given jointly with fluoroquinolones may result in decreased fluoroquinolone absorption; it should be avoided, but if it is necessary it should be given six hours before or two hours after fluoroquinolone administration.
- The enteric-coated formulation of ddi can be used concomitantly without this precaution.

Ethionamide/prothionamide and ART

- Based on limited existing information of the metabolism of the thioamides (ethionamide and prothionamide), this drug class may have interactions with ARV drugs. Ethionamide/prothionamide is thought to be metabolized by the CYP450 system, though it is not known which of the CYP enzymes are responsible.
- Whether doses of ethionamide/prothionamide and/or certain ARV drugs should be modified during the concomitant treatment of DR-TB and HIV is completely unknown. At present, no adjustment is recommended.

Clarithromycin and ART

- Clarithromycin is a substrate and inhibitor of CYP3A and has multiple drug interactions with PIs and NNRTIs.
- If possible, avoid the use of clarithromycin because of both its weak efficacy against TB and its multiple drug interactions.

Bedaquiline and ART

- Bedaquiline is metabolized by CYP3A4. EFV, based on a single-dose study in healthy volunteers, appears to reduce the amount of bedaquiline through inducing CYP3A4. CYP3A4 inhibitors (e.g., azole antifungal drugs, some macrolides, protease inhibitors, and many others) can raise the level of bedaquiline.
- Experience with bedaquiline and ART is extremely limited, and the reader should refer to the drug insert published by the company and forthcoming WHO publications on the use of bedaquiline.
- Any use of bedaquiline with ART should be done under: (1) close consultation with an HIV/ART specialist familiar with bedaquiline's pharmacokinetics, potential drug-drug interactions, and adverse effects; (2) full disclosure to the patient regarding the unknown risks and possible drug-drug interactions that could compromise either or both TB and HIV treatments; and (3) the consideration for possible adjustments to bedaquiline, anti-TB drugs, or ART based on therapeutic drug monitoring or theoretical concerns.

6.4 Adherence support and clinical monitoring in patients on MDR-TB/HIV cotreatment

Adherence support is important for coinfecting patients

- A large pill burden and numerous side effects make MDR-TB/HIV cotreatment very difficult.
- ART must be taken daily without exception to prevent the evolution of HIV drug resistance.
- Concomitant DOT of second-line TB drugs and ART is strongly recommended, along with other types of adherence support.
- Both MDR-TB and HIV can result in serious stigma and discrimination.
- MDR-TB/HIV coinfecting patients may require special socio-economic, nutritional, and psychosocial support in order to successfully complete treatment.

Clinical monitoring of ART success

- CD4 cell count should be monitored at least every six months but may be difficult to interpret in the setting of MDR-TB and other opportunistic infections.
- Viral load should be done regularly during MDR-TB treatment or at least whenever ART failure is suspected.
- If the viral load indicates virological failure, then HIV genetic resistance testing is strongly recommended before changing the ART regimen.

A typical MDR-TB/HIV coinfecting patient > 60 kg often has a large pill burden

Morning dose	Evening dose
Pyrazinamide (500mg): 4 tablets	Ethionamide (250 mg): 2 tablets
Kanamycin (1-g vial): 1 g IM	Cycloserine (250 mg): 2 capsules
Levofloxacin (500 mg): 2 tablets	PAS (4-g sachet): 1 sachet
Ethionamide (250 mg): 1 tablet	Pyridoxine (50 mg): 4 tablets
Cycloserine (250 mg): 1 capsule	
PAS (4-g sachet): 1 sachet	
AZI/3TC combination: 1 tablet	AZI/3TC combination: 1 tablet
Cotrimoxazole: 1 tablet	EFV (600 mg): 1 tablet
Total pill burden in morning: 9 tablets, 1 capsule, 1 sachet and 1 intramuscular injection	Total pill burden in evening: 8 tablets, 2 capsules, 1 sachet

Daily number of medications: 17 tablets, 3 capsules, 2 sachets, and 1 intramuscular injection (excluding ancillary drugs for adverse effects).

6.5 Immune reconstitution inflammatory syndrome (IRIS)

- TB-IRIS is a paradoxical worsening of the clinical status after a patient starts ART after being stable on TB treatment.
- There have been no studies on IRIS during MDR-TB treatment, but cohort studies have shown that true IRIS is not very common, even if ART is started early in MDR-TB treatment.
- IRIS is a diagnosis of exclusion. The most common reason for worsening fever, cough, and sputum during MDR-TB treatment is MDR-TB treatment failure.
- Patients suspected of IRIS should have multiple sputum samples sent for culture and second-line DST to rule out acquisition of second-line drug resistance. They should also have a careful evaluation for other opportunistic infections and other conditions that can mimic IRIS.
- The treatment of IRIS is complex and depends on the manifestations and severity. NSAIDs have been used in mild disease and corticosteroids in moderate to severe IRIS. Most patients can be treated without interruption of MDR-TB treatment or ART.

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7 Initial evaluation of MDR-TB patients

7.1 Pretreatment evaluation and screening

- The objective of the pretreatment evaluation is to identify those patients at a greater risk of adverse effects and to establish a baseline for monitoring.
- The pretreatment evaluation should include a thorough medical history, physical examination, and laboratory investigations.
- The following comorbidities may affect the initial treatment regimen or other important management decisions:
 - HIV infection.
 - Diabetes mellitus.
 - Hypertension.
 - Acute or chronic renal insufficiency.
 - Acute or chronic liver disease.
 - Thyroid disease.
 - Mental illness.
 - Drug or alcohol dependence.
 - Pregnancy.
 - Chronic epilepsy or seizure disorder.
- All patients starting MDR-TB treatment should have the following tests:
 - Sputum smear, culture, and DST.
 - Baseline potassium, creatinine, and liver function tests.
 - Baseline audiometry (where it is available).
 - HIV rapid testing.
 - Pregnancy test for women of child-bearing age.
 - Thyroid-stimulating hormone (TSH) if there are symptoms of hypothyroidism or goiter.
- Patients coinfecting with HIV should have additional tests:
 - CBC (especially if planning to start AZT in the future).
 - CD4 cell count (CD4 percent in children).
- Patients receiving bedaquiline should have a baseline ECG to rule out QT prolongation.
- Additional laboratory tests may be indicated based on the medical history, physical examination, and results of initial screening tests.

7.2 Educating and preparing the patient for treatment

Counseling tips for MDR-TB patients

If the patient does not know what MDR-TB is Explain that MDR-TB:

- Is created when TB patients do not take anti-TB drugs regularly.
- Is transmitted through the air.
- Can be easily transmitted to people living with HIV.

If the patient does not understand MDR-TB treatment Explain:

- That second-line drugs are weaker than first-line drugs, so it is important to take all doses on time.
- That the injectable will be taken for at least eight months and at least four months after culture conversion.
- That the total duration of treatment is at least 20 months and at least 18 months after culture conversion.

If the patient has had difficulties adhering to treatment in the past Explain: “It is very important for you to take all of your doses. Tell me about difficulties you have had with taking treatment in the past.”

If the patient does not know his/her HIV serostatus Provide HIV counseling and offer HIV testing.

If the patient lives with other family members Explain:

- Most infectious before starting treatment and during the first few weeks of treatment.
- Leave windows and doors open in the home to increase ventilation.
- Don’t sleep in the same bed as other family members during this time.
- Practice good cough hygiene.

If a method for DOT has not been arranged Discuss with the community team about finding a community health worker or arranging for DOT at a nearby health center.

If the patient lives far from the clinic or has food insecurity Arrange for transportation reimbursement and food packages.

If the patient is worried about adverse effects of MDR-TB treatment Explain: “This treatment can have many side effects, especially at the beginning of treatment. If you are having any side effects, you should tell the community health worker immediately. Side effects get better with time.”

7.3 Family planning

All women of childbearing age should be using a reliable contraceptive method

- All women of childbearing age should have a pregnancy test during the initial evaluation before starting MDR-TB treatment.
- Birth control is strongly recommended for all women receiving MDR-TB treatment.
 - Oral contraceptives are not recommended. MDR-TB patients often have nausea and vomiting due to side effects. There are also drug interactions with rifamycins. Nonadherence over the long course of treatment is a problem with oral contraceptives.
 - Other options for birth control include medroxyprogesterone administered by intramuscular injection every 13 weeks or placement of an intrauterine device.
 - All patients are encouraged to use condoms to prevent sexually transmitted disease, but condoms should not be relied upon as the sole method of birth control.

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8 Monitoring of MDR-TB treatment

8.1 Monitoring treatment progress

TB symptoms

- Cough, sputum production, fever, and weight loss generally improve within one to two months of treatment.

Bacteriology

- Most patients who are adherent to an effective regimen will convert cultures to negative by three months of treatment.
- Patients with fewer effective drugs in their treatment regimens (e.g., XDR-TB patients) will convert more slowly.
- Persistently positive cultures beyond month six of treatment are a sign of likely treatment failure.
- Recurrence of positive cultures after culture conversion is a sign of likely treatment failure, especially if it occurs after month six of treatment.

Chest X-ray

- Many chest X-rays will be unchanged or show only slight improvement during MDR-TB treatment, especially in patients with chronic pulmonary lesions.
- Chest X-rays do not need to be taken monthly. Chest X-rays should be taken:
 - At the initiation of treatment as a baseline.
 - As needed during the treatment course (e.g., clinical deterioration or surgical intervention).

Height and weight

- For adults, weight should be recorded monthly.
 - At the beginning of treatment it is necessary for drug dosing.
 - During treatment, weight gain is a sign of clinical improvement. Drug dosing may also need to be adjusted.
- Height for all adults should be taken at the start of treatment and recorded on the treatment card. Without the height, BMI cannot be calculated and nutrition status cannot be assessed.
- For children, weight-for-age and weight-for-height should be plotted for children between 0 and 5 years; BMI should be plotted for all children between 5 and 19 years. A normal growth rate should resume after a few months of successful treatment.

Ask

- How have you been?
- Have you needed urgent medical care? If yes, ask for record/diagnosis.
- Have your TB symptoms improved?
 - Cough? Sputum?
 - Difficult breathing?
 - Fever/night sweats?
 - Weight loss?
- Have you had any adverse effects?
 - Nausea/vomiting?
 - Fatigue?
 - Confusion?
 - Skin rash?
 - Tingling in hands or feet?
 - Difficulty hearing? Ringing of ears?
 - Dizziness?
 - Headache?
 - Seizures? Loss of consciousness?
 - Feeling anxious? Feeling sad or unhappy?
- Have you had any other symptoms, even if you think it is not important or related to treatment?
- What problems have you had taking the medicines? Have you missed any doses? Ask questions in a respectful and non-judgmental way. Pose the questions in a manner that makes it easier for patients to be truthful:
 - “Many patients have trouble taking their medications. What trouble do you have?”
 - “When is it most difficult for you to take the pills? Have you missed any doses?”
 - If the patient has missed doses determine the reason.
- Have you had any problems with your treatment supporter?
- Have you felt discriminated against at the clinic, household, or work because of the disease or its treatment?
- What else do you want to talk about?

8.2 Screening for adverse effects

Screening of adverse effects is an important part of MDR-TB treatment

- Close monitoring of patients is necessary to ensure that adverse effects of second-line drugs are recognized quickly. The ability to monitor patients for adverse effects daily is one of the major advantages of DOT over self-administration of MDR-TB treatment.
- The majority of adverse effects are easy to recognize, and patients will readily explain that they are experiencing them. It is important, however, to have a systematic method of patient interviewing since some patients may be reluctant to report adverse effects, even severe ones. Other patients may be distracted by one adverse effect and forget to tell the health care provider about others.
- Laboratory screening is necessary for detecting certain adverse effects that are occult (not obviously noted by taking the patient's history or through physical examination).
- Some national programs will have pharmacovigilance reporting protocols. Clinicians should comply with these protocols in case of serious adverse effects.

Monitoring renal function

- Nephrotoxicity is a known complication of the injectable drugs, both of the aminoglycosides (kanamycin and amikacin) and of capreomycin. This adverse effect is initially asymptomatic, but it can be fatal.
- Serum creatinine should be checked monthly while the patient is taking an injectable.
- Patients with a history of renal disease (including comorbidities, such as HIV and diabetes), advanced age, or receiving any other potentially nephrotoxic drug should be monitored more closely—weekly at the start of treatment.

Monitoring serum electrolytes

- Electrolyte wasting is a known complication of the injectables, especially capreomycin. It is generally reversible once the injectable drug is suspended.

- Very low potassium or other serum electrolytes can be fatal.
 - Since electrolyte depletion is often asymptomatic in the early stages and can be easily managed with electrolyte replacement, serum potassium should be checked monthly while receiving the injectable.
 - Serum magnesium should also be monitored regularly or if serum potassium is found to be low, since hypomagnesemia is commonly associated with hypokalemia.
- Serum electrolyte monitoring is especially important in patients with pre-existing renal disease (diabetes, HIV) and in all patients taking capreomycin.

Screening for hypothyroidism

- Hypothyroidism is an adverse effect of PAS and/or ethionamide/prothionamide; it is relatively common when both drugs are used.
- Hypothyroidism can be diagnosed in MDR-TB patients by testing the serum level of TSH.
 - An elevated TSH indicates hypothyroidism due to suppression of the thyroid gland.
 - No other thyroid tests (free T_4 , T_3) are necessary for diagnosis or treatment monitoring of hypothyroidism due to anti-TB drug toxicity.
- TSH should be checked at least every six months after starting MDR-TB treatment with PAS or ethionamide/prothionamide. However, patients may develop symptoms as early as a few weeks after starting treatment.
- Hypothyroidism is reversible after the offending drugs are stopped.

Monitoring liver function

- Hepatotoxicity can result from pyrazinamide and PAS, and less commonly with the other second-line drugs. Liver enzymes should be checked for all patients who have symptoms or signs of hepatitis, such as nausea, vomiting, or jaundice. HIV-positive patients taking pyrazinamide should have serum liver enzymes checked monthly.

Screening for hearing loss

- Ototoxicity is commonly observed in patients receiving large cumulative doses of injectables. Concomitant use of furose-

mide, particularly in the setting of renal insufficiency, may exacerbate ototoxic effects of the injectables.

- Where available, audiometry is an excellent way to detect early hearing loss. Audiometry can detect clinically insignificant hearing loss (for example, loss of high frequencies), and treatment is often continued if there is loss only in the high-frequency range.
- It is important for clinicians to ask the patient and those close to the patient about hearing loss at every evaluation. Any hearing loss detectable with this type of screening is guaranteed to be clinically significant.

Screening for psychosis and depression

- Depression can result in thoughts of suicide or suicide attempts.
- Clinicians should assess the psychosocial condition of the patient, including asking, “Are you having thoughts of suicide?” routinely at the monthly visit.
- Screening for some types of cycloserine neurotoxicity such as psychosis, anxiety, or seizures may require interviewing the patient’s family, since the patient may not be aware of these adverse effects.

Pregnancy testing

- All women of childbearing age should have a urine pregnancy test at baseline and whenever the menstrual period is delayed. At every evaluation, all women of childbearing age should be asked about the date of their last menstrual period.
- A reliable method of contraception should be strongly encouraged in all patients receiving MDR-TB treatment. Counseling for male partners should be provided as well.

Screening for myelosuppression

- All patients starting AZT should have a CBC checked before starting AZT, after one month, and every three months thereafter. CBC should also be checked whenever there are any symptoms or signs of anemia.
- All patients starting linezolid should have a CBC checked before starting linezolid, then weekly initially and monthly afterwards. CBC should also be checked if there are any symptoms or signs of myelosuppression.

8.3 Schedule of clinical and laboratory follow-up

Follow-up schedule for uncomplicated MDR-TB patients

Month	Clinical consult	Weight	Smear	Culture	DST	ChestX-ray	LFT	Cr, K	TSH
0 (baseline)	✓	✓	✓	✓	✓	✓	✓	✓	
1	Every two weeks	✓	✓	✓				✓	
2	Every two weeks	✓	✓	✓				✓	
3	Every two weeks	✓	✓	✓				✓	
4	Monthly	✓	✓	✓	If culture pos			✓	
5	Monthly	✓	✓	✓				✓	
6	Monthly	✓	✓	✓	If culture pos			✓	✓
7	Monthly	✓	✓	✓				✓	
8	Monthly	✓	✓	✓	If culture pos			✓	
9	Monthly	✓	✓	✓					If on inj.
10	Monthly	✓	✓	✓	If culture pos				If on inj.
11	Monthly	✓	✓	✓					If on inj.
12	Monthly	✓	✓	✓	If culture pos				If on inj.
Until completion	Monthly		Monthly	Monthly	If culture pos				Every six months

More frequent screening may be advisable for certain types of patients

- Creatinine and potassium may be done weekly in the first month of treatment in the elderly, HIV coinfecting, and those with pre-existing renal disease.
- Liver function tests may be done monthly in patients with liver disease, the HIV coinfecting, and those taking bedaquiline.
- TSH may be done every three months in the HIV coinfecting or those living in geographical areas where hypothyroidism is frequently seen.
- Regular HIV serology testing in high HIV prevalence settings.

Additional screening tests for specific drugs

- AZT: Check a baseline hemoglobin when starting, after one month, and then every three months thereafter.
- Linezolid: Check CBC at baseline and then monthly.
- Gatifloxacin: Check fasting blood sugar at baseline and then monthly.
- Bedaquiline: Check an ECG (QT interval) before initiation of treatment, and then 2, 12, and 24 weeks after starting treatment (more frequently if heart conditions, hypothyroidism, or electrolyte disturbances are present). If QT prolongation is detected, check serum potassium, calcium, and magnesium.
- Ethambutol or linezolid: Use the Ishihara Color Test to test for visual changes (test all patients at baseline, as a certain percentage of people have color blindness as a genetic variation; repeat if there is suspicion of a change in vision).

Less frequent culture monitoring may be acceptable in some settings

- Programs with very limited culture capacity may consider doing smears monthly but may do cultures every other month for the continuation phase.
- Monthly culture monitoring is likely to identify possible treatment failure earlier than less frequent monitoring.

Follow-up after successful completion of MDR-TB treatment

- Check sputum culture at 6 and 12 months after completion date to evaluate for possible recurrence.
- Instruct the patient to return to clinic if cough persists for more than two weeks or persistent fever and weight loss return.

References

- *Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008* (WHO/HTM/STB/2008.402). Geneva: World Health Organization; 2008.
- *Management of MDR-TB: A field guide* (WHO/HTM/TB/2008.402a). Geneva: World Health Organization; 2009.

9 Management of adverse drug effects

9.1 General considerations

- Second-line drugs have more adverse effects than first-line anti-TB drugs. These adverse effects should be managed promptly and aggressively to give the patient the best chance to tolerate the regimen, maintain adherence, and achieve a positive treatment outcome.
- The patient should be educated regarding the potential for adverse drug effects before starting treatment.
 - Review the common adverse effects associated with each prescribed medication in the regimen.
 - Patients should be told to anticipate that most medication adverse effects manifest themselves at the beginning of treatment. They should be reassured that the majority will improve over time.
 - Warning signs of important complications requiring immediate medical attention should be stressed.
 - Patient should also be instructed on how to notify a health care provider if they develop any concerns about their health while on MDR-TB treatment.
- DOT supporters should play a major role in helping the patient deal with side effects. Supporters are crucial in early detection and triage of symptoms and provide psychosocial support while side effects are being controlled. Patient support groups are another means of providing psychosocial support to patients.
- Mild adverse effects are common. They should be managed symptomatically with the ancillary drugs while continuing the treatment regimen. Mild adverse effects may disappear or diminish with time, and patients may be able to continue receiving the drug without interruption.
- The adverse effects of a number of second-line drugs are highly dose-dependent. With cycloserine and ethionamide, for example, a patient may be completely intolerant at one dose and completely tolerant at a slightly lower dose.
 - Reducing the dose should be done only in cases where the reduced dose is still expected to produce adequate serum levels and not compromise the regimen.

- Unfortunately, given the narrow therapeutic margins of these drugs, lowering the dose may also affect efficacy, every effort should be made to maintain an adequate dose of the drug according to body weight.
- Lowering the dose by more than one weight class should be avoided.
- Temporary suspension of medications can also be used if an adverse effect is particularly resistant to dose adjustment. Complete discontinuation of drugs, however, should be avoided if possible. In patients with highly resistant TB, a satisfactory replacement drug may not be available, making the treatment regimen less potent.
- Any decision to suspend a drug must be made while weighing the risk of continued side effects against the benefit of improving the chances of curing a deadly disease.

9.2 Allergy: Anaphylaxis

Possible anti-TB drug causes: Any drug

Possible ART causes: NVP, ABC, EFV, d4T, and others

Suggested management strategy

1. Perform basic life support by maintaining the patient's airway, breathing, and circulation.
2. Administer an epinephrine intramuscular injection to control the allergic reaction.
3. Hospitalize the patient emergently.
4. Suspend all potential offending drugs, including all anti-TB medications. Review the patient's medication list to determine the most likely offending drug.
5. Once the allergic reaction has been controlled and the patient has returned to their usual state of health, reintroduce anti-TB therapy as a partial dose challenge. If a particular drug has been identified as the likely culprit, do not re-challenge with this drug and suspend its use permanently.

Comments

- Anaphylaxis is rare but one of the most severe manifestations of allergic reaction. It develops rapidly after exposure to the offending drug, manifesting as rash, angioedema with airway compromise, gastrointestinal symptoms, and hypotension. Symptoms can progress to respiratory failure and death.
- Anaphylaxis can be caused by any of the anti-TB drugs.
- If any drug is identified to cause anaphylaxis, never use the drug again in the patient. Inform the patient that they can never take the drug again and should also avoid drugs from the same drug class (i.e., if anaphylaxis occurred to levofloxacin, avoid all fluoroquinolones).

9.3 Allergy: Rash

Possible anti-TB drug causes: Any drug

Possible ART causes: NVP, ABC, EFV, d4T, and others

Suggested management strategy

1. Evaluate for signs of severe rash, including involvement of mucous membranes, angioedema, and skin necrosis. For severe rash, stop all therapy pending resolution of reaction. In the case of anaphylaxis, manage with standard emergency protocols.
2. Check liver enzymes, since many rashes can be accompanied by hepatitis.
3. Review the patient's active medications to identify the likely offending drug. Eliminate other potential causes of allergic skin reaction (like scabies or other environmental allergens).
4. Initiate ancillary medications to control symptoms of minor skin reactions, including:
 - Antihistamines.
 - Hydrocortisone cream for localized rash.
 - Prednisone in a low dose of 10 to 20 mg per day for several weeks in refractory cases.
5. Once rash resolves, reintroduce remaining drugs one at a time with the most likely culprit last. Consider not reintroducing in the challenge any drug that is highly likely to be the culprit.
6. Suspend permanently any drug identified to be the cause of a serious reaction.

Comments

- History of previous drug allergies should be carefully reviewed. Any known drug allergies should be noted on the treatment card.
- Drug eruptions can have a variety of manifestations, ranging from mild maculopapular rashes and hives to severe systemic reactions like toxic epidermal necrolysis and Stevens-Johnson syndrome.
- Flushing reaction to rifampicin or pyrazinamide is usually mild and resolves with time. Antihistamines can be used. Hot flashes, itching, and palpitations can be caused by combining isoniazid and tyramine-containing foods (cheese, red

wine). If this occurs, advise patients to avoid foods that precipitate the reaction.

- Dry skin is a common and significant problem with clofazimine. It may cause itching (especially in diabetics), which can be eased with the liberal use of moisturizing lotion.
- NVP can cause a mild to moderate rash that is occasionally severe and accompanied by hepatitis. NVP-related rash usually occurs in the first few weeks after starting NVP, so it is unlikely that a new rash in an MDR-TB patient is due to NVP if the patient has been tolerating this drug previously. Starting NVP at half-dose for the first two weeks decreases the probability of a serious reaction.
- Hypersensitivity to ABC is a rare adverse effect that can sometimes present as an isolated rash, though more often it is part of a syndrome that includes fever and gastrointestinal symptoms (nausea, vomiting, and diarrhea) within the first six weeks. If ABC is substituted with another NRTI and the rash resolves, then ABC hypersensitivity should be considered likely, and ABC should not be rechallenged because this can result in more severe reactions, sometimes life-threatening.
- Cotrimoxazole can also cause skin rash, especially in HIV-positive patients.
- Any drug that is thought to have caused anaphylaxis or Stevens-Johnson syndrome should never be reintroduced to the patient, not even as a challenge.

9.4 Gastrointestinal: Nausea and vomiting

Possible anti-TB drug causes: Pto/Eto, PAS, H, E, Z, Amx/Clv, Cfz, Lzd, Imp/Cln, Bdq

Possible ART causes: RTV, d4T, NVP, and most others

Suggested management strategy

1. Assess for danger signs including dehydration, electrolyte disturbances, and hepatitis. Serum electrolytes and renal function should be checked. Vomit that looks like coffee grounds is a sign of upper gastrointestinal tract bleeding, usually from a stomach ulcer, and should be considered a medical emergency.
2. Patients with dehydration should be treated with oral or intravenous rehydration therapy immediately to correct volume status. Electrolyte disturbances should be corrected.
3. Adjust timing of anti-TB drug dosing (without lowering overall dose or compromising the regimen):
 - Give the Eto/Pto at night.
 - Give Eto twice daily or PAS three times daily.
 - Give PAS two hours after other anti-TB drugs.
 - Give a light snack (biscuits, bread, rice, tea) before the medications.
4. Start antiemetic therapy if nausea and vomiting persist despite adjustments to the dosing schedule. Patients may respond to one antiemetic but not another, even for drugs within the same class. Patients who do not have a satisfactory response to one drug should have a second attempt made with a different drug. Often a daily standing dose (typically 30 minutes before taking anti-TB drugs) is needed.
 - Metoclopramide 10 mg taken 30 minutes before anti-TB drugs (maximum dose is 15 mg twice daily).
 - Ondansetron 8 mg taken 30 minutes before anti-TB drugs, repeated every eight hours (can be used alone or in conjunction with metoclopramide, dose can be increased to 24 mg taken 30 minutes before anti-TB drugs for refractory nausea). Ondansetron is a 5-HT₃ receptor antagonist, the strongest class of anti-emetics.
 - Promethazine 25 mg taken 30 minutes before anti-TB drugs or before meals, up to three times daily (the dose can be increased to promethazine 50 mg three times daily to control symptoms).

- Other anti-emetics include dimenhydrinate, domperidone, promethazine and others.
- 5. Decrease the dose of the offending drug if symptoms are not controlled with antiemetics.
- 6. Alternatively, symptoms can often be controlled by stopping the offending drug for a few days (two to four days) and then adding it back by gradually increasing the dose. Whenever stopping a medicine in this manner, advise the patient the medicine is being stopped temporarily and will be increased back gradually. This often results in better tolerance.
- 7. Permanent discontinuation is rarely necessary but can be considered in extreme cases when all other interventions have failed.

Comments

- Nausea and vomiting are common in early weeks of therapy but usually improve over time and with supportive therapy. Some degree of symptoms may need to be tolerated in the initial period of treatment.
- Symptoms are usually reversible upon discontinuation of the offending drug.
- For patients who are particularly anxious about the nausea, or have anticipatory nausea/vomiting, a small dose of an anti-anxiety medicine (5 mg of diazepam or 0.5 mg of lorazepam) can help 30 minutes prior to the anti-TB drugs. (Warning: Benzodiazepines have the potential for addiction, and it is advised not to use daily standing doses of benzodiazepines for nausea treatment).
- In HIV coinfecting patients, persistent vomiting and abdominal pain may be a result of developing lactic acidosis (especially common with long-term d4T use) and/or hepatitis secondary to medications.
- Nausea and vomiting can also be signs of a new pregnancy or early signs of hepatitis.
- Do not use metoclopramide if neurological problems such as tardive dyskinesia develop (an adverse effect that can develop with the long-term use of metoclopramide).
- Ondansetron can increase the QT interval, and it is recommended to avoid this drug in patients taking medicines that significantly increase the QT interval (moxifloxacin, clofazimine, bedaquiline, and others).

9.5 Gastrointestinal: Gastritis and abdominal pain

Possible anti-TB drug causes: PAS, Pto/Eto, Cfz, fluoroquinolones, H, E, and Z

Possible ART causes: Most ARVs have been associated with abdominal pain

Suggested management strategy

1. Initiate symptomatic management with the use of H₂ blockers (ranitidine 150 mg twice daily or 300 mg once daily) or proton-pump inhibitors (omeprazole 20 mg once daily).
2. Decrease the dose of the offending drug if symptoms are not controlled with H₂ blockers or proton pump inhibitors.
3. For severe abdominal pain, stop suspected drug for short periods of time (one to seven days). Discontinue suspected drug permanently if this can be done without compromising regimen.

Comments

- Gastritis is a common side effect of MDR-TB treatment, especially in patients who have received multiple previous treatments.
 - Symptoms associated with gastritis include bloating, nausea, epigastric burning or discomfort, and a sour taste in the mouth. Symptoms are often exacerbated in the morning or prior to eating.
 - Severe gastritis or gastric ulceration as manifested by severe postprandial pain or blood in the vomit or stool is relatively rare.
- Abdominal pain can also be associated with serious adverse effects, such as pancreatitis, lactic acidosis, and hepatitis.
- Gastritis is so common that some clinicians may choose to start prophylactic H₂ blockers or proton pump inhibitors at the beginning of MDR-TB treatment.
- Avoid the use of antacids as they decrease absorption of fluoroquinolones. If antacids must be used, they should be administered two hours before or three hours after MDR-TB drugs so as to not interfere with the absorption of the fluoroquinolones.
- Consider other possible causes of gastritis and abdominal pain.

- Stop any nonsteroidal anti-inflammatory drugs (e.g., ibuprofen) that the patient may be taking.
- Diagnose and treat *Helicobacter pylori* infections.
- Severe abdominal distress and acute abdomen have been reported with the use of clofazimine. Although these reports are rare, if this effect occurs, clofazimine should be suspended.
- In HIV coinfecting patients, abdominal pain is a common adverse effect and often related to ART. Abdominal pain, however, may also be an early symptom of severe adverse effects, such as pancreatitis, hepatitis, or lactic acidosis (especially common with long-term d4T use).

9.6 Gastrointestinal: Diarrhea

Possible anti-TB drug causes: PAS, Eto/Pto, fluoroquinolones, Amx/Clv

Possible ART causes: All protease inhibitors, didanosine (ddI; buffered formulation)

Suggested management strategy

1. Assess for danger signs including dehydration and electrolyte disturbances (especially hypokalemia) if diarrhea is severe. Fever or blood in the stools indicates the diarrhea may be secondary to something other than an adverse effect of the anti-TB drugs.
2. Consider other causes of diarrhea:
 - *Clostridium difficile* infection can develop in the setting of broad-spectrum antibiotics such as the fluoroquinolones. Infection can progress to colitis, which can be life-threatening. Fever, bloody diarrhea, intense abdominal pain, and increased white blood cells are danger signs of possible pseudomembranous colitis.
 - Other endemic water-borne bacterial and parasitic infections.
 - Lactose intolerance is common, especially if patient has been exposed in a hospital to new foods not normally part of their diet.
3. Encourage fluid intake.
4. Treat uncomplicated diarrhea (no blood in stool and no fever) with loperamide 4 mg by mouth initially followed by 2 mg after each loose stool to a maximum of 10 mg per 24 hours.

Comments

- Loose stools are common in the initial phase of MDR-TB therapy. Mild symptoms may need to be tolerated by the patient during this period.
- Loperamide can be used in children over 2 years.

9.7 Gastrointestinal: Hepatitis

Possible anti-TB drug causes: Z, H, R, Pto/Eto, PAS

Possible ART causes: NVP, EFV, all protease inhibitors (RTV > others), all NRTIs

Suggested management strategy

1. If enzymes are more than five times the upper limit of normal, stop all anti-TB drugs and any other hepatotoxic drugs.
2. Evaluate and treat other potential causes of hepatitis.
 - Check serology for hepatitis A virus, hepatitis B virus, hepatitis C virus, and cytomegalovirus.
 - Alcohol use should be investigated and alcoholism addressed if found.
3. Reintroduce anti-TB drugs once liver enzymes return to baseline. Anti-TB drugs should be reintroduced in serial fashion by adding a new medicine every three to four days. The least hepatotoxic drugs should be added first, while monitoring liver function tests after each new exposure.
4. Consider suspending the most likely offending drug permanently if it is not essential to the regimen. This is often the case for pyrazinamide if it is less likely to be effective by clinical history.

Comments

- Mild elevation of liver enzymes, especially at baseline, may be related to TB rather than an adverse effect of treatment.
- Hepatitis is characterized by nausea, vomiting, jaundice, scleral icterus, tea-colored urine, pale stool, and diminished appetite in the setting of elevated liver function tests.
- Generally, hepatitis due to medications resolves upon discontinuation of suspected drug.
- Any history of hepatitis should be carefully analyzed to determine most likely causative drugs; these drugs should be avoided when designing a treatment regimen.
- In HIV coinfection, cotrimoxazole can be a cause of hepatotoxicity.
- NVP hepatotoxicity usually occurs shortly after exposure, accompanied by flu-like symptoms with or without rash. It can also happen late as an isolated hepatitis without constitutional symptoms. Patients who experience NVP hepatotoxicity should not be rechallenged.

9.8 Gastrointestinal: Pancreatitis

Possible anti-TB drug causes: Rare reports with Lzd, H

Possible ART causes: d4T, ddI

Suggested management strategy

1. Assess the severity of the pancreatitis. Check liver function tests, amylase, lipase, and CBC.
2. Permanently discontinue the offending drug.
3. Consider gallstones or excessive alcohol use as other potential causes of pancreatitis.

Comments

- Drug pancreatitis is a severe side effect and can be life-threatening. A full description of management is outside the purview of this guide.
- Pancreatitis is more commonly associated with ART than MDR-TB therapy.
- Common clinical manifestations include epigastric abdominal pain, nausea, vomiting, and fever.
- Do not use any of the potentially pancreatitis-producing ARVs (d4T or ddI) in patients with a history of pancreatitis.

9.9 Musculoskeletal: Arthralgias

Possible anti-TB drug causes: Z, fluoroquinolones, Eto/Pto, Bdq

Possible ART causes: ABC

Suggested management strategy

1. If acute swelling, redness, and warmth are present in a joint, consider aspiration for diagnosis (for example, gout, infection, and autoimmune disease).
2. Initiate therapy with nonsteroidal anti-inflammatory drugs: Indomethacin 50 mg twice daily or ibuprofen 400 to 800 mg three times a day.
3. Lower dose of suspected drug (most commonly pyrazinamide) if this can be done without compromising regimen.
4. Discontinue suspected drug if this can be done without compromising regimen.

Comments

- Arthralgias, arthritis, and myalgias are transient symptoms most commonly encountered in the early months of MDR-TB therapy.
- Symptoms generally diminish over time without intervention.
- Uric acid levels may be elevated in patients on pyrazinamide. There is little evidence to support the addition of allopurinol for arthralgias, although if gout is present it should be used.

9.10 Musculoskeletal: Tendonitis and tendon rupture

Possible anti-TB drug causes: Fluoroquinolones

Possible ART causes: None

Suggested management strategy

1. If significant inflammation of tendons or tendon sheaths occurs:
 - Consider stopping the fluoroquinolone.
 - Initiate a nonsteroidal anti-inflammatory drug (ibuprofen 400 mg four times daily).
 - Rest the joint.
2. If treatment failure is likely without the fluoroquinolone:
 - Reduce the dose if possible.
 - Maintain strict rest of the joint.
 - Inform patient of the possible risk of tendon rupture and discuss the risks and benefits of continuing the fluoroquinolone.

Comments

- Joint pain and swelling occur commonly in people taking fluoroquinolones.
- Symptoms usually improve after stopping fluoroquinolones.
- Tendon rupture with fluoroquinolone use is more likely in patients doing new physical activities and more common in older patients and diabetics. Tendon rupture is relatively rare.

9.11 Renal: Electrolyte abnormalities

Possible anti-TB drug causes: Cm, Km, Am, S

Possible ART causes: TDF (rare)

Suggested management strategy

1. Monitor serum potassium, magnesium, and calcium frequently in patients with vomiting/diarrhea and patients receiving injectables.
 - Hypokalemia is defined as serum potassium < 3.5 mEq/L.
 - Severe hypokalemia is < 2.0 mEq/L, or symptomatic hypokalemia.
 - Hypomagnesemia is defined as serum magnesium < 1.5 mEq/L.
2. Hospitalization is necessary in severe cases of hypokalemia.
3. Check for signs of dehydration in patients with vomiting and diarrhea. Start oral or intravenous rehydration therapy immediately until volume status is normal.
4. Replete potassium and magnesium; see tables for guidance.
 - Hypokalemia may be refractory if concurrent hypomagnesemia is not also corrected.
 - If unable to check serum magnesium, give empiric oral replacement therapy in all cases of hypokalemia with magnesium gluconate 1000 mg twice daily.
5. Check an electrocardiogram in patients with significant serum electrolyte disturbances. Drugs that prolong the QT interval should be discontinued in patients with evidence of QT interval prolongation.
6. Electrolyte abnormalities are reversible upon discontinuation of the injectable. Even after suspending the injectable, it may take weeks or months for this syndrome to disappear, so electrolyte replacement therapy should continue for several months after completion of the injectable phase of MDR-TB treatment.

Comments

- Hypokalemia and hypomagnesemia are often asymptomatic.
 - Moderate cases may present with fatigue, myalgias, cramps, paresthesias, lower extremity weakness, behavior or mood changes, somnolence, and confusion.
 - Severe disturbances can lead to tetany, paralysis, and life-threatening cardiac arrhythmias.

- Hypokalemia and hypomagnesemia are common in patients receiving MDR-TB treatment. Common causes in MDR-TB patients are:
 - Vomiting and diarrhea.
 - Renal tubular toxicity from the injectable (probably more common in capreomycin than the aminoglycosides).
 - ♦ The injectables can cause a syndrome of electrolyte wasting, including potassium, magnesium, calcium, and bicarbonate.
 - ♦ This syndrome is more common and severe in HIV coinfecting patients; hospitalization and aggressive serum electrolyte monitoring and correction may be necessary.
- Formulations of oral potassium chloride vary by manufacturer and country. Slow-release versions are common in resource-limited settings. The amount of potassium is often different than the tablet size. For example, one 200-mg tablet of Slow-K contains 8 mEq of potassium.
 - Oral potassium and magnesium should be administered either two hours before or four to six hours after fluoroquinolones as they can interfere with fluoroquinolone absorption.
 - Oral potassium can cause nausea and vomiting. Oral magnesium can cause diarrhea.
- Dietary intake of potassium should be encouraged. Bananas, oranges, tomatoes, and grapefruit juice are good sources of supplementation.
- Amiloride 5 to 10 mg PO daily or spironolactone 25 mg PO daily may decrease potassium and magnesium wasting due to the injectable and may be useful in severe cases that are refractory to replacement therapy.

Potassium replacement therapy

Potassium level	Dosing	Monitoring frequency
4.0 or more	None	Monthly
3.6-4.0	None	Monthly
3.3-3.5	40 mEq PO daily	Monthly
2.9-3.2	60-80 mEq PO daily	Weekly
2.7-2.8	60 mEq PO three times a day	One to two days
2.4 -2.6	80 mEq PO every eight hours	Daily
< 2.4	10 mEq/hr IV and 80 mEq PO every six to eight hours	One hour after infusion, every six hours with IV replacement

Note: The normal preparation of a potassium chloride infusion is 40 mEq in 200 mL of normal saline. Do not exceed an infusion rate of 20 mEq/hr (100 mL/hr).

Magnesium replacement therapy

Magnesium level	Total daily dose	Monitoring frequency
2.0 or more	None	Monthly
1.5-1.9	1,000 mg-1,200 mg	Monthly
1.0-1.4	2,000 mg	One to seven days
< 1.0	3,000 mg-6,000 mg	Daily

Note: Quantities greater than 2,000 mg are usually given IV or IM. The normal preparation is magnesium sulfate 2 g in 100 mL or 4 g in 250 mL of 5 percent dextrose or normal saline. Do not exceed an infusion rate of 150 mg/min (2 g in 100 mL administered over one to two hours, 4 g in 250 mL administered over two to four hours).

Calcium replacement therapy

Calcium level (total nonionized calcium value adjusted for low albumin)	Dosing	Monitoring frequency
> 8.5 mg/dL (> 4.2 mEq/L)	None	
7.5–8.4	500 mg three times a day	Monthly
7.0–7.4	1,000 mg three times a day	One to two weeks
< 7.0	Consider IV and taper to 1,000 mg three times a day	One to four days

Note: Normal calcium is 8.5 to 10.3 mg/dL (2.12 to 2.57 mmol/L). To adjust for low albumin in nonionized values of calcium, use this formula: Corrected calcium = $0.8 \times (4.0 - \text{measured albumin}) + \text{reported calcium}$. If ionized calcium is being tested, it does not need to be adjusted for low albumin and normal value is 4.5 to 5.6 mg/dL (1.11 to 1.30 mmol/L).

Notes on commonly used units in dosing of electrolyte supplements

- Milligram (mg): Refers to the mass of the dose.
 - Often used with the word “elemental”. For example, “98 mg of elemental magnesium” is the amount of magnesium in 1 gram of MgSO_4 .
- Millimole (mmol): Refers to the number of atoms in the dose.
 - For chemical purposes, the number of atoms is usually more important than the mass of those atoms.
 - $\text{mg} = \text{mmol} \times \text{atomic weight}$.
 - ♦ Potassium = 39.1 mg/mmol.
 - ♦ Calcium = 40.1 mg/mmol.
 - ♦ Magnesium = 24.3 mg/mmol.
- Milliequivalent (mEq): Refers to the chemical combining power, which is related to the valence of the element.
 - $\text{mEq} = \text{mmol} \times \text{valence}$.
 - ♦ Valence of potassium is 1; calcium and magnesium is 2.
- For example, 1 mmol of magnesium = 2 mEq = 24.3 mg elemental magnesium.

9.12 Renal: Nephrotoxicity (acute renal failure)

Possible anti-TB drug causes: S, Km, Am, Cm

Possible ART causes: TDF (rare)

Suggested management strategy

1. Monitor serum creatinine and electrolytes frequently in patients receiving injectables. Patients with pre-existing kidney disease, diabetes, or HIV are at high risk of injectable nephrotoxicity and may be monitored more frequently. See Section 8.3.
 - Any increase of serum creatinine above normal limits should be considered acute renal insufficiency.
 - A doubling of serum creatinine above baseline, even if within normal limits, should be considered worrisome for acute renal insufficiency and monitored carefully.
2. Repeat electrolytes if necessary.
 - Injectable nephrotoxicity may be associated with injectable-induced electrolyte wasting. For example, it is possible to see elevated creatinine and severe hypokalemia/hypomagnesemia at the same time.
 - The etiology of this phenomenon is unclear, but it may occur more often in HIV coinfecting patients.
3. Discontinue the suspected drug (usually the injectable). If the acute renal failure is severe, then stop all drugs.
 - Nephrotoxicity due to the injectable is frequently reversible after the injectable is stopped, but permanent damage can result if it is not detected early.
 - If the acute renal insufficiency is severe or resolving slowly, the dose of other renally excreted drugs should be adjusted.
4. Consider other contributing etiologies (prerenal, intrinsic renal, and postrenal).
5. Follow serum creatinine and electrolytes closely until the creatinine has returned to baseline or has stabilized.
6. Consider reintroducing the injectable with an intermittent dosing schedule (two or three times a week) if the drug is essential to the regimen.
 - Consider using capreomycin if an aminoglycoside had been the prior injectable in regimen.
 - Consider strict weight-based dosing of the injectable if the patient's weight is less than 50 kg.

- Suspend the injectable permanently if the nephrotoxicity recurs despite intermittent dosing.

Comments

- The injectables (aminoglycosides and capreomycin) are the most common cause of acute renal failure in MDR-TB patients.
 - Capreomycin may be less nephrotoxic than the aminoglycosides.
- Injectable nephrotoxicity is often asymptomatic in the early stages and can only be diagnosed with routine laboratory monitoring. End-stage renal failure may present with oliguria/anuria or signs of volume overload including peripheral edema and shortness of breath. Mental status changes due to uremia or electrolyte abnormalities are a late symptom.
- Other common causes of acute renal failure:
 - Prerenal etiologies include hypovolemia due to dehydration from vomiting or diarrhea as a side effect of anti-TB therapy. Hypotensive shock in critically ill patients can also cause prerenal physiology.
 - Etiologies intrinsic to the kidney include acute tubular necrosis due to aminoglycosides and capreomycin or acute interstitial nephritis from other antibiotics like beta-lactams and sulfa drugs.
- TDF may cause renal injury with the characteristic features of Fanconi syndrome: Hypophosphatemia, hypouricemia, proteinuria, normoglycemic glycosuria and, in some cases, acute renal failure.
 - Even without the concurrent use of TDF, HIV-infected patients have an increased risk of renal toxicity secondary to aminoglycosides and capreomycin. Frequent creatinine and electrolyte monitoring is recommended.
 - Avoid TDF in patients receiving aminoglycosides or capreomycin. If TDF is absolutely necessary, serum creatinine and electrolytes should be monitored frequently (weekly at the start of treatment).

9.13 Neurological: Ototoxicity (hearing loss or vestibulopathy)

Possible anti-TB drug causes: S, Km, Am, Cm, Clr

Possible ART causes: TDF (rare)

Suggested management strategy

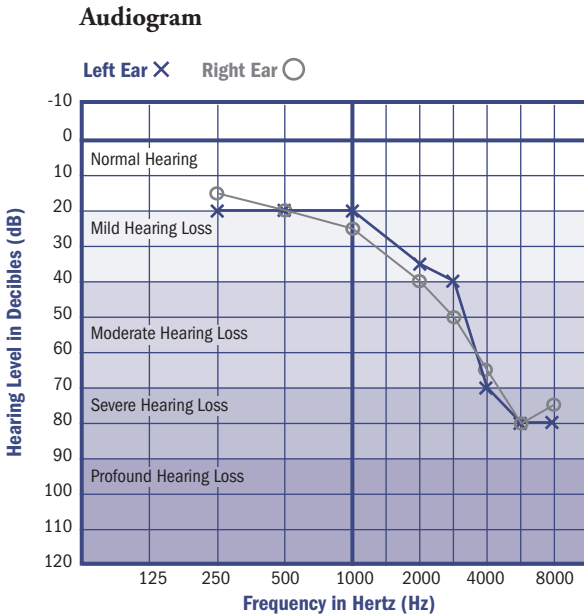
1. Perform a monthly assessment of hearing loss and balance. Audiometry may be helpful if it is available and the hearing loss is mild.
2. If the patient is experiencing clinically significant ototoxicity, decrease the dosing frequency of the injectable to two to three times a week. Consider switching to capreomycin.
3. Stop the injectable if symptoms worsen despite dose adjustment, and additional drugs are available to reinforce the regimen.
 - Even when additional drugs are not available, stopping the injectable agent can be considered based on the patient's desire to maintain hearing.
 - Ototoxicity is one of the few adverse effects that can be permanent and may necessitate discontinuation of a class of agents.

Comments

- Ototoxicity refers to damage of the hearing apparatus of the inner ear, including the cochlea, vestibule, semicircular canals, and cranial nerve VIII.
- Symptoms include hearing loss and tinnitus, as well as vestibular symptoms such as disequilibrium and vision problems.
- Ototoxicity is commonly observed in patients receiving large cumulative doses of injectable agents. Capreomycin may be less ototoxic than the aminoglycosides.
- Some degree of hearing loss occurs with most patients taking an injectable, but high-frequency loss may not significantly affect the patient's quality of life.
- Patients with previous exposure to aminoglycosides may have already sustained a degree of hearing loss. These patients are at the highest risk of incurring further ototoxicity. In such patients, audiometry may be helpful in guiding therapy to prevent further damage.

- Concomitant use of furosemide, particularly in the setting of renal insufficiency, may exacerbate ototoxic effects of the injectables.
- Hearing loss and vestibular dysfunction are generally not reversible upon discontinuation of therapy.
- Mild disequilibrium can also be caused by cycloserine, fluoroquinolones, ethionamide/prothionamide, isoniazid, or linezolid. Stopping all anti-TB drugs for several days can help to distinguish the cause of disequilibrium.
- Some patients may choose to tolerate significant hearing loss to achieve a higher chance of cure. This should be discussed between the patient and a physician trained in MDR-TB. Continuing the injectable in such situations almost always results in permanent hearing loss and sometimes complete deafness.
- Substitution with newer agents such as bedaquiline when signs of auditory or vestibular toxicity appear has little experience to date but may prove to be a useful strategy.
- The benefit of hearing aids is minimal to moderate in overcoming auditory toxicity but may be helpful in some patients.

Example of an audiogram showing high-frequency hearing loss due to aminoglycosides



Source: Auditory Neuroscience: Making sense of Sound. Accessed June 2013 http://auditoryneuroscience.com/acoustics/clinical_audiograms

Notes on audiogram

- This audiogram represents high-frequency hearing loss, which is often the first sign of auditory toxicity due to injectable agents.
- The patient with this audiogram could still hear conversations. Frequencies around 2,000 Hz are the most important for understanding conversations, and the patient has only moderate hearing loss in this area.
- Often patients do not notice hearing loss above 4,000 Hz.
- An audiogram that demonstrates hearing as illustrated above is a good example of a situation where suspending (or substituting) a different anti-TB drug is indicated; this can prevent further loss of hearing.

9.14 Neurological: Peripheral neuropathy

Possible anti-TB drug causes: Cs, Lzd, H, S, Km, Cm, H, fluoroquinolones, Pto/Eto, E

Possible ART causes: d4T, ddI

Suggested management strategy

1. Assess other potential causes of neuropathy (diabetes mellitus, HIV, alcohol use, hypothyroidism, other drugs, and vitamin deficiencies). Correct any vitamin or nutritional deficiencies.
2. Increase pyridoxine to the maximum daily dose of 200 mg per day.
3. Consider lowering the dose of likely offending drugs, if possible without compromising the regimen. Switching from an aminoglycoside to capreomycin may also be helpful.
4. Nonsteroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms.
5. Tricyclic antidepressants have also been used successfully. Start amitriptyline 25 mg at bedtime. The dose may be increased to a maximum of 150 mg daily for refractory symptoms. Do not use tricyclic antidepressants with selective serotonin reuptake inhibitors.
6. Gabapentin may also be effective in relieving pain and other symptoms of peripheral neuropathy.

Comments

- Peripheral neuropathy is a common side effect of MDR-TB treatment caused by drug toxicity to the nerves of the peripheral nervous system.
- Diagnosis is usually clinical. Nerve conduction studies are the gold standard.
- Symptoms first manifest in the lower extremities. Sensory disturbances like numbness, tingling, burning, pain, and loss of temperature sensation are common. More severe manifestations include decreased deep tendon reflexes, weakness, and gait instability.
- Patients taking isoniazid, cycloserine, or linezolid should receive prophylactic pyridoxine.

- Patients with comorbidities (e.g., diabetes, HIV, alcohol dependence) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of second-line anti-TB drugs.
- Neuropathy may be irreversible, but many patients experience improvement when offending drugs are suspended.
- The neuropathy associated with linezolid is common after prolonged use and often permanent. For this reason, suspension of this drug should be considered when neuropathy develops.
- In HIV coinfecting patients, avoid use of d4T or ddI in combination with cycloserine or linezolid because of an increased risk of peripheral neuropathy.

9.15 Neurological: Depression

Possible anti-TB drug causes: Cs, fluoroquinolones, H, Eto/Pto

Possible ART causes: EFV

Suggested management strategy

1. Assess the degree of depression. Question the patient regarding suicidal ideation.
 - If patient has suicidal ideation, cycloserine should be suspended immediately. The patient should be hospitalized and placed under 24-hour safety surveillance until the risk of suicide has passed. Psychiatric consultation should be sought for assistance with management.
2. Assess patients for other potential causes of depression including hypothyroidism and substance abuse. Refer to treatment if appropriate.
3. Assess and address underlying psychosocial stressors.
4. Initiate individual psychotherapy (or group counselling if the patient is smear- and culture-negative).
5. Initiate antidepressant therapy with amitriptyline, fluoxetine, or a similar drug when depression is moderate to severe or symptoms are refractory to psychotherapy. Tricyclic antidepressants and selective serotonin reuptake inhibitors should not be given together and should not be given to patients on linezolid.
6. Lower the dose of the suspected offending drug if this can be done without compromising the regimen.
 - The dose of cycloserine is commonly lowered to 500 mg daily in an attempt to reduce depressive symptoms.
7. In rare situations, the suspected offending drug may need to be discontinued due to extreme refractory symptoms.

Comments

- Depression is a mood state that causes a persistent feeling of sadness. Other symptoms include loss of interest in previously enjoyed activities, lack of energy, psychomotor retardation, appetite and sleep disturbances, feelings of guilt, helplessness or hopelessness, inability to concentrate, and suicidal ideation.
- Depression is common in patients with MDR-TB due to underlying psychosocial stressors, chronic disease, stigma, and anti-TB medications.

- Socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression. Depression may fluctuate during therapy and may improve as illness is successfully treated.
- History of previous depression is not a contraindication to the use of the drugs listed but may increase the likelihood of depression developing during treatment. If significant depression is present at the start of treatment, avoid a regimen with cycloserine if possible.
- EFV is associated with depression. Consider substitution if severe depression develops.

9.16 Neurological: Headache

Possible anti-TB drug causes: Cs, Bdq

Possible ART causes: AZT, EFV

Suggested management strategy

1. Rule out more serious causes of headache including bacterial meningitis, cryptococcal meningitis, and other infections of the central nervous system.
 - HIV coinfecting patients should receive a head CT scan and cerebrospinal fluid analysis.
2. Start analgesics like ibuprofen or paracetamol. Also encourage good hydration.
3. Consider low-dose tricyclic antidepressants for refractory headaches.

Comments

- Headaches are common during the initial months of MDR-TB therapy. They can present as migraine or cluster headaches.
- In order to minimize headaches at the start of therapy, cycloserine is often started at lower doses of 250 to 500 mg and gradually increased over one to two weeks to achieve the target dose.
- Headaches due to cycloserine, AZT, and EFV are usually self-limited.
- Pyridoxine (vitamin B6) should be given to all patients receiving cycloserine to help prevent neurotoxicity. The recommended dose is 50 mg for every 250 mg of cycloserine prescribed.

9.17 Neurological: Psychosis

Possible anti-TB drug causes: Cs, H, fluoroquinolones, Eto/Pto

Possible ART causes: EFV

Suggested management strategy

1. Evaluate potential causes of psychosis including anti-TB drugs, psychosocial stressors, depression, hypothyroidism, other medications, and illicit drug and alcohol use.
2. Check serum creatinine in patients with new-onset psychosis to rule out a decrease in renal function as a cause for high blood levels of cycloserine and resulting psychosis.
3. Stop cycloserine while psychotic symptoms are brought under control.
4. Initiate antipsychotic therapy with haloperidol 0.5 to 5.0 mg twice daily or risperidone 0.5 to 5.0 mg twice daily if moderate to severe symptoms of psychosis are present. Hospitalize the patient in a ward with psychiatric expertise if there is a risk to the patient or others.
5. Increase pyridoxine to maximum daily dose (200 mg per day).
6. Once psychosis has resolved, reinstitute cycloserine at a lower dose if this can be done without compromising the regimen.
 - The most common approach is to restart cycloserine at 500 mg daily.
 - If cycloserine is continued at a lower dose, antipsychotic therapy may need to be continued while the patient remains on the medication.
7. In situations with recurrent or refractory symptoms, cycloserine may need to be discontinued if this can be done without compromising the regimen.
8. Once all symptoms resolve and patient is off cycloserine, antipsychotic therapy can be tapered.

Comments

- Psychosis refers to a constellation of symptoms that reflect a disintegration of personality or a loss of contact with reality. Visual or auditory hallucinations, paranoia, catatonia, delusions, and bizarre behavior are hallmarks of the syndrome.
- Psychosis is most commonly associated with cycloserine, but other anti-TB drugs have also been implicated.

- Previous history of psychiatric disease is not a contraindication to cycloserine, but it may increase the likelihood of psychotic symptoms.
- Some patients will need to continue antipsychotic treatment throughout MDR-TB therapy. Attempts to taper antipsychotics should be done with a psychiatrist trained in the adverse effects of second-line anti-TB drugs.
- Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending drug.
- Pyridoxine (vitamin B6) should be given to all patients receiving cycloserine to help prevent neurotoxicity. The recommended dose is 50 mg for every 250 mg of cycloserine prescribed.
- EFV has a high rate of CNS adverse effects (dizziness, impaired concentration, depersonalization, abnormal dreams, insomnia, and confusion) in the first two to three weeks of use but typically resolve on their own. Frank psychosis is rare with EFV alone. At present, there are limited data on the use of EFV with cycloserine; concurrent use is accepted practice as long as there is frequent monitoring for CNS toxicity.

9.18 Neurological: Seizures

Possible anti-TB drug causes: Cs, H, fluoroquinolones

Suggested management strategy

1. Evaluate possible causes of seizure including anti-TB medications, infection, hypoglycemia, electrolyte abnormalities, hypoxia, alcohol withdrawal, other drugs, uremia, and hepatic failure.
 - Check serum electrolytes including potassium, sodium, bicarbonate, calcium, magnesium, and chloride.
 - Check serum creatinine in patients with new-onset seizures to rule out a decrease in renal function as a cause for high blood levels of cycloserine and resulting seizure.
2. Hold cycloserine, fluoroquinolones, and isoniazid pending resolution of seizures.
3. Initiate anticonvulsant therapy (carbamazepine, phenytoin, or valproic acid is most commonly used).
 - Phenytoin: Load 10 to 20 mg/kg (1,000 mg in typical adult) IV, no faster than 50 mg/min. Oral load: 400 mg initially, then 300 mg in 2 hours and 4 hours. Maintenance: 5 mg/kg or 100 mg PO three times a day.
 - Carbamazepine: 200 to 400 mg PO twice or four times a day.
 - Valproic acid: Start 15 mg/kg PO daily or in two daily divided doses, maximum 60 mg/kg daily.
 - All of the above have significant drug-drug interactions with ART and many other drugs.
4. Increase pyridoxine to maximum daily dose (200 mg per day).
5. When seizures have resolved, restart medications one at a time. Cycloserine should not be restarted unless it is absolutely essential to the regimen. If cycloserine is reinitiated, start at a dose one weight band lower.

Comments

- A seizure is an abnormal, paroxysmal, electrical activity of the brain. It can manifest as tonic-clonic movements, convulsions, or altered mental status. Presentation may include a preceding aura, loss of consciousness, bowel-bladder incontinence, and a postictal state of confusion or somnolence.

- Anticonvulsants are generally continued until MDR-TB treatment is completed or until the suspected drug is discontinued.
- Patients with history of previous seizures may be at increased risk for development of seizures during MDR-TB therapy. Cycloserine should be avoided in these patients if possible without compromising the regimen.

9.19 Neurological: Optic neuritis

Possible anti-TB drug causes: E, Eto/Pto, Lzd, Cfz, rifabutin, H, S

Possible ART causes: dDI

Suggested management strategy

1. Screen patients monthly for signs of optic neuritis.
2. Stop ethambutol immediately in patients with optic neuritis. Do not restart the medication.
3. Refer patient to an ophthalmologist for further evaluation and management.

Comments

- Optic neuritis is inflammation of the optic nerve resulting in vision loss.
- It is most commonly caused by ethambutol. Symptoms of ethambutol-induced optic neuritis also include central scotomas and loss of red-green color vision.
- Optic neuritis generally improves following cessation of offending drug, if it can be stopped early enough.
- Patients with diabetes are at increased risk for optic neuritis. They should be managed with tight glucose control as a means of prevention.
- Patients with advanced kidney disease are also at increased risk for optic neuritis.

9.20 Neurological: Dysgeusia (metallic taste)

Possible anti-TB drug causes: Eto/Pto, Clr, fluoroquinolones

Suggested management strategy

1. Encourage the patient to tolerate this side effect.
2. Sucking hard candy or chewing gum can be helpful in disguising the metallic taste.

Comments

- Dysgeusia is a change in the perception of taste.
- Patients taking certain anti-TB drugs like ethionamide/prothionamide often report a metallic taste.
- Normal taste returns when treatment is stopped.

9.21 Endocrine: Hypothyroidism

Possible anti-TB drug causes: Eto/Pto, PAS

Possible ART causes: d4T

Suggested management strategy

1. TSH levels should be checked every six months after starting MDR-TB treatment with ethionamide/prothionamide or PAS.
2. In patients with hypothyroidism, most adults will require 100 to 150 mcg of levothyroxine daily.
 - Young healthy adults can be started on 75 to 100 mcg daily.
 - Older patients should begin treatment with 50 mcg daily.
 - Patients with significant cardiovascular disease should start at 25 mcg daily.
3. Monitor TSH every one to two months and increase dose by 25 to 50 mcg until TSH is in normal range. Adjust dose more slowly in the elderly and patients with cardiac conditions.
4. Hypothyroidism is reversible upon discontinuation of ethionamide/prothionamide or PAS. As a result, thyroid hormone replacement may be stopped several months after completion of MDR-TB treatment.

Comments

- Ethionamide (or prothionamide) and PAS have a direct toxic effect on the thyroid that interferes with thyroid hormone synthesis. The exact incidence of hypothyroidism is unknown, but it is probably more common than traditionally thought.
- Patients may develop symptoms as soon as a few weeks after exposure to offending medications.
- Symptoms of hypothyroidism include fatigue, somnolence, cold intolerance, dry skin, coarse hair, and constipation, as well as depression and inability to concentrate. Thyromegaly and delayed deep tendon reflexes may be encountered on exam.
- In primary hypothyroidism, the diagnosis is confirmed by a serum level of TSH greater than 10.0 mU/L, indicating suppression of the thyroid hormone production by the thyroid

gland. No other thyroid tests (e.g., free T_4 , T_3) are necessary for diagnosis or treatment monitoring.

- Children clear thyroxine faster than adults, so daily replacement doses may be higher.
 - Children (4-15 years): 4 mcg/kg/day (maximum dose is 200 mcg).
 - Infants (1-3 years): 10-15 mcg/kg/day (maximum dose is 200 mcg).
- In HIV coinfecting patients there is some evidence that sub-clinical hypothyroidism may be associated with some ARVs, particularly d4T.

9.22 Endocrine: Gynecomastia

Possible anti-TB drug causes: Eto/Pto

Possible ART causes: EFV

Suggested management strategy

- Encourage patients to tolerate this side effect.

Comments

- Gynecomastia, or an abnormal enlargement of breast tissue, is caused by ethionamide and prothionamide. It has also been reported with EFV. Galactorrhea has also been reported.
- Resolution occurs after treatment is stopped.

9.23 Endocrine:Alopecia

Possible anti-TB drug causes: H, Eto/Pto

Suggested management strategy

- Encourage patients to tolerate this side effect.

Comments

- Hair loss or significant thinning of the hair can occur as a result of anti-TB therapy.
- Hair loss is temporary and resolves following treatment. Significant cosmetic change has not been reported.

9.24 Endocrine: Dysglycemia and hyperglycemia

Possible anti-TB drug causes: Gfx, Eto/Pto

Possible ART causes: PIs

Suggested management strategy

1. Stop gatifloxacin and replace with a different fluoroquinolone like moxifloxacin.
2. Treat diabetes as needed. Good glucose control is important during treatment.

Comments

- Gatifloxacin is a fluoroquinolone that causes dysglycemia—hypoglycemia and hyperglycemia. It is not recommended for routine use in the treatment of MDR-TB until more data on its safety is available. It has generally been pulled from the market by its manufacturers due to safer alternatives for the diseases for which the drug was registered, but still may be available in some locations.
- Ethionamide/prothionamide tends to make insulin control in diabetics more difficult, and can result in hypoglycemia and poor glucose regulation.
- PIs tend to cause insulin resistance and hyperglycemia.

9.25 Endocrine: Lipodystrophy

Possible anti-TB drug causes: None

Possible ART causes: NRTIs (especially d4T and ddI), PIs

Suggested management strategy

1. Assess fat distribution prior to starting treatment by measuring arm, thigh, waist, hip, and neck circumference, then periodically while on ART.
2. Consider switching PIs to an NNRTI to decrease further fat redistribution.

Comments

- Signs of lipodystrophy include fat accumulation at the base of the neck and shoulders, abdomen, and breasts, as well as fat loss at the face, arms and legs, and buttocks.
- The combination of NRTIs and PIs is most strongly associated with lipodystrophy. The length of exposure to these drugs is directly proportional to the chance of developing lipodystrophy.

9.26 Endocrine: Hyperlipidemia

Possible anti-TB drug causes: None

Possible ART causes: PIs, EFV

Suggested management strategy

1. Assess a baseline lipid profile prior to starting ART; monitor levels at least once a year while on therapy.
2. Pursue lifestyle modifications to control hyperlipidemia, including weight control, aerobic exercise, smoking cessation, and alcohol abstinence.
3. Initiate cholesterol-lowering medications.
 - Statins are typically considered first-line therapy for hyperlipidemia.
 - Alternative treatments include fibrates and niacin.
4. Consider altering the ART regimen if hyperlipidemia is refractory to lifestyle modification and cholesterol-lowering medication.

Comments

- Hyperlipidemia is an increase in cholesterol and triglycerides in the blood.
- Patients with HIV infection have a higher overall risk for cardiovascular disease, which is likely due to chronic inflammation, hyperlipidemia, and immune activation following the initiation of ART.

9.27 Skin: Superficial fungal infections and oral thrush

Possible anti-TB drug causes: Fluoroquinolones and other antibiotics

Suggested management strategy

1. Treat candidiasis with topical or short-course oral antifungal drugs.
2. Exclude other diseases if response to treatment is not prompt (such as HIV).

Comments

- Vaginal or penile candidiasis, oral thrush, or cutaneous candidiasis in skin folds may occur with anti-TB treatment.

9.28 Metabolic: Lactic acidosis

Possible anti-TB drug causes: Lzd

Possible ART causes: d4T, ddI, AZT, 3TC

Suggested management strategy

1. Check serum electrolytes and renal function, arterial blood gas, and lactate levels in patients with possible lactic acidosis.
2. Stop linezolid and NRTIs if lactic acidosis occurs.
3. Provide supportive care.
4. After lactic acidosis resolves, replace offending medication in the regimen with a drug less likely to cause lactic acidosis.

Comments

- Lactic acidosis occurs when lactic acid builds up in body tissues, lowering the body's pH. Medications like linezolid and older-generation NRTIs have been associated with lactic acidosis. These medications are thought to disrupt mitochondrial metabolism, leading to increased levels of lactic acid.
- Symptoms and signs of lactic acidosis include nausea, vomiting, tachypnea, abdominal pain, lethargy, anxiety, anemia, hypotension, and tachycardia.
- Early detection and management of high blood lactate levels are critical in preventing development of full-blown lactic acidosis and associated complications, which can be fatal.
- Sodium bicarbonate therapy to correct a low pH has not been shown to be of benefit in lactic acidosis.

9.29 Cardiovascular: QT prolongation

Possible anti-TB drug causes: Fluoroquinolones, Cfx, Bdq

Possible ART causes: PIs, EFV

Suggested management strategy

1. Any patient found to have a QTc value greater than 480 ms should be managed carefully.
 - Repeat ECG and confirm the prolongation.
 - Bedaquiline should be stopped for QTc value greater than 500 ms. Consider stopping other drugs that prolong the QT interval.
 - Check potassium, calcium, and magnesium. Electrolyte levels should be maintained in the normal range.
 - It is suggested to maintain potassium levels of more than 4 mEq/L and magnesium levels of more than 1.8 mg/dL.
 - Avoid other drugs that increase the QT interval.
2. Monitor the patient's renal and hepatic function and adjust dose of fluoroquinolones if impairment is present.
3. Consider suspension of the fluoroquinolone if risk of torsades de pointes outweighs the benefits of the drug.

Comments

- The QT interval is measured from the end of the QRS complex to the beginning of the T wave on a standard electrocardiogram. The QT is corrected for heart rate, which is referred to as the QTc and calculated by most ECG machines. A normal QTc is generally < 440 ms.
- Values above QTc 440 ms are referred to as prolonged. Patients with prolonged QTc are at risk for developing cardiac arrhythmias like torsades de pointes, which can be life-threatening. Patients with QTc greater than 500 ms are at the greatest risk for developing these arrhythmias.
- The fluoroquinolones cause prolongation of the QTc. Moxifloxacin causes the greatest QTc prolongation, while levofloxacin and ofloxacin have a lower risk of QTc prolongation.
- Currently, electrocardiogram monitoring prior to the initiation and during MDR-TB therapy is not required, as the therapeutic benefit of fluoroquinolones is considered to outweigh the risks associated with QT prolongation.
- Electrocardiogram monitoring is required for patients receiving bedaquiline (see Chapter 8).

9.30 Hematologic: Anemia or pancytopenia

Possible anti-TB drug causes: Lzd

Possible ART causes: AZT

Suggested management strategy

1. Perform additional laboratory tests to assess potential cause of anemia.
 - Check mean corpuscular volume (MCV) to assess whether anemia is normocytic versus microcytic versus macrocytic.
 - Check reticulocyte count to assess whether the bone marrow is producing red cell precursors.
 - Check LDH, bilirubin, and haptoglobin to assess for hemolysis.
2. Stop drugs that are likely to cause anemia.
3. Consider blood transfusion if anemia is severe.

Comments

- Anemia is defined as a decrease in red blood cells, measured as a hematocrit (Hct) < 41 percent or hemoglobin (Hb) < 13.5 g/dL in men, and Hct < 36 percent or Hb < 12 g/dL in women.
- Symptoms of anemia include fatigue, exertional dyspnea, and angina. Physical exam findings include pallor, tachycardia, and orthostatic hypotension.
- The differential diagnosis of anemia is broad. It is generally divided into disorders of red blood cell underproduction and red blood cell increased destruction. Underproduction syndromes are further divided into microcytic, normocytic, and macrocytic anemias based on the MCV results.
 - Causes of microcytic anemia include iron-deficiency anemia, synthesis defects (including thalassemias), and sideroblastic defects (including lead toxicity).
 - Causes of normocytic anemias include anemia of chronic disease and aplastic anemias.
 - Causes of macrocytic anemia include deficiency of vitamin B12 or folate, hypothyroidism, alcoholism, and AZT and other drugs that inhibit DNA replication.
- The most common cause of macrocytic anemia in patients with HIV is usually AZT. Cotrimoxazole can also infrequently cause macrocytic anemia. AZT can also cause neutropenia.

- There are fewer possible causes of pancytopenia (combination of anemia, thrombocytopenia, and neutropenia):
 - Aplastic anemia.
 - Folate or cobalamin deficiency.
 - Viral infections (hepatitis).
 - Marrow infiltration by TB or fungal infections.
 - Hematologic malignancy.
 - HIV/AIDS.
- Linezolid can cause aplastic anemia and thrombocytopenia.

9.31 Commonly used ancillary drugs for the management of adverse effects

Drug Class	Medicine and dosage	Comments
Gastrointestinal drugs		
Antiemetics	<p>Metoclopramide 10 mg PO/IM/IV three or four times a day PRN, usually given 30 minutes prior to meals or medications.</p> <p>Dimenhydrinate 50-100 mg PO/IM/IV every four to six hours.</p> <p>Prochlorperazine 5-10 mg PO/IM/PR three or four times a day.</p> <p>Promethazine 12.5-25.0 mg PO/IM/PR every four to six hours.</p> <p>Ondansetron 4-8 mg PO 30 minutes before anti-TB drugs, repeated every eight hours.</p>	<p>Many of these drugs have side effects including extrapyramidal reactions, drowsiness, sedation, etc.</p> <p>Stop if tardive dyskinesia develops.</p>
Medications for antiematory vomiting	<p>Lorazepam 0.5-2.0 mg PO 30 to 60 minutes prior to anti-TB drugs.</p> <p>Diazepam 2.0-10 mg PO 30 to 60 minutes prior to anti-TB drugs.</p>	<p>Because of its shorter half-life, lorazepam is preferable over diazepam.</p> <p>Warning: Potential for addiction.</p>
Antacids	<p>CaHCO₃, MgSO₄, aluminum hydroxide; the most common formulation is combination of magnesium and aluminum hydroxide 1-30 mL PO three times a day PRN.</p>	<p>Must be taken three hours before or two hours after taking anti-TB medications.</p> <p>Magnesium-containing antacids can cause diarrhea, and aluminum-containing antacids can cause constipation.</p>
H ₂ blockers	<p>Ranitidine 300 mg PO at night.</p>	<p>Alternatives are cimetidine, famotidine, and nizatidine.</p>
Proton pump inhibitors	<p>Omeprazole 20 mg PO at night.</p>	<p>Alternatives are esomeprazole, lansoprazole, pantoprazole, rabeprazole.</p>

Drug Class	Medicine and dosage	Comments
Gastrointestinal drugs		
Antifungal drugs	Fluconazole 200 mg single dose, or 100 mg daily for 5 to 14 days. Clotrimazole 1 troche (10 mg) 5 times daily for 14 days.	HIV-negative MDR-TB patients may also have oral candidiasis. These drugs have significant interactions with rifampicin, oral hypoglycemics, phenytoin, theophylline, and other medications.
Antidiarrheals	Loperamide 4 mg initially, then 2 mg PO after each unformed stool for a maximum of 16 mg/day.	Diarrhea is common in patients receiving PAS. Do not use for diarrhea associated with fever or blood in the stool.
Rehydration	Oral rehydration packets as needed. IV fluids with electrolytes as needed.	IV hydration may be preferred if nausea and vomiting are associated with the dehydration.
Psychiatric drugs		
Tricyclic antidepressants	Amitriptyline: Start 25-100 mg PO at night, gradually increase the dose to usual effective dose 50-300 mg/day.	Avoid in patients with risk of arrhythmias.
Selective serotonin reuptake inhibitors	Fluoxetine: Start 20 mg PO daily, usual effective dose 20-40 mg/day, maximum dose 80 mg/day. Sertraline: Start 25-50 mg PO daily, usual effective dose 50-200 mg/day, maximum dose 200 mg/day.	Other alternatives include citalopram, fluvoxamine, paroxetine.

Benzodiazepines	<p>Lorazepam 0.5-2.0 mg PO every four to six hours PRN.</p> <p>Diazepam 2.0-10.0 mg PO two or three times a day PRN.</p> <p>Clonazepam: Start 0.25-0.50 mg PO three times a day, maximum 20 mg/day (often doses much less than this are effective).</p>	<p>Many benzodiazepines have a long half-life and should be used with caution.</p> <p>Warning: Potential for addiction.</p>
Antipsychotics	<p>Haloperidol: Start 0.5 to 5.0 mg PO two or three times a day. Usual effective dose 2-10 mg/day for cycloserine-induced psychosis.</p> <p>Risperidone: Start 0.5 to 5.0 mg PO two or three times a day. Usual effective dose 2-10 mg/day for cycloserine-induced psychosis.</p>	<p>Risperidone is more expensive, but has fewer side effects.</p> <p>Benztropine 1-4 mg PO QD/BID or biperiden 2 mg QD/BID may be used to treat extrapyramidal side effects.</p>
Neurological drugs		
Benzodiazepines	Diazepam: Active seizing: 0.2-0.4 mg/kg up to 5-30 mg IV.	Diazepam may be used to control active seizures.
Anticonvulsants	<p>Phenytoin: Load 10-20 mg/kg (1,000 mg in typical adult) IV, no faster than 50 mg/min. Oral load: 400 mg initially, then 300 mg in two hours and four hours. Maintenance 5 mg/kg or 100 mg PO three times a day.</p> <p>Carbamazepine: 200-400 mg PO two or four times a day.</p> <p>Valproic acid: Start 15 mg/kg PO daily or divided in two daily doses, maximum 60 mg/kg.</p> <p>Phenobarbital: Load 15-20 mg/kg up to 300-800 mg IV at 25-50 mg/min. Maintenance 60 mg PO two or three times a day.</p>	

Drug Class	Medicine and dosage	Comments
Neurological drugs		
Vitamins	Pyridoxine: Use at least 50 mg for every 250 mg of cycloserine.	Pyridoxine is important for the prevention of peripheral neuropathy and other neurotoxicity in patients receiving cycloserine. Consider using high doses of 300 mg per day in patients with refractory side effects.
Tricyclic antidepressants	Amitriptyline: Start 25-100 mg PO at night; gradually increase the dose to usual effective dose 50-300 mg/day.	Low-dose amitriptyline is effective for the symptomatic treatment of peripheral neuropathy. Avoid in patients with risk of arrhythmias.
Antihistamines	Meclizine 25 mg PO every six hours.	May be effective in patients with vestibular symptoms.
Analgesics	Ibuprofen 200-800 mg PO three or four times a day PRN. Acetaminophen 325-650 mg PO every four to six hours PRN.	Analgesics may be helpful for headache or peripheral neuropathy. Alternatives include other similar nonsteroidal anti-inflammatory (NSAID) drugs, paracetamol, or aspirin.
Opioid-containing analgesics	Codeine, often in combination with acetaminophen, for severe refractory headaches can be used: 15-60 mg every four to six hours.	Warning: Potential for addiction.
Drugs for cutaneous reactions		
Corticosteroid creams and ointments	Hydrocortisone (1 percent to 2 percent): Apply to affected area two or four times a day.	

Antipruritus lotions	Calamine, Caladryl lotions: Apply to affected area two or four times a day.
Antihistamines	Diphenhydramine 25-50 mg PO every four to six hours. Chlorpheniramine 4 mg PO every four to six hours. Dimenhydrinate 50-100 mg PO/IM/IV every four to six hours.
Corticosteroids	See sections below on drugs for systemic hypersensitivity reactions.
Drugs for arthralgias, nongouty arthritis	
Analgesics	Ibuprofen 200-800 mg PO three or four times a day PRN. Acetaminophen 325-650 mg PO every four to six hours PRN. Can also use similar nonsteroidal anti-inflammatory (NSAID) drug or aspirin.
Drugs for hypothyroidism	
Thyroid replacement hormone	Levothyroxine: Start 50-100 mcg per day (start 25-50 mcg in the elderly or patients with cardiac disease) and increase dose by 12.5-25 mcg every three to eight weeks. Usual maintenance dose is 100-200 mcg/day.
Drugs to manage fluids and electrolytes	
Loop diuretics	Furosemide 20-80 mg IV/IM/PO every 6-24 hours. Added ototoxicity when used with an aminoglycoside.
Potassium-sparing diuretics	Amiloride 5 mg PO daily, maximum dose 20 mg/day. Used for uncontrolled potassium wasting.
Electrolyte replacement therapy	There are various formulations of potassium, magnesium, and calcium replacement therapy.

Drug Class	Medicine and dosage	Comments
Drugs for bronchospasm		
Beta-agonist inhalers	Albuterol inhaler 90 mcg per spray, two puffs every four to six hours.	For acute bronchospasm, use 400-500 mcg (four to five puffs).
Beta-agonist nebulizers	Albuterol solution for nebulization 2.5 mg (0.5 mL of 0.5 percent solution) every six hours.	
Inhaled corticosteroids	Beclomethasone, budesonide, or fluticasone HFA inhaler dosing depends on brand.	
Oral corticosteroids	Prednisone 1–2 mg/kg per day; taper dose as indicated.	Injectable steroids can be used for severe cases of bronchospasm and rarely epinephrine is needed (see hypersensitivity section in this table for dosing).
Drugs for systemic hypersensitivity reactions		
Antihistamines	Diphenhydramine 25–50 mg PO/IM/IV every four to six hours.	
Oral corticosteroids	Prednisone 1–2 mg/kg per day then taper dose as indicated.	
Injectable corticosteroids	Dexamethasone: Doses vary, 4 mg every 6–12 hours.	Other alternatives are prednisolone, methylprednisolone, and others.
Other drugs	Epinephrine 0.1–0.5 mg SC (1:1,000 solution).	May repeat after 20 minutes.

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10 Management of complications of MDR-TB

10.1 Respiratory insufficiency

Differential diagnosis of sudden shortness of breath during MDR-TB treatment

Diagnosis	Signs	Treatment
Bronchospasm	Wheezing and increased expiratory phase on physical examination; X-ray unchanged.	Mild wheezing: Beta-agonist inhaler. Severe wheezing: Nebulized beta-agonist, oral or IV corticosteroids.
Pneumothorax	New pneumothorax on X-ray.	Consider chest tube placement.
PCP	New infiltrates in an HIV-positive patient not taking cotrimoxazole preventive therapy, CD4 count usually less than 200.	Cotrimoxazole: 15 mg of the trimethoprim component per kg per day x 21 days. Usual oral dose for adults less than 65 kg is two double-strength tabs three times daily. Prednisone may be needed in severely ill patients.
Systemic infections and complications	Systemic symptoms in HIV-positive patient, such as altered mental status.	Check serum electrolytes, creatinine, and urea. Consider CSF analysis.

Notes

- Bronchospasm is common in TB patients and may actually increase in some patients after the initial months of treatment.
 - TB destroys the normal architecture of the lung and can create chronic obstructive pulmonary disease (COPD).
 - Some patients can experience severe, life-threatening exacerbations that are indistinguishable from severe asthma or severe COPD.
 - Supportive therapy such as bronchodilators and corticosteroids should be used but may have limited efficacy due to a lack of a reversible component of airway obstruction.
- Bacterial pneumonia is rare during MDR-TB treatment because of the broad-spectrum activity of levofloxacin/moxifloxacin that is generally part of MDR-TB regimens.

- Pneumothorax is common in TB patients.
 - In MDR-TB patients with chronically scarred lungs, partial pneumothorax is common.
 - Conservative therapy (supplemental oxygen and close monitoring) is often the best choice, because of the risk of secondary infection with chest tube placement.
 - Indication for chest tube placement:
 - ♦ Tension pneumothorax.
 - ♦ Large pneumothorax with significant respiratory compromise.
 - ♦ Significant pneumothorax that does not reinflate after several days of conservative therapy.

10.2 Hemoptysis

Blood-stained sputum

- Generally not serious and requires only reassurance.
- Can continue for months after MDR-TB treatment is started, especially in chronically ill patients with significant lung damage.

Large-volume hemoptysis (greater than 200 cc, or a small cup)

- Caused by a cavitory lesion eroding into a vein.
- Since it is a sign of advanced disease, massive hemoptysis is most common before starting treatment or early in the treatment course.
- Effective MDR-TB treatment is the most important treatment for large-volume hemoptysis.
- Patients with massive hemoptysis generally die of asphyxiation, not blood loss.

Large-volume hemoptysis should be considered a medical emergency and the patient should be hospitalized

- If vital signs are stable:
 - Strict bed rest.
 - Humidified oxygen at bedside.
 - Check hemoglobin and transfuse if necessary.
 - Consider codeine-containing cough suppressant.
 - Try to identify which side the blood is coming from (often the bleeding side will have severe lung disease on chest X-ray or there may be a gurgling sound that can be auscultated). Position the patient such that the presumed bleeding lung is in the dependent position. For example, if the left lung is likely to be bleeding position the patient on their side with the left lung down.
- If vital signs are unstable, start resuscitation:
 - Oxygen via nasal cannula or facemask.
 - Place two large IV catheters.
 - Ringer's lactate or normal saline running wide open.
 - Urgent blood transfusion.
 - Consider surgical resection or bronchoscopy techniques if available.
- Full discussion of surgery, bronchoscopy techniques to stop bleeding, and mechanical ventilation techniques, is beyond the scope of this book.

10.3 Hematemesis or melena

Bleeding from the upper gastrointestinal tract is a danger in any sick, hospitalized patient

- The most common cause of upper gastrointestinal tract bleeding is stress ulcers.
- All inpatients with risk factors for upper gastrointestinal bleeding (low BMI, low albumin, advanced pulmonary disease) should receive omeprazole 20 mg daily as primary prophylaxis.

Hematemesis

- Vomiting of “coffee ground” material is usually caused by a relatively slow bleed from a stress ulcer in the stomach.
- Blood that is partially digested by stomach acid turns dark; vomiting of dark red blood is a sign of fast bleeding.

Melena

- Melena is a black, tarry feces that is caused by bleeding from the upper GI tract (stomach or duodenum).
- The black color is caused by oxidation of the iron as the blood passes through the ileum and colon.
- Red blood from the rectum is a sign of bleeding from the lower GI tract.

Any sign of hematemesis or melena should be treated as a medical emergency, as slow bleeding often turns into fast bleeding

- If vital signs are stable:
 - Nothing per mouth.
 - Start omeprazole if not receiving already.
 - Check hemoglobin and transfuse if necessary.
 - Nasogastric aspiration to see how much blood is in the stomach.
- If vital signs are unstable, start resuscitation:
 - Oxygen via nasal cannula.
 - Place two large IV catheters.
 - Ringer’s lactate or normal saline running wide open.
 - Urinary catheter to monitor urine output.
 - Urgent blood transfusion.

10.4 Pleural effusion and empyema

Pleural effusions in MDR-TB are common

- Pleural effusions that are not empyemas usually do not need to be drained if the patient is clinically stable. These are usually chronic and have developed during multiple retreatment episodes.
- Small, loculated effusions may not be easily drained by a chest tube. Even if the effusion is large and free-flowing, there may not be recuperable lung tissue.

Empyema

- Empyemas are caused by large amounts of bacteria in the pleural space.
- There are usually associated symptoms such as fever, productive cough, or chest wall pain.
- Diagnostic thoracentesis is simple and will quickly determine if a pleural effusion is an empyema (yellow/green thick fluid, pH < 7.2, etc.).
- Empyemas need to be drained, but the underlying cause of the empyema needs to be addressed.

New empyema during MDR-TB treatment may be a sign of treatment failure

- An empyema that occurs during MDR-TB treatment is usually caused by the formation of new bronchopleural fistula that allows oral flora to enter the pleural space.
- Bronchopleural fistula can be diagnosed by asking the patient to cough after the chest tube is placed. A large air leak is diagnostic of a bronchopleural fistula.
- An MDR-TB patient who develops a new empyema should be carefully evaluated for possible treatment failure, including culture and DST. If the treatment regimen is not adequate, placement of a chest tube will lead to a chronic bronchopleurocutaneous fistula unless the treatment regimen is changed.

11 Adherence to treatment

11.1 Monitoring adherence

Ask	Advice
“Are you becoming frustrated with the adverse effects?”	“We can manage your adverse effects if you keep communicating with the clinical and community teams. Many adverse effects improve with time.”
“Are you feeling better?”	“Even though you feel better, your MDR-TB is not cured. You must keep taking drugs for the entire treatment period.”
“Is it convenient for you to take your treatment each day?”	“We can arrange things so that it is more convenient for you to take treatment. We can give you reimbursement for transportation.”
“Are you planning to travel soon?”	“We can make arrangements so that you will not miss any doses.”
“Are you planning to go back to work?”	“We can make arrangements so that your treatment is more convenient to your workplace. We can also talk to your employer if you agree.”
“How is your relationship with your clinical team/community health worker?”	“If anyone on the clinical or community team is disrespectful, we apologize. Please let us know how we can treat you better.”

Notes

- It is important to be aware of potential problems with adherence before they occur—before a dose or appointment is missed. Ask open-ended questions at every clinical evaluation.

11.2 Common adherence problems and their solutions

Problems	Possible solutions
The patient does not want to take treatment because of adverse effects.	This is the most common reason for default. Treat the adverse effects immediately.
The patient does not want to take treatment because he/she is feeling better.	Explain: "Even though you feel better, you are not cured. There is still MDR-TB in your lungs that will start growing again if you stop treatment."
The patient has economic problems that affect ability to be adherent.	Assess basic housing, food, and clothing needs and explore ways to address these needs.
The patient is suffering from alcohol or drug abuse.	Discuss possible alcohol or drug abuse with the family and the patient. Refer patient to drug treatment programs.
The patient has a bad relationship with the health worker supervising treatment.	Discuss these issues with the community team and the health worker supervising treatment. Change the health worker if these problems cannot be resolved.
The patient is experiencing isolation, stigma, or discrimination.	Educate the family and community. Consider involving community leaders if the patient agrees.

Notes

- Adherence problems should be addressed in a sympathetic, friendly, and nonjudgmental manner.
- Adherence interventions should be triggered when the patient misses a dose or scheduled appointment.
 - Discussion with the community team: According to the community health worker, why did the patient miss a dose?
 - Home visit: Are problems within the home or family interfering with treatment?
 - Patient interview: Does the patient have medical or social problems interfering with treatment?

11.3 Reinitiating treatment after an interruption

Perform a review of the clinical record and a full clinical evaluation

- When did the patient stop taking treatment?
- How long did the patient take treatment before stopping?
- What sort of adverse effects was the patient experiencing the last time he/she was taking treatment?
- Was the patient smear- or culture-positive at the time that he or she stopped treatment?

Why did the patient stop taking treatment?

- Meet with the community team and discuss ways to improve adherence before restarting treatment.
- Restarting treatment without addressing the issues that led the patient to stop will lead to the same result.

Reinitiation of treatment after an interruption

Length of treatment received prior to interrupting therapy	Result of last culture prior to interrupting treatment -OR- Result of smear and culture upon return to treatment	Action
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Less than three months	N/A	Restart original regimen; patient will need full course of treatment. Send sputum for culture and DST and adjust regimen according to the results.
More than three months	Positive	Restart original regimen; patient will need full course of treatment. Send sputum for culture and DST and adjust regimen according to the results. If treatment failure was suspected before interruption, consider designing a new regimen instead of restarting original regimen.
	Negative	Restart the regimen the patient was taking before the interruption. If patient was in the continuation phase and there has been no evidence of clinical deterioration during the interruption, the continuation phase can be restarted. If the patient has any subsequent positive smears or cultures in the next few months, consider the patient as bacteriologically positive and restart a full course of MDR-TB treatment (from the injectable phase). Send sputum for culture and DST; total length of treatment will depend on whether the sputum culture is positive. All patients in this category should get a minimum of 24 months of therapy total.

Note

- If interruption is more than six months and patient is clinically stable and bacteriologically negative, it may be advisable to first to determine if the patient has active TB before restarting treatment.

12 Management of patients in whom MDR-TB treatment has failed

12.1 Assessment of patients at risk for failure

- Patients who do not show signs of improvement after four months of treatment are at high risk for treatment failure.
- Review the bacteriological data.
 - Positive smears and cultures are the strongest evidence that a patient is not responding to therapy.
 - One single positive culture in the presence of an otherwise good clinical response can be caused by a laboratory contaminant or error. Subsequent cultures that are negative or in which the number of colonies is decreasing may help prove that the apparently positive result did not reflect treatment failure.
 - Positive smears with negative cultures may be caused by the presence of dead bacilli and therefore may not indicate treatment failure.
 - Repeated culture- and smear-negative results in a patient with clinical and radiographical deterioration may indicate that the patient has a disease other than MDR-TB.
- Assess adherence carefully.
 - Interview the patient in a nonconfrontational manner about potential adherence problems.
 - If the patient is receiving community-based care, interview the DR-TB Supporter alone. Consider switching the DR-TB Supporter if DOT is not being done correctly for any reason.
 - If adherence is suspect, consider changing the way the patient receives DOT. If the patient is receiving clinic-based care, consider switching clinics. Consider hospitalizing the patient.
- Evaluate the patient clinically.
 - Consider illnesses that decrease absorption of medicines (e.g., chronic diarrhea) or may result in immune suppression (e.g., HIV/AIDS).
 - Consider illnesses that mimic failure (chronic infection with non-TB mycobacteria).

- Review the treatment regimen in relation to medical history, contacts, and all DST reports. Second-line DST should be performed if not already done.
- Changes in treatment can be made as early as four to six months if conversion is not seen and if there is clinical deterioration.
- Consider compassionate use of new anti-TB drugs.
- Do not add one or two drugs to a failing regimen. When a new regimen is started due to failure, the final outcome should be recorded in the MDR-TB treatment register and a new treatment registration number given.
- Consider surgical resection.

12.2 Identifying MDR-TB treatment failure in patients where it has been determined that all treatment options have been exhausted

Criteria for MDR-TB treatment failure

- It takes six to eight months to evaluate whether a change in treatment plan or regimen has been effective. If the patient continues to deteriorate despite the measures described in the previous section, treatment failure should be considered.
- There is no clear set of parameters or absolute time frame to determine whether a treatment regimen is failing. But there often comes a point during the treatment when it becomes clear that the patient is not going to improve.
 - Persistently positive smears or cultures despite 8 to 10 months of treatment.
 - Progressive extensive and bilateral lung disease on chest X-ray with no option for surgery.
 - High-grade resistance (often XDR-TB) with no option to add two additional drugs.
 - Overall deteriorating clinical condition that usually includes weight loss and respiratory insufficiency.
- It is not necessary for all of these signs to be present to identify failure of the treatment regimen. However, a cure is highly unlikely when they are all present.

Approach to suspending MDR-TB treatment

- The approach to suspending therapy should start with discussions among the clinical team, including all physicians, nurses, and DOT supporters involved in the patient's care.
- Once the clinical team decides that treatment should be suspended, a clear plan should be prepared for approaching the patient and the family. This process usually requires a number of visits and takes place over several weeks. Home visits during the process offer an excellent opportunity to talk with family members and the patient in a familiar environment.
- The decision to suspend MDR-TB treatment should consider the danger of adverse effects, the benefit of continued treatment to the patient, and the risk of further amplification of resistance.
- Treatment should not be suspended before the patient understands and accepts the reasons to do so.

12.3 Palliative care for patients in whom all the possibilities of treatment have failed

Definition of palliative care

- Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems—physical, psychosocial, and spiritual.
- Effective support at the end of life requires a broad multidisciplinary approach that includes the family and makes use of available community resources; it can be successfully implemented even if resources are limited. It can be provided in tertiary care facilities, in community health centers, and even in the patient's home.

End-of-life supportive measures

- **Pain control and symptom relief.** Paracetamol, or codeine with paracetamol, gives relief from moderate pain. If possible, stronger analgesics, including morphine, should be used when appropriate to keep the patient adequately comfortable. WHO has developed analgesic guides, pain scales, and a three-step “ladder” for pain relief.
- **Relief of respiratory insufficiency.** Oxygen can be used to alleviate shortness of breath. Morphine also provides significant relief from respiratory insufficiency and should be offered if available.
- **Nutritional support.** Small and frequent meals are often best for a person at the end of life. It should be accepted that the intake will reduce as the patient's condition deteriorates during end-of-life care. Nausea and vomiting or any other conditions that interfere with nutritional support should be treated.
- **Continuation of ancillary medicines.** All necessary ancillary medications should be continued as needed. Codeine helps control cough, as well as pain. Other cough suppressants can be added. Bronchospasm symptoms can be controlled with a meter-dosed inhaler with a spacer or mask. Depression and anxiety, if present, should be addressed. Antiemetics may still be needed. Treat fever if the patient is uncomfortable.

- **Regular medical visits.** When therapy stops, regular visits by the treating physician and support team should not be discontinued. This is particularly important if palliative care is provided at home.
- **Hospitalization, hospice care, or nursing home care.** Having a patient die at home can be difficult for the family. Hospice-like care should be offered to families who want to keep the patient at home. Inpatient end-of-life care should be available to those for whom home care is not available.
- **Preventive measures.** Oral care, prevention of bedsores, bathing, and prevention of muscle contractures are indicated in all patients. Regularly scheduled movement of the bedridden patient is very important. Encourage patients to move their bodies in bed, if able. Keep beds dry and clean.
- **Infection control measures.** The patient who is taken off anti-TB treatment because of failure often remains infectious for long periods of time. Infection control measures should be continued, including environmental and personal N95 mask use for caregivers.

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13 Community care for MDR-TB

13.1 Treatment delivery models

Community-based treatment—patients receive DOT in their homes

Negative aspects	Positive aspects
<p>A network of DR-TB Supporters must be trained, supervised, and compensated to support patients.</p> <p>Injections may be difficult to administer in the community depending on local regulations.</p> <p>Infection control for patients failing treatment can be complicated.</p>	<p>Treatment at home is often more convenient for patients than traveling to a clinic each day or staying at an inpatient facility.</p> <p>Decongests hospital MDR-TB wards and allows programs to scale up quickly.</p> <p>Clinical teams have a better understanding of the socioeconomic living conditions of MDR-TB patients.</p>

Clinic-based treatment—patients travel daily from home to clinic to receive DOT

Negative aspects	Positive aspects
<p>The patient may be too sick or weak to travel every day to the clinic.</p> <p>Out-of-pocket costs to the patient for travel.</p> <p>Travel to the clinic is time-consuming and may not allow the patient to have a job.</p> <p>Patients may have to relocate to live near a clinic, which is expensive and puts the patient away from family support.</p> <p>Clinics may not be able to observe the evening dose of MDR-TB treatment.</p> <p>Transmission of the disease can occur in transit to the clinic or in the clinic to staff and other patients.</p>	<p>The patient may desire to maintain strict confidentiality and not wish to receive treatment at home or in a place where visible to others.</p> <p>A more skilled health care provider is available to observe doses and address problems daily.</p> <p>Medicines for adverse effects are readily available.</p> <p>Access to physicians is often easier.</p> <p>One health care provider can do DOT for many patients.</p>

Hospital-based treatment

Negative aspects	Positive aspects
<p>Many hospitals do not have good infection control measures.</p> <p>The lack of MDR-TB hospital beds has become a significant bottleneck to scale-up in many countries.</p> <p>Hospitalization is costly, especially for the whole duration of MDR-TB treatment.</p> <p>Even where treatment is mainly hospital-based, a strong community-based system needs to be developed to support patients when they are ready to return home.</p>	<p>Hospitals can provide a higher level of care to patients with adverse drug reactions, adherence problems, severe comorbid conditions, or surgical needs.</p> <p>Can often provide comprehensive care, including nutritional support.</p>

13.2 The DR-TB Supporter

Roles and responsibilities of a DR-TB Supporter

- Supervise all doses of second-line TB drugs in the community.
- Identify possible side effects or complications and report them promptly to the DR-TB Community Nurse.
- Accompany the patient to all medical consultations.
- Assist the patient in producing sputum samples monthly.
- Receive the monthly drug kit and verify that it is correct.
- Screen household contacts for TB and HIV and refer them for diagnosis.
- Provide education and emotional support for the patient and family.

Notes

- When possible, the DR-TB Supporter should be a community health worker or someone in the health system who has basic health knowledge. Many programs train a layperson to become a community health worker. Regardless, the DR-TB Supporter must be a person who is motivated beyond the financial incentive.
- A family member should not be a DR-TB Supporter. The family relationship may interfere with the ability to monitor treatment and could be subjected to subtle manipulation by the patient or relative. Children should also be assigned a DR-TB Supporter, as the parents of the child are not appropriate to supervise doses.
- DR-TB Supporters should live near the patient to allow twice-daily visits to provide DOT. Many programs will do once-a-day dosing, but an option for a patient not tolerating the medicines is to take them twice a day under DOT. Additionally, in case of medical emergencies, the family should be able to contact the DR-TB Supporter quickly.

- DR-TB Supporters need to be compensated for their work. Unpaid volunteers who are not trained, closely supervised, and compensated cannot be expected to support MDR-TB patients.

13.3 DOT at home

- During each visit to the patient's home the DR-TB Supporter should observe the patient taking all doses of medications as written on the patient's treatment card and tick the card immediately after administering the morning or evening dose.
- DR-TB Supporters may administer the injection during the intensive phase if the country regulations and skills of the DR-TB Supporter allow.
- DOT is an opportunity for monitoring the patient. Patients should be asked if they have any adverse drug reactions or need any additional support.
- Clinical developments should be communicated to the clinical team during the next clinic evaluation or immediately if urgent action is required (e.g., new adverse effects).
- DOT is an opportunity for HIV testing and counseling to family members in high HIV-prevalence settings or if the patient is HIV-positive.

13.4 Supervision of the DR-TB Supporter

- Supervision of the DR-TB Supporter is often done by a DR-TB Community Nurse (or mid-level health professional).
- Supervisory home visits that are conducted sporadically by the DR-TB Community Nurse can be an excellent way to provide supportive monitoring and feedback to the DR-TB Supporter.
 - The DR-TB Community Nurse should visit the patient's home first to ask the patient and family about the DR-TB Supporter (e.g., "Does he or she work around the patient's schedule? Is the relationship good?").
 - The DR-TB Supporter should then be called to provide feedback, discuss issues, and reinforce teaching points.
 - The DR-TB Community Nurse should count the remaining pills and compare this number to the amount of pills that should be remaining based on the number of days since the medication was replenished.

13.5 Socioeconomic interventions (incentives and enablers)

- Socioeconomic problems, including hunger, homelessness, and unemployment, are common among MDR-TB patients. They should be addressed to enable patients to adhere to MDR-TB treatment.
- These problems have been successfully tackled through socio-economic interventions that include the use of provisions in the form of “incentives” and “enablers”.
 - Incentives are rewards that encourage patients to adhere to treatment.
 - Enablers are goods or services that make it easier for patients to adhere to treatment, such as the provision of transportation vouchers or clothing.
- Social workers or other designated professionals can help assess the patients with the most need and monitor delivery.
- Community-based organizations that already support community members may be engaged to provide economic support to MDR-TB patients. This can strengthen linkages with other types of support provided by these organizations and may result in a more sustainable support system.

13.6 Psychosocial and emotional support

- Having MDR-TB can be an emotionally devastating experience for patients and their social networks.
- Considerable stigma is attached to the disease, and this may interfere with adherence to therapy.
- Informal support can also be provided by physicians, nurses, DR-TB Supporters, and family members. Most programs use a multidisciplinary support team (social workers, nurses, health educators, companions, and doctors).
- Support may focus on problems related to different stages of treatment, stigma and discrimination, treatment adherence, side effects, socioeconomic difficulties, treatment failure, and death.
- The establishment of support groups may allow patients with MDR-TB to meet, socialize with other patients, and provide emotional support to each other.

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14 Infection control for MDR-TB

14.1 Administrative controls

Outpatient settings

- Patients should be screened for cough as they enter into the health care facility and receive basic education about TB.
- Patients with a cough of over two weeks should be sent to a separate, well-ventilated waiting area and fast-tracked to sputum examination.
- All coughing patients should receive tissues or face masks, and should be asked to cover their mouth and nose when they cough.

Inpatient settings

- The circulation of visitors, patients, and their attendants in the hospital needs to be strictly controlled.
 - Patients should be encouraged to spend as much time as possible outdoors.
 - Visiting areas should be well-marked. Restricted areas should have signage forbidding visitors to enter.
 - Encourage visits outside the building, in open air, especially for contagious patients.
 - If visits outside are not possible, visitors should be provided masks while visiting with patients if the patient is contagious.
- TB wards must be well-ventilated and separated from the other wards in the health structure compound.
 - Ideally, patients may be placed in single rooms.
 - If single rooms are not possible, cohort isolation must be implemented. Patients are separated by degree of contagiousness (smear/culture status), DST pattern, and immune status.
 - ✦ Sputum smear-positive patients may be separated from less or noncontagious forms of TB: Smear-negative pulmonary TB, extrapulmonary TB, patients who have converted.
 - ✦ Known or suspected MDR-TB patients may be separated from drug-susceptible TB patients, and XDR-TB patients may be separated from MDR-TB patients without XDR-TB.
 - ✦ Immunosuppressed patients (such as HIV-positive patients) should be separated from contagious TB patients.

14.2 Environmental controls

Ventilation

- Ventilation is the most effective means for reducing the concentration of *M. tuberculosis* suspended in the air.
- Areas where TB transmission might occur should have a minimum ventilation rate of 6 to 12 air changes per hour (ACH).
- Natural ventilation relies on the movement caused by the wind and convection in order to achieve dilution and renewal of air.
 - Natural ventilation can be very effective, especially when cross-ventilation (windows/doors in opposite sides of the room) is achieved.
 - Natural ventilation should be done with the windows and doors open.
 - Keep inside doors closed so that the flow of air is directed outside and not toward interior corridors.
- If natural ventilation alone is not sufficient, other mechanical devices can be used to augment it:
 - Simple propeller fans.
 - Wind-driven roof turbines.
 - Chimneys.
- When natural ventilation cannot reach adequate rates, centralized mechanical ventilation should be considered in some settings, such as cold climates.
 - Centralized mechanical ventilation relies on the use of mechanical equipment to maintain an air pressure difference between two areas in order to draw air into a room and vent it to the outside.
 - It requires continuous and meticulous maintenance, which is costly and difficult to implement and operate.

Architectural considerations

- TB infection control should be considered during the planning stages of new health structures and those being modified.
- Building layouts and designs should maximize natural ventilation.
 - Waiting areas should be open on three sides.
 - Avoid internal hallways with doors from the rooms and wards opening into them.
 - Doors should open to outside hallways that are open-air.

- Service areas with a high risk of *M. tuberculosis* transmission (e.g., waiting rooms) and procedures (e.g., sputum collection, sputum induction, etc.) should be relocated into more isolated, better ventilated areas.
- Layouts should allow patient flow to be manipulated to reduce exposure of at-risk patients to infectious patients (e.g., separate waiting rooms for different cohorts, one patient per room).
- For TB wards, spaces incorporating plenty of single rooms or small rooms with two to four beds allow for easier separation of different patient cohorts.
- General hospitals should also have isolation rooms available for TB suspects and contagious patients.
- Sputum collection and sputum induction areas may be established outside in open air where bacilli will naturally be dispersed by wind.
 - In cold-climate regions, indoor rooms with UVGI and at least six ACHs could be an option.

Ultraviolet germicidal irradiation (UVGI)

- *M. tuberculosis* is sensitive to germicidal radiation of UV light found in the UV-C portion of the ultraviolet spectrum. The UV-C radiation in natural light does not inactivate the TB bacillus, but UVGI lamps can provide an appropriate germicidal dose.
- UVGI lamps are reserved for high-risk areas (sputum collection, sputum induction areas, poorly ventilated spaces with less than six ACHs, etc.) where other environmental measures are not sufficient due to climatic (hot arid or cold regions) or structural constraints.
- UV lamp usage requires specific procedures and present several main challenges:
 - Lack of expertise in design, installation, and testing.
 - Need for rigorous monitoring and maintenance, with lamps being replaced yearly.
 - Requires electricity, relative humidity of less than 70 percent, and good air mixing.
 - Disposal could be difficult due to the risk of mercury poisoning in case of broken or mishandled lamps.
 - Exposure to UV radiation may be harmful.

14.3 Personal protection

Respirators

- Respirators (also known as high-filtration masks, N95 masks, or FFP2 masks) provide a bacterial filtration efficiency of greater than 95 percent if challenged with 0.3-micron particles.
- *M. tuberculosis* is trapped in the filter of a mask, which will not be released with shaking or other physical movements of the mask. It eventually dies once outside the human body.
- These masks should be worn:
 - When in contact with contagious patients (either suspects or confirmed cases).
 - When collecting and examining sputum samples and when collecting and disposing of sputum containers.
 - In areas where droplet nuclei could be present (i.e., a room that has been occupied by a confirmed TB case) prior to the time required for air cleaning.
- Attendants and visitors must wear a high-filtration mask (like those worn by staff) when entering a contagious TB patient's room.
- Respirators classified as disposable can be reused by the staff as long as they are not wet, or damaged in any way, and provided they do not have loosened straps. The filter materials remain functional for weeks or months, however, the fitting may decrease with frequent wearing.
- If the filter material is damaged or the mask has loose straps, the respirator should be discarded. There is no set limit of days of use, but if a respirator is used extensively for seven days, it may be discarded. If it is only used a few hours two to three times per week, it can be kept and reused for several weeks. Storage should not crush or damage the mask.
- Respirators can be disposed in normal waste and do not need to be incinerated. Masks should not be shared between staff.

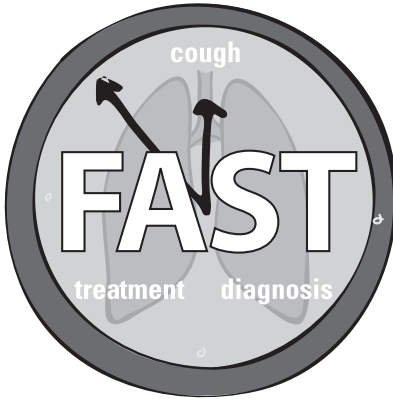
Simple cloth masks and surgical masks

- Contagious patients must wear a simple cloth, surgical, or face mask when they leave their rooms to go to another department or any other enclosed area. The mask is intended to prevent projection of *M. tuberculosis* by the patient.

Waste management

- In wards, where patients are coughing regularly, sputum containers should be about 200 mL, sealable, nonsterile containers.
- Laboratory sputum containers are smaller (25-35 mL), with hermetic cap, nonsterile, and for single use.
- Used containers should be collected in a trash bag and incinerated. Do not reuse. Do not fill the containers with chlorine solution before incineration (this can produce toxic gases).
- Standard infectious health care waste treatment related to sharp and soft waste should be respected. There are no specific measures for TB services.

14.4 FAST infection control strategy



Finding TB
Actively
Separating safely
Treating effectively

- In English, FAST stands for **F**inding TB **A**ctively, **S**eparating safely, and **T**reating effectively.
- The key concept of the FAST strategy is that effective TB treatment reduces TB spread rapidly, even before sputum smear and culture turn negative.
- Within both outpatient and inpatient health care settings FAST can be used to reduce TB and MDR-TB transmission within both general medical settings and TB-specific settings, like TB hospital wards or clinics.

Illustration of FAST in action in a general medical clinic

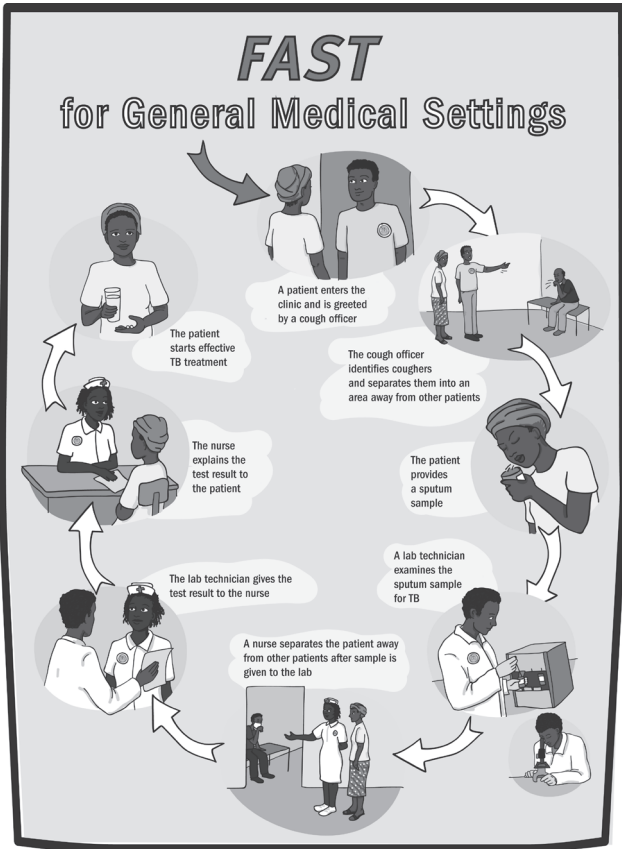
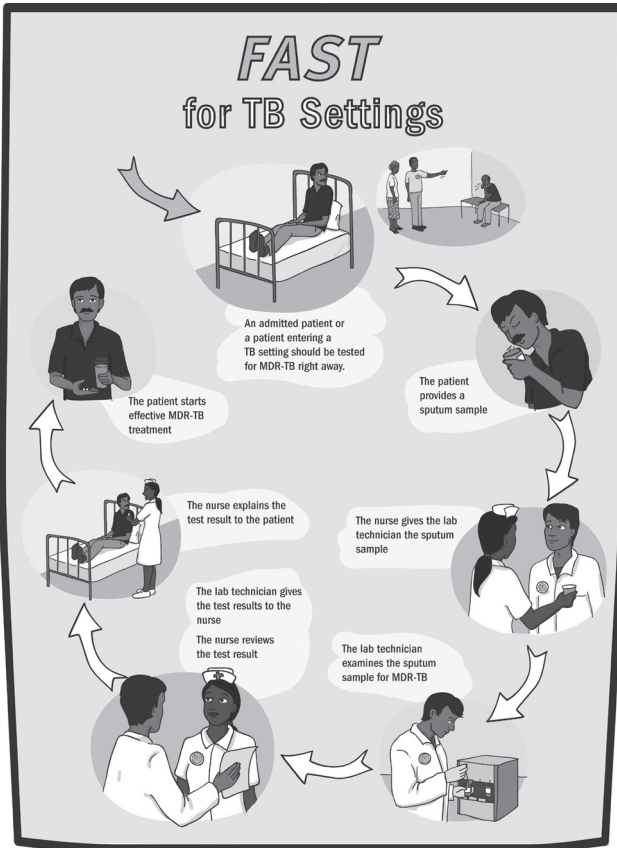


Illustration of FAST in action in a TB ward setting



14.5 Infection control in the community

Administrative measures

- In assessing the home of an MDR-TB patient, information on the number of people that live in the house, number of rooms, etc., should be collected.
- HIV testing of family members is very important. Family members who are HIV-positive should not care for infectious MDR-TB patients.
- When mothers with infectious TB are with their infants, this common time should be spent in well-ventilated areas or outdoors. The mother should use a surgical mask while visiting with the baby until she becomes sputum smear-negative. Until the mother is smear-negative (and ideally culture-negative also) the bulk of the infant care should be done by other family members if possible.
- Provide TB education on transmission, airborne precautions, waste management, clinical symptoms, etc.

Environmental measures

- Ideally, the patient should sleep in a separate room from other family members.
- Communal spaces should be well-ventilated (often done by keeping windows/doors open at all times).

Personal protective measures

- If culture-positive, the patient should wear a cloth or surgical mask when in contact with family members.
- Any person attending to the patient in enclosed spaces should use a respirator (N95 mask). A fit test should be performed and the person should be educated on the proper use of masks.
- Environmental and personal protective measures should be followed at least until patient's smear status is negative, ideally until culture conversion for close contacts.

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15 MDR-TB workplace safety programs

15.1 Pre-employment evaluation

Before starting to work with TB patients, health care providers should have an evaluation that includes the following:

- Baseline chest X-ray.
- HIV testing and counselling.
- Education about:
 - TB transmission.
 - Symptoms of TB.
 - Basic infection control practices for preventing transmission.
 - The increased risk of active TB if immunocompromised (e.g., HIV-infected, pregnant women, diabetics).

If the facility intends to provide preventive therapy for health care providers who are infected with TB on the job, the evaluation should also include:

- Baseline tuberculin skin test (TST) or interferon-gamma release assay (IGRA).
- Determination of BCG immunization status.

Confidentiality

- The most common reason why health care providers are reluctant to be tested for HIV is that they do not feel that confidentiality can be maintained within the workplace.
- It is the responsibility of the workplace to create an HIV counselling and testing system that strictly maintains the confidentiality of its health care providers.
- Confidentiality must also be maintained for treatment and care of HIV-positive health care providers.

Healthcare providers who should not work with TB patients

- HIV-infected health care providers should not work in settings where the risk of TB transmission is high.
- Pregnant women should not work in a TB facility or be exposed to contagious patients.
- These health care providers should be offered the opportunity to transfer to work sites that have the least risk of TB transmission.

15.2 BCG vaccination

Should health care providers be vaccinated with BCG?

- There is limited evidence for benefit of BCG vaccination in adults who previously have not had BCG vaccination, and this may not provide any benefit at all.
- Despite the limited evidence of efficacy, it is generally recommended to vaccinate health care providers with negative TST in situations with a significant exposure to MDR-TB (facilities treating MDR-TB, prisons, or regions with high prevalence of MDR-TB).
- Testing for TST response soon after BCG vaccination is given is not recommended.

BCG vaccination should only be given if:

- The person is HIV-negative.
- The person is not pregnant. Pregnancy is not an absolute contraindication, but generally live vaccines should not be administered. In general, vaccination status should be clarified before they become pregnant.
- The person has previously never had BCG vaccination.
- The person has previously never had active TB.
- The person is TST-negative.

15.3 Screening and preventive therapy for health care providers with regular exposure to MDR-TB

Regular screening for active TB disease includes:

- Regular screening for symptoms of active TB disease.
- Clinical evaluation, chest X-ray, and bacteriological studies for anyone with symptoms.
- HIV testing and counselling once a year.

Preventive therapy in health care workers with new latent TB infection likely to be MDR

- A program of treatment of latent MDR-TB infection for health care providers requires:
 - Pre-employment screening of health care workers with TST/IGRA before starting work at an MDR-TB facility.
 - Regular screening of health care workers TST/IGRA once a year.
- Healthcare providers with a positive TST/IGRA during the pre-employment screening should not receive treatment for latent MDR-TB.
- Many MDR-TB treatment programs choose not to have a program for treatment of latent MDR-TB infection in staff because of the limited evidence to support the practice. Instead, such programs use a strategy of good infection control measures and regular screening for TB in health care providers.
- If the facility performs regular screening for new latent TB and offers preventive therapy for health care providers who develop latent MDR-TB infection, the preventive therapy strategy described in Section 16.4 should be followed.

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16 Contact investigation and management of latent MDR-TB infection

16.1 Why do household contact investigation?

The prevalence of active MDR-TB in household contacts of MDR-TB patients is very high

- Household contacts are likely to be infected because they are in close contact with infectious patients for prolonged periods of time.
- Household contacts are likely to develop active TB because they have recently been infected, and active TB is more likely soon after infection.
- Household contacts of MDR-TB patients have usually been exposed for months or years, longer than household contacts of drug-susceptible TB patients.
- The prevalence of active MDR-TB in household contacts of MDR-TB patients is likely to be higher than that of household contacts of drug-susceptible index cases, and that of XDR-TB higher still.

Advantages of contact investigation

- Early treatment of MDR-TB is cheaper and more effective compared to MDR-TB that is detected late.
- Contacts of MDR-TB patients can be treated immediately with an MDR-TB regimen and prevented from starting an ineffective regimen.
- Contact investigation of MDR-TB prevents the transmission of this strain to others inside or outside of the home.
- Contact investigation is an excellent opportunity to educate family members about the risk of TB, MDR-TB, and other comorbidities such as HIV.

Who should do the contact investigation?

- The community team that provides DOT of the MDR-TB regimen is best situated to do a home visit and the contact investigation, and make sure that household contacts with symptoms are investigated promptly and correctly.
- The clinical team that is responsible for the MDR-TB patient should also be responsible for any diagnostic workup needed by the patient's close contacts.

- The clinical and community team is best suited to make sure that close contacts of the MDR-TB patient do not receive empiric treatment for drug-susceptible TB.
- The clinical and community team should interview close contacts as soon as possible after MDR-TB treatment starts, since contacts are most likely to develop active TB soon after becoming infected.

16.2 Diagnostic workup of household contacts of MDR-TB patients

- A household contact lives in the same household as the MDR-TB patient or spends many hours a day together with the MDR-TB patient in the same indoor living space.
 - Close contacts are people who do not live in the same household as the MDR-TB patient but spend significant time together in the workplace or other settings. Depending on the setting, close contacts may be managed similarly to household contacts.
- Household contact investigation should be integrated into all community-based care programs, as this step generally requires a home visit.
- Routine screening of all household contacts should include:
 - Asking about cough, fever, weight loss, and other symptoms of TB.
 - HIV counseling and testing in areas of high HIV prevalence, or if anyone in the household is known to be HIV-positive.
- A household contact with any symptoms suggestive of active TB should receive all of the following:
 - Evaluation by a physician, including history and physical examination.
 - ♦ The chest X-ray and Xpert MTB/RIF testing may be done before the physician evaluation.
 - Chest X-ray to look for signs of active TB (e.g., infiltrates, cavities) or inactive TB (e.g., scarring, granulomas).
 - ♦ The chest X-ray should be kept on file by the clinical team to compare with subsequent X-rays if the contact continues to have symptoms or develops new symptoms in the future. This is particularly important for household contacts with comorbid pulmonary disease (e.g., COPD or silicosis).
 - ♦ A chest X-ray should be done even if extrapulmonary TB is suspected, since the contact may have unsuspected pulmonary TB at the same time.
 - Bacteriological investigations of sputum or other samples:
 - ♦ Xpert MTB/RIF is the recommended initial diagnostic test because it provides diagnosis of TB and MDR-TB rapidly.
 - ♦ Culture and DST may be sent if Xpert MTB/RIF is negative and suspicion of active TB or MDR-TB remains high.

16.3 Treatment of active TB in household contacts of MDR-TB patients

Household contacts of MDR-TB patients with active TB should almost always be treated with an MDR-TB regimen

- Household contacts of MDR-TB patients who develop active TB almost always have MDR-TB themselves, even if the pattern of resistance is not always exactly the same. Young children are even more likely than other close contacts to be infected in the home with an MDR-TB strain.
- If rapid molecular DST is not available, household contacts with active TB should be empirically treated with the same regimen as the index patient if culture-based DST is expected to take several months. If the DST eventually shows that the contact was infected outside the home by a pan-susceptible strain, the contact can be switched to a regimen of first-line drugs.

Household contacts of MDR-TB patients with extrapulmonary TB

- Extrapulmonary TB is often culture-negative and DST will not be available. These contacts should be started on an MDR-TB regimen based on the DST of the index patient.
- Every effort should be made to culture aspirates of pleural, peritoneal, or cerebrospinal fluid, depending on the site, but there is no need to wait for laboratory confirmation of MDR-TB.

Household contacts of MDR-TB patients with culture-negative TB

- If cultures are negative or contaminated, close contacts should be continued on the empiric regimen based on the DST of the index patient for the full duration of treatment.

Household contacts of MDR-TB patients with a previous history of TB treatment and unknown resistance pattern

- Sometimes an older family member with a history of chronic TB for many years is discovered to be the “true” index patient within the family.
- Often the history may suggest MDR-TB even though there is no DST. For example, the older family member may have received multiple first-line TB treatments and been deemed cured or have no clear outcome.

- These family members should receive careful clinical and bacteriological evaluation.
 - They may have a different drug resistance pattern if they received TB treatment previously.
 - Any empiric treatment regimen should be based on their past history of TB treatment, as well as the DST of other MDR-TB patients in the family.
- Contact investigation is an excellent opportunity to treat these family members for MDR-TB and address any social or economic barriers to treatment that have prevented the family member from receiving effective treatment in the past.

16.4 Treatment of latent infection in household contacts of MDR-TB patients

Isoniazid preventive therapy is not recommended for household contacts of MDR-TB patients

- Some categories of household contacts will receive isoniazid preventive therapy as part of routine contact tracing efforts. This is effective if the index case has drug-susceptible TB, but unlikely to be effective if the index case has MDR-TB.
- Household contacts under 5 years of age may receive routine isoniazid preventive therapy in many countries. This is safe but unlikely to be effective if the index case has MDR-TB, as young children are likely to be infected in the home.
- In high HIV-prevalence countries, HIV-positive contacts may receive routine isoniazid preventive therapy as part of national HIV guidelines. This is unlikely to be effective to prevent MDR-TB.

There has never been a clinical trial of MDR-TB preventive therapy with second-line anti-TB drugs

- Some major clinical guidelines recommend only “watchful waiting” for close contacts while others recommend preventive therapy with second-line drugs.
- On the basis of the currently available evidence, the routine treatment of presumed latent MDR-TB infection in household contacts with second-line anti-TB drugs is not recommended.

“Watchful waiting”

- Perform an initial symptom screen of all household contacts at the time the index case is enrolled in MDR-TB treatment.
- Test all household contacts for HIV, especially in high HIV-prevalence settings or if anyone in the family is HIV-positive. HIV-positive household contacts should be evaluated for ART and started immediately if eligible.
- The first year after infection has the highest risk for developing active TB, but since many MDR-TB patients have been chronically infectious, their family members may have been exposed for much longer than that.
- Educate all family members about the signs and symptoms of active TB disease and how to prevent transmission of TB within the home.

- Provide a full clinical evaluation whenever household contacts develop symptoms suggestive of TB.
- Follow all household contacts with presumed latent MDR-TB for a minimum of two years following exposure, with symptom review every six months.
- If active disease develops, start treatment with an MDR-TB regimen.

Treatment of latent MDR-TB can be provided on a case-by-case basis

- Considerations include:
 - Heavy exposure such as spending large amounts of time with the index case.
 - A recent TST or IGRA conversion after exposure to MDR-TB.
 - Children under 5 years.
 - People living with HIV.
- If the chest X-ray is abnormal, there is a higher risk of misdiagnosing active TB. In these cases, it is important to obtain negative sputum cultures before considering preventive therapy. Follow-up clinical and radiological examinations are advisable.
- While there is little risk of amplification of resistance if active disease is not present, it is likely that patients who develop active TB while on a fluoroquinolone-based preventive regimen will be resistant to the fluoroquinolone.
- Levofloxacin- or moxifloxacin-based regimens are the most commonly used. Pyrazinamide is not recommended as a companion drug due to the high incidence of side effects.
- Dosing of drugs used in treatment of latent MDR-TB infection is the same as used in the treatment of active MDR-TB disease.

Possible preventive therapy regimens for MDR-TB contacts

DST of index patient	Regimen	Duration	Comments
Susceptible to fluoroquinolones	Levofloxacin or moxifloxacin	9-12 months*	Monotherapy is employed by some experts and is well-tolerated.
Susceptible to fluoroquinolones and ethambutol	Levofloxacin or moxifloxacin + ethambutol	9-12 months*	Often ethambutol is resistant or susceptibility is uncertain, in which case this regimen should not be used.
Susceptible to fluoroquinolones and resistant (or likely resistant) to ethambutol	Levofloxacin or moxifloxacin + a Group 4 drug	9-12 months*	Ethionamide, cycloserine, and PAS may be used as the Group 4 drugs. Side effects are a concern with this sort of regimen.

*HIV-infected, children, and patients with comorbidities that increase susceptibility to TB should receive 12 months of treatment.

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17 Recording and reporting

17.1 Registration of cases

Case definitions

- **Bacteriologically confirmed TB case:** A biological specimen is positive by smear microscopy, culture, or WHO-approved rapid diagnostic (such as Xpert MTB/RIF).
- **Clinically diagnosed TB case:** Has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. Includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extrapulmonary cases without laboratory confirmation.

Bacteriologically confirmed or clinically diagnosed cases of TB are also classified according to:

- Anatomical site of disease.
 - **Pulmonary tuberculosis (PTB):** Any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree.
 - ♦ Miliary TB is classified as PTB because there are lesions in the lungs.
 - ♦ Tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extrapulmonary TB.
 - ♦ A patient with both pulmonary and extrapulmonary TB should be classified as a case of PTB.
 - **Extrapulmonary tuberculosis (EPTB):** Any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs (e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges).
- History of previous treatment.
 - **New.**
 - ♦ A patient who has received no or less than one month of anti-TB treatment.
 - ♦ A patient should only be placed in the registration category of “new” if they are placed on second-line anti-TB treatment from the start of their first TB treatment (usu-

ally because of a rapid molecular DST result showing resistance) or if the patient has received less than one month of first-line drug treatment before they are started on second-line TB treatment (usually because DST results have returned, indicating MDR-TB or RR-TB) shortly after the patient started a first-line anti-TB treatment).

– **Relapse.**

- ◆ A patient who was previously treated for TB and whose most recent treatment outcome was “cured” or “treatment completed,” and who is subsequently diagnosed with bacteriologically positive TB by sputum smear microscopy, Xpert MTB/RIF, or culture.

– **Treatment after being lost to follow-up.**

- ◆ A patient who returns to treatment, bacteriologically positive by sputum smear microscopy, Xpert MTB/RIF, or culture, following interruption of treatment for two or more consecutive months.

– **After failure of first treatment with first-line drugs.**

- ◆ A patient who has received first-line drug treatment for TB and in whom treatment has failed.
- ◆ Treatment failure of a first-line treatment regimen is defined as a sputum smear or culture that is positive at five months or later during treatment, as well as identification of MDR-TB strain (or RR-TB) at any point of time during the treatment regardless of smear status. The only exception is if during the first month of taking a first-line anti-TB treatment, an MDR-TB (or RR-TB) strain is identified and the patient is switched to a second-line anti-TB treatment; these patients can be registered as “new” and not as “after failure.”

– **After failure of retreatment regimen with first-line drugs.**

- ◆ A patient who has received first-line drugs for previously treated TB in whom treatment has failed.

– **Other: Patients who may not fit into any of the above categories.**

- ◆ Sputum smear-positive patients with unknown previous treatment outcome.
- ◆ Sputum smear-positive patients who received treatment other than standardized first-line regimens.

- ♦ Previously treated patients with extrapulmonary TB; patients who have received several unsuccessful treatments, were considered incurable by health staff, and have lived with active TB disease with no or inadequate treatment for a period of time until second-line TB treatment became available—so-called “backlog” or “chronic” patients.
- Drug resistance.
 - **Confirmed RR-TB or MDR-TB:** DST-documented resistance in a sample from the patient.
 - **Presumptive RR-TB or MDR-TB:** Patients may be registered and started on second-line anti-TB treatment solely based on significant risk for DR-TB and before laboratory confirmation of resistance.
 - **Polyresistant TB:** Some cases with polyresistant TB by DST may require second-line anti-TB treatment, in which case they should be entered on the second-line TB treatment register.
- HIV status.
 - **HIV-positive TB patient:** Any bacteriologically confirmed or clinically diagnosed case of TB who has a positive result from HIV testing conducted at the time of TB diagnosis or other documented evidence of enrollment in HIV care, such as enrollment in the pre-ART register or in the ART register once ART has been started.
 - **HIV-negative TB patient:** Any bacteriologically confirmed or clinically diagnosed case of TB who has a negative result from HIV testing conducted at the time of TB diagnosis. Any HIV-negative TB patient subsequently found to be HIV-positive should be reclassified accordingly.
 - **HIV status unknown TB patient:** Any bacteriologically confirmed or clinically diagnosed case of TB who has no result of HIV testing and no other documented evidence of enrollment in HIV care. If the patient’s HIV status is subsequently determined, he or she should be reclassified accordingly.

Summary of case registration

Registration groups based on outcome of last treatment		Further classification
New		1. PTB or EPTB? If EPTB, indicate site. 2. Bacteriologically confirmed or clinically diagnosed TB case? 3. Subcategory of bacteriological status: <ul style="list-style-type: none"> • Smear positive/negative/not done. • Culture positive/negative/not done. • Molecular test positive/negative/not done. 4. If previously treated: <ul style="list-style-type: none"> • Document last regimen received. • History of second-line drug use. 5. DST pattern: Confirmed H resistance and R susceptible, RR-TB, MDR-TB, or XDR-TB, or susceptible to H and R. 6. HIV status (negative/positive/not done). 7. Other comorbidities?
Previously treated	Relapse	
	Failure	
	Lost to follow-up	
Other		

17.2 The six mutually exclusive outcome definitions

1. Cured

- Treatment regimen completed without evidence of failure and 3 or more consecutive cultures taken at least 30 days apart are negative after 8 months of therapy.

2. Treatment completed

- Treatment regimen completed without evidence of failure but no record that 3 or more consecutive cultures taken at least 30 days apart are negative after 8 months of therapy.
- The sum total of “cured” and “treatment completed” is commonly used as an indicator of favorable outcome, or “treatment success”. The outcome “cured” is restricted to pulmonary TB cases only.

3. Treatment failed

- Treatment terminated or need for permanent treatment change of at least two classes of anti-TB drugs because of one or more of the following:
 - ♦ Lack of monitoring cultures converting to negative by eight months for MDR-TB.
 - ♦ Bacteriological reversion in the continuation phase (at least two positive smears or cultures at least seven days apart) after monitoring smears or cultures have become negative.
 - ♦ Acquired resistance to second-line injectables or fluoroquinolones during treatment.
 - ♦ A clinical decision has been made to terminate treatment early due to adverse events. These latter failures can be indicated separately in order to do subanalysis.
- Lack of conversion or reversion with clinical deterioration can prompt a change of regimen and a final outcome of failure earlier than eight months.

4. Died

- Death for any reason during the course of MDR-TB treatment.

5. Lost to follow-up

- Treatment interrupted for two or more consecutive months for any reason without medical approval.

6. Not evaluated

- No treatment outcome evaluated.

17.3 Interim indicators for MDR-TB program monitoring

- **MDR-TB cases on MDR-TB treatment that died:** Number of confirmed MDR-TB cases registered and started on MDR-TB treatment who died of any cause by the end of month 6/total number of confirmed MDR-TB cases started on treatment for MDR-TB during the period.
- **MDR-TB cases on MDR-TB treatment that interrupted:** Number of confirmed MDR-TB cases started on MDR-TB treatment who interrupted by the end of month 6/total number of confirmed MDR-TB cases started on treatment for MDR-TB during the period.
- **MDR-TB cases on MDR-TB treatment with negative culture:** Number of microbiologically confirmed pulmonary MDR-TB cases registered and started on MDR-TB treatment with negative culture at month 6/total number of microbiologically confirmed DR-TB cases registered and started on treatment for DR-TB during the period.
- **MDR-TB cases on MDR-TB treatment with positive culture:** Number of microbiologically confirmed pulmonary MDR-TB cases registered and started on DR-TB treatment with positive culture at month 6/total number of microbiologically confirmed DR-TB cases registered and started on treatment for DR-TB during the period.

17.4 Final outcome indicators

Treatment outcome indicators

- **Proportion of cured:**

$$\frac{\text{Number of confirmed TB cases declared cured}}{\text{Total number of confirmed TB cases put under treatment during the period}}$$

- **Proportion of treatment completed:**

$$\frac{\text{Number of patients registered as treatment completed}}{\text{Total number of patients put under treatment for the period}}$$

- **Proportion with successful outcome:**

$$\frac{\text{Number of patients registered as cured or treatment completed}}{\text{Total number of patients put under treatment during the period}}$$

- **Proportion of lost to follow-up:**

$$\frac{\text{Number of patients registered as lost to follow-up}}{\text{Total number of patients put under treatment during the period}}$$

- **Proportion of death:**

$$\frac{\text{Number of patients registered as dead}}{\text{Total number of patients put under treatment during the period}}$$

- **Proportion of failure:**

$$\frac{\text{Number of patients registered as failures}}{\text{Total number of patients put under treatment during the period}}$$

HIV indicators

- **Proportion of patients for whom HIV status is known:**

$$\frac{\text{Number of patients for whom HIV status is known by the end of treatment}}{\text{Total number of patients put under treatment during the period}}$$

- **TB-HIV coinfection rate:**

$$\frac{\text{Number of HIV-infected TB patients}}{\text{Total number of TB patients put under treatment during the period and for whom HIV status is known at the end of treatment}}$$

Reference

- *Definitions and reporting framework for tuberculosis—2013 revision* (WHO/HTM/TB/2013.2). Geneva: World Health Organization; 2013.

18 Compassionate use and expanded access programs for new anti-TB drugs

18.1 New drugs and therapy

Recent developments

- In recent years, considerable research has been conducted in the hunt for new drugs and better TB therapy.
- Bedaquiline and delamanid are the two new anti-TB drugs furthest along in terms of receiving approval, with a number of other drugs in the pipeline.
- It should be noted that bedaquiline is approved under the U.S. Food and Drug Administration's (FDAs) accelerated approval program, which allows the FDA to approve a drug to treat a serious disease based on clinical data showing that the drug has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients. This program provides patients earlier access to promising new drugs while the pharmaceutical company conducts additional studies to confirm the drug's clinical benefit and safety.
- Programs may be able to employ two new anti-TB drugs in the near future.
- In addition to new anti-TB drugs there are other avenues under study to improve DR-TB therapy; however, to date none are involved in compassionate use or expanded access programs. In the future, compassionate use or expanded access programs could benefit these avenues as well and include:
 1. New TB indications of existing drugs: Linezolid, clofazimine, and the later-generation fluoroquinolones.
 2. Immunomodulators.
 3. New routes of drug administration such as via nebulizers or liposomes that can be used as anti-TB nanocarriers.

Keeping informed on new drugs

- WHO has a Task Force for New Drug Policy Development: http://www.who.int/tb/advisory_bodies/newdrugs_taskforce/en/index.html.
- The task force web page provides policy guidance and “how-to” information in a timely fashion on all new anti-TB drugs developed.

18.2 Definition of compassionate use/expanded access

Compassionate use

- Refers to the application of potentially life-saving experimental treatments to patients suffering from a disease for which no satisfactory authorized therapy exists and/or who cannot enter a clinical trial. For many patients, these treatments represent their last hope.
- Usually a physician applies directly to the manufacturer.
- The manufacturer provides the drug to the physician for use in that specific patient, and the patient's condition must meet criteria established by the manufacturer, usually based on the absence of any other treatment with any likelihood of success.
- The manufacturer provides guidelines on the use of the drug, but does not monitor use or outcomes.
- In general, the country of residence must have regulations in place permitting such "compassionate use" of an unapproved drug.
- The physician is responsible for following local regulations, such as for importation or the need for Institutional Review Board (IRB) approval.

Expanded access

- Refers to programs that focus on enrolling groups of patients; in this way they are a type of clinical trial.
- Rather than evaluating individual patients case-by-case on the basis of need, as is the case in compassionate use, a target population for enrollment is defined and only patients meeting enrollment criteria can participate.
- There is more emphasis on patient's follow-up than in the compassionate use mechanism, and collection of safety and follow-up/treatment outcome data is the rule.
- The drug is used on an open-label basis (the patient knows that they are receiving the drug and there is no placebo arm), and its use must follow program guidelines.
- In this situation, an expanded access program is established in specific countries, where it is registered as a clinical trial. Thus, access is limited to countries where the trial is taking place.

18.3 Program issues

Program responsibilities and minimum requirements

- Compassionate use should only be considered if conditions for adequate management of MDR-TB patients are in place: Optimal treatment regimen; clinical, biological, and bacteriological monitoring; adherence support and follow-up.
- Results of DST by a validated laboratory are critical.
- In addition to the basic components of regular MDR-TB case management, specific monitoring might be required for the use of a new drug.
- It is essential that a reporting system is in place in order to diligently report any adverse events. This is referred to as pharmacovigilance.
- A single new anti-TB drug should never be added to a failing regimen. Always try to add at least two or more new companion drugs or drugs highly likely to be effective. Ideally regimens with new drugs should have at least four effective drugs in them. There should be a guarantee of uninterrupted supply of the companion drugs.

Ethical issues

- The patient must be well-informed about the drug, its intended actions and potential side effects, and its possible impact on other conditions or treatments.
- It is critical that the patient is informed of treatment alternatives, if any, and understands that there is no guarantee of benefit from the preapproval drug.
- Any drug not yet approved by a regulatory authority should be provided free of charge to the patient.
- Patients must consent in writing to be treated under a compassionate use/expanded access program.

Regulatory authorities

- In most countries, only drugs for which a marketing authorization has been granted by the national regulatory agency can be used in humans.
- Some national regulatory agencies have developed mechanisms to facilitate the access to new drugs at different stages of development but before market approval. In this case, a party can apply for approval of a new investigational anti-TB

drug and then seek the proper permission to import the drug to a country. This often requires permission from the proper national regulatory authorities and/or country ethic boards.

References

- Caminero JA, ed. *Guidelines for Clinical and Operational Management of Drug-Resistant Tuberculosis*. Paris: International Union Against Tuberculosis and Lung Disease; 2013.
- *A practical handbook on the pharmacovigilance of medicines used in the treatment of TB*. Geneva: World Health Organization; 2012.
- *Tuberculosis: Practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries*. Médecins Sans Frontières and Partners In Health; 2013.

19 Procedures

19.1 Fine needle aspiration

General considerations

- Fine needle aspiration is an easy way to obtain material from lymph nodes that can be used to diagnose TB.
- Careful cleaning of the skin with povidone-iodine or chlorhexidine is important to avoid infection.

Equipment

- Needle 21 to 23 gauge (up to a 20-gauge needle can be used).
- 10-mL syringe.
- Slides.
- Povidone-iodine, sterile gauze, gloves.

Technique

- Disinfect the area.
- With the needle attached to the syringe, insert the needle deep into the lymph node.
- After the needle has entered the mass, pull back on the syringe plunger to create a vacuum.
- Move the needle in a to-and-fro fashion to allow material to be sucked into the syringe (without the needle tip leaving the lymph node).
- When blood or material appears in the needle hub the aspiration should be stopped. Try to aspirate as much material as possible.
- Release the negative pressure before taking out the needle from the lymph node. Do not continue aspirating while taking out the needle.
- Detach the needle from the syringe immediately after the aspiration and put in needle box.

Testing

- Aspirated material may be sent for smear microscopy, culture, and Xpert MTB/RIF.
- If available, preparation of cytology slides can be very helpful for the diagnosis of TB and other diseases. Observation of the slides requires a competent reader with skills in cytology (not all granulomatous inflammation is TB, and further staining and studies are often required to confirm TB).

19.2 Sputum induction

General considerations

- Sputum induction 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.
- The procedure can be repeated twice on the same day, at least four 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 and appropriate infection control measures must be taken:
 - An appropriate site must be available. The minimum requirement is a small room with good ventilation.
 - Staff must use respirators, eye protection, and nonsterile gloves.

Material required

- Mask (respirator) for the operator and caregiver (if present).
- Eye protection and nonsterile gloves for operator.
- Oxygen (on standby in case of emergency).
- Pulse oximeter.
- Request form.
- Spacer device (holding chamber) and mask.
- Salbutamol metered-dose inhaler.
- Mask, chamber, and tubing.
- Antibacterial filter.
- Nebulizer (ultrasonic is the preferred type).
- Sterile solution of 3 percent to 6 percent sodium chloride, refrigerated if possible (more irritant).
- Sputum collection container.
- For children under 5 years who require nasopharyngeal suction:
 - Suction catheter (7F or 8F).
 - Mechanical suction device and mucus trap (if not available, obtain a 50-mL syringe).
 - Sterile solution of 0.9 percent sodium chloride.

Infection control measures

- 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 percent 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).
- 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 two hours.
- Severe respiratory distress.
- Oxygen saturation less than 92 percent 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

- 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 five minutes before starting nebulization.
- Prepare a sputum container.
- Fill the nebulizer with 5 mL of 3 percent to 6 percent 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 the 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 one to two 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 percent 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 postprocedure. Give oxygen if saturation has dropped below 90 percent.

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

- Coughing spells (~40 percent): If severe, stop the procedure and administer salbutamol. Oxygen should be available and can be administered in severe cases.
- Nosebleeds (~8 percent): Stop the procedure and apply constant pressure of 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 percent): Monitor the child closely. Stop the procedure if wheezing increases. Administer salbutamol and oxygen if severe.
- Vomiting (< 1 percent): Stop the procedure and observe the child closely until the vomiting stops.

19.3 Gastric aspiration

General considerations

- Gastric aspiration can be used in children when sputa cannot be spontaneously expectorated or 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 accidentally induced by the procedure), eye protection, and nonsterile gloves.
- Gastric aspiration should not be done for smear alone as the yield is low and not worth the invasiveness of the test.

Contraindications

- Child has not fasted for four hours.
- Low platelet count or bleeding tendency.

Material required

- Nonsterile 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 percent).
- Alcohol/chlorhexidine.

Procedure

- Position child on his/her back or side.
- Have an assistant 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 to 5 mL of air into the stomach and listening with a stethoscope over the stomach.
- If no fluid is aspirated, insert 5 to 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 four hours).
- Give the child his or her usual food.

Reference

- *Tuberculosis: Practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries*. Médecins Sans Frontières and Partners In Health; 2013.

20. Forms

20.1 Enrollment form

MDR-TB Treatment Intake Form

I. Demographic Data

Last Name _____ First Name _____

Registration No. _____ Health Center _____

Date of Birth _____ Gender: Male Female

Address _____

District _____ Province _____

Telephone number _____ No telephone available

Civil status: Married Single Partnered Widowed Divorced/Separated

Employment status: Employed Retired Student Unemployed

Occupation _____ Last Level of Education _____

II. Tuberculosis History

Previous active TB disease: Yes No

Pulmonary: Yes No Smear status: Positive (Result _____) Negative Date _____

Culture status: Positive (Result _____) Negative Date _____

Extra-pulmonary: Yes No Site _____

Previous TB Treatment

Outcomes: Cured, Treatment Completed, Treatment Failed, Lost To Follow-Up, Not Evaluated

	Start Date (DD-MM-YY)	Finish Date (DD-MM-YY)	Duration	Regimen				Treatment Center	Outcome
				Cat I	Cat II	Cat IV	Other		
1			m					C TC F LTF NE	
			d						
2			m					C TC F LTF NE	
			d						
3			m					C TC F LTF NE	
			d						
4			m					C TC F LTF NE	
			d						
5			m					C TC F LTF NE	
			d						
6			m					C TC F LTF NE	
			d						
7			m					C TC F LTF NE	
			d						

Has received treatment with the following medications:

H R E Z S KM AMK CM OFX MXF LFX ETH CS PAS AMX-CLV LZD CFZ BDQ

Other: _____

Additional comments:

MDR-TB Treatment Intake Form

Last Name _____ Registration No. _____

III. TB Contacts No contacts:

Household Contacts	Relationship	Age	Ever Treated for TB? (Yes / No)	Symptoms of Active TB? (Yes / No)	Xpert Testing? (Yes / No)

IV. Past Medical History

HIV/AIDS Yes No Convulsions, epilepsy Yes No
 Diabetes mellitus Yes No Cardiovascular disease Yes No
 Chronic renal insufficiency Yes No Psychiatric history Yes No
 Chronic hepatitis or cirrhosis Yes No Severe malnutrition Yes No
 Gastritis Yes No Other: _____

V. Medications: None

Medication	Indication	Dosage	Frequency	Route	Start Date	Stop Date	Continues
							<input type="checkbox"/>
							<input type="checkbox"/>
							<input type="checkbox"/>
							<input type="checkbox"/>
							<input type="checkbox"/>

VI. Allergies or adverse drug reactions (medication and reaction):

Rash, Angioedema, Stevens-Johnson, Hepatitis

Penicillin	R	A	S	H	Other:	Z	R	A	S	H	Other:
Sulfa	R	A	S	H	Other:	S	R	A	S	H	Other:
H	R	A	S	H	Other:	Quinolone	R	A	S	H	Other:
R	R	A	S	H	Other:	Other:	R	A	S	H	Other:
E	R	A	S	H	Other:	Other:	R	A	S	H	Other:

VII. Habit History

Currently smoking: Yes No _____ packs/day, for _____ yearsCurrently drinking alcohol: Yes No _____ drinks/dayCurrently substance dependent: Yes No Substance(s): _____

VIII. Pregnancy History

Last menstruation date ___/___/___ (DD-MM-YY)

History of pregnancy Yes No Number _____

Number of delivered pregnancies _____

Contraceptive use: Yes No

MDR-TB Treatment Intake Form

Last Name _____ Registration No. _____

IX. Current Presentation

Fever Yes <input type="checkbox"/> No <input type="checkbox"/>	Weight Loss Yes <input type="checkbox"/> No <input type="checkbox"/>	Cough Yes <input type="checkbox"/> No <input type="checkbox"/>	Dyspnea Yes <input type="checkbox"/> No <input type="checkbox"/>
Duration (mos) _____	Amount (kg) _____	Duration (mos) _____	
	Normal weight _____	Hemoptysis Yes <input type="checkbox"/> No <input type="checkbox"/>	

Other symptoms:

X. Physical Examination

BP _____/_____	Normal	Abnormal	Comments
Pulse _____/min	Head, ears, eyes, nose, throat		
Temp _____°C	Lymph nodes		
RR _____/min	Heart		
Weight _____kg	Lungs		
Height _____cm	Abdomen		
	Skin		
	Urogenital		
	Musculoskeletal		
Functional status:	Neurological		
Able to work Y <input type="checkbox"/> N <input type="checkbox"/>	Extremities		
Ambulatory Y <input type="checkbox"/> N <input type="checkbox"/>	Other		
Bedridden Y <input type="checkbox"/> N <input type="checkbox"/>			

XI. Laboratory Results

HIV Antibody: Positive Negative Date _____ HCG: Positive Negative Date _____

Potassium	Magnesium	Calcium	Creatinine	Creatinine Clearance
Date	Date	Date	Date	Date
Date	Date	Date	Date	Date

ALT (SGPT)	AST (SGOT)	Bilirubin	Albumin	Glucose
Date	Date	Date	Date	Date
Date	Date	Date	Date	Date

WBC	Hematocrit	Platelets	CD4
Date	Date	Date	Date
Date	Date	Date	Date

Other Results:

MDR-TB Treatment Intake Form

Last Name _____ Registration No. _____

XII. Microbiology

Gene Xpert MTB/RIF Test Results

Date sample collected (DD-MM-YY)	MTB Result			RIF Result		
	TB detected	Not detected	Error or invalid	Resistance detected	Not detected	Indeterminate

Conventional Drug Susceptibility Test Results

Laboratory	Date	Sample N°	H	R	E	Z	S	Kn	Cm	Lfx	Cs	Eth	PAS			

XIII. Chest X-ray

Date _____ (DD-MM-YY)

Upper Right Lobe

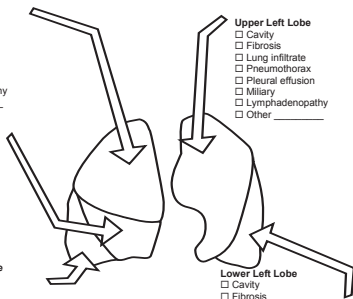
- Cavity
- Fibrosis
- Lung infiltrate
- Pneumothorax
- Pleural effusion
- Miliary
- Lymphadenopathy
- Other _____

Middle Right Lobe

- Cavity
- Fibrosis
- Lung infiltrate
- Pneumothorax
- Pleural effusion
- Miliary
- Lymphadenopathy
- Other _____

Lower Right Lobe

- Cavity
- Fibrosis
- Lung infiltrate
- Pneumothorax
- Pleural effusion
- Miliary
- Lymphadenopathy
- Other _____



Upper Left Lobe

- Cavity
- Fibrosis
- Lung infiltrate
- Pneumothorax
- Pleural effusion
- Miliary
- Lymphadenopathy
- Other _____

XIV. Electrocardiogram Date _____ (DD-MM-YY) Heart Rate _____ QT_c interval _____

Note: QT_c = QT / √(60 - heart rate)

XV. Other diagnostic studies

MDR-TB Treatment Intake Form

Last Name _____

Registration No. _____

XVI. Assessment and Plan

Registration group	Tick
New	
Previously treated – Relapse	
Previously treated – Treatment after failure	
Previously treated – Treatment after loss to follow-up	
Previously treated – Other	
Unknown previous TB treatment history	

XVII. Proposed Regimen and Dosing Guide

New medications prescribed at this interview (list anti-TB meds first)	Dosage	Frequency	Route	Start date	Indication

Anti-TB Drug Dosing Guide

Group	Drug	Daily Dose in mg (Per Patient Weight in kg)		
		33-50 kg	51-70 kg	>70 kg (max dose)
Group 1	Ethambutol (25 mg/kg)	1250	1750	1750
	Pyrazinamide (30-40 mg/kg)	1000-1750	1750	2000-2500
Group 2	Kanamycin (15-20 mg/kg)	500-750	1000	1000
	Amikacin (15-20 mg/kg)	500-750	1000	1000
	Capreomycin (15-20 mg/kg)	500-750	1000	1000
Group 3	Levofloxacin	750	750-1000	1000
	Moxifloxacin	400	400	400
Group 4	Ethionamide (15-20 mg/kg)	500	750	1000
	Cycloserine (15 mg/kg)	500	750	1000
Group 5	Para-aminosalicylic acid	8000	8000	8000
	Bedaquiline	400 mg/day for first two weeks then 200 mg three times per week		
	Linezolid	600	600	600
	Amoxicillin/Clavulanic acid	2600	2600	2600
	Clofazimine	200	200	200

Clinician's signature _____

Clinician's name (block letters) _____

Date _____ (DD-MM-YY)

20.2 Follow-up form

MDR-TB Treatment Monthly Follow-Up Form

Month _____ Date ____/____/____

Name _____

Registration No. _____

I. Medical presentation

Fever Yes No Other symptoms:
 Weight Loss Yes No
 Cough Yes No
 Hemoptysis Yes No
 Dyspnea Yes No

Pulmonary TB	Yes <input type="checkbox"/> No <input type="checkbox"/>
Extrapulmonary TB	Yes <input type="checkbox"/> No <input type="checkbox"/>
HIV Coinfection	Yes <input type="checkbox"/> No <input type="checkbox"/>

Record all new events or changes in pre-existing conditions since last interview						
Event	Date onset	Date resolved	Outcome [§]	Severity [‡]	Seriousness [§]	Rechallenge [¶]

§ Outcome

R1 Recovered/resolved
 R2 Recovering/resolving
 S Recovered with sequelae
 N Not recovered/not resolved
 D Died
 U Unknown

‡ Severity

1 Mild
 2 Moderate
 3 Severe

§ Seriousness

N Not serious
 H Hospitalization
 P Permanent disability
 C Congenital abnormality
 L Life threatening
 D Death

¶ Rechallenges

1 No rechallenges
 2 Recurrence of event
 3 No recurrence
 4 Result unknown

Side Effect	Question to Ask Patient	Patient Response	Action Taken
Hearing loss	Are you having trouble hearing?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Tinnitus and dizziness	Do you have any ringing in your ears or dizziness?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Nausea	Have you had nausea the last week?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Vomiting	Have you vomited in the last month?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
	Have you vomited up your medications?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Diarrhea	Have you had diarrhea in the last month?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Abdominal Pain	Have you had abdominal pain?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
	Have you had black stools or vomited blood?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Anorexia	Do you have a poor appetite?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Neuropathy	Have you had pain or burning in your legs?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Low Potassium	Have you had leg cramping?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
	Do you feel weak?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Depression	Do you feel sad?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
	Do you have thoughts of committing suicide?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Anxiousness	Do you feel anxious or agitated?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Psychosis	Do you hear voices or see things that may not be there?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Hepatitis	Have you noticed yellowing of your eyes or your skin?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Allergy	Do you have any rashes?	Yes <input type="checkbox"/> No <input type="checkbox"/>	
Joint Pain	Do you have any joint pain?	Yes <input type="checkbox"/> No <input type="checkbox"/>	

Name _____ Registration No. _____

II. Co-morbidities

Diabetes Yes No Chronic kidney disease Yes No Chronic liver disease Yes No
 Pregnant Yes No Uncertain Date of LMP: _____ or estimated current gestation _____
 Breastfeeding Yes No

III. Contact Tracing

Family members with fever, weight loss, cough, dyspnea: Yes No
 Relationship: _____

IV. Socio-economic Issues

Social or economic issues that could interrupt treatment: Yes No

Comments:

V. Physical Examination

Temp _____°C BP _____/_____ Pulse _____/min RR _____/min Weight _____ kg Height _____ cm

Physical exam normal: Yes No

Abnormal physical findings:

VI. Laboratory Results

Potassium		Magnesium		Calcium		Creatinine		Creatinine Clearance	
Date		Date		Date		Date		Date	
Date		Date		Date		Date		Date	

ALT (SGPT)		AST (SGOT)		Bilirubin		Albumin		Glucose	
Date		Date		Date		Date		Date	
Date		Date		Date		Date		Date	

WBC		Hematocrit		Platelets		CD4	
Date		Date		Date		Date	
Date		Date		Date		Date	

Most recent sputum smear: Date _____ Negative Positive (Result _____)

Most recent sputum culture: Date _____ Negative Positive (Result _____)

VII. Electrocardiogram Date _____ (DD-MM-YY) Heart Rate _____ QT_c interval _____

Note: QT_c = QT / √(60 / heart rate)

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