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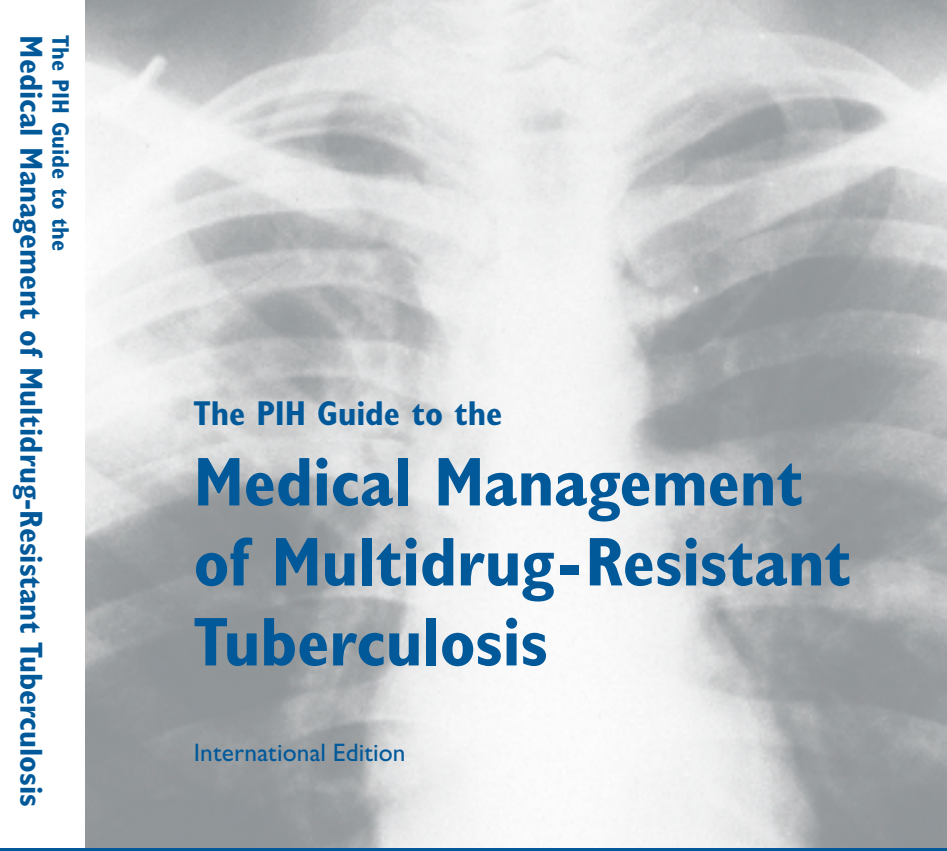
The PIH Guide to the
Medical Management of Multidrug-Resistant Tuberculosis



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International Edition

Partners In Health
Program in Infectious Disease and Social Change, Harvard Medical School
Division of Social Medicine and Health Inequalities, Brigham and Women's Hospital

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This manual is dedicated to
the community health workers, whose tireless efforts
make our mission a reality,
and to our patients, who inspire us to do better.

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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 multidrug-resistant tuberculosis (MDR TB) in DOTS-Plus projects. 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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Preface

Partners In Health (PIH) emerged from a group of health care workers providing primary health care, including TB control, in rural Haiti. Since the 1980s, PIH has worked to provide quality health services to some of the most impoverished and marginalized communities in the Western Hemisphere. As a consortium of physicians, social scientists, public health specialists, and social activists, PIH has built each of its programs on the foundation of full partnership with local communities, seeking to achieve health equity through culturally sensitive, epidemiologically informed, and clinically effective programs. The work of PIH is supported by its academic arm, the Program in Infectious Disease and Social Change at Harvard Medical School, and by the Division of Social Medicine and Health Inequalities at the Brigham and Women's Hospital, Boston, MA.

In 1996, with our Peruvian affiliate, Socios En Salud, and the Peruvian Ministry of Health, PIH initiated the world's first community-based treatment program for MDR TB in the shantytowns of northern Lima, Peru. Socios En Salud, the lead organization in this effort, is a community-based group of physicians, nurses, social scientists, community health workers, and activists who had been working in the Carabayllo area of northern Lima since 1995. Socios and PIH had joined forces to fight the plagues of childhood malnutrition, childhood disease, and diseases afflicting women living in poverty. When the epidemic of MDR TB was uncovered, these two organizations formed an expanded partnership with the highly successful Peruvian National Tuberculosis Program (NTP) to create a treatment strategy that would cure patients of their disease while at the same time stop ongoing community transmission of MDR TB.

Any approach that uses the principles of the WHO-recommended DOTS strategy and includes a strategy for the treatment of MDR

TB has been termed "DOTS-Plus." As of yet, there are no standardized DOTS-Plus recommendations for programs to follow.

The *DOTS-Plus Handbook: Guide to the Community-Based Treatment of MDR TB*[1], published in 2002 by Partners In Health and the Program in Infectious Disease and Social Change, provides the rationale for expanding DOTS to include DOTS-Plus in settings where MDR TB has emerged, and describes the steps necessary to design and implement effective programs based on the DOTS-Plus strategy. *The PIH Guide to the Medical Management of Multidrug-Resistant Tuberculosis* is written specifically for clinicians caring for patients with MDR TB within a DOTS-Plus program. This more concise clinical management book may be used in conjunction with the larger *DOTS-Plus Handbook* for a comprehensive, programmatic approach to the problem of MDR TB in resource-poor settings.

This pocket guide has grown out of our experience in treating MDR TB in three very different regions of the world – Peru, rural Haiti, and Western Siberia – where it is clear that successful, community-based treatment of MDR TB can be achieved, even in resource-poor settings. It is hoped that other TB programs implementing DOTS-Plus can adapt these protocols for both local and national programs.

This manual will be available in electronic form for downloading at the PIH web site at http://www.pih.org. In the near future, we will post versions in Spanish, Russian, and possibly other languages. Other TB material is also available at this Internet site, including useful forms designed to be used in MDR TB treatment programs and the aforementioned handbook on community-based treatment.

Abbreviations

ABG	Arterial blood gas
ACE	Angiotensin enzyme
AFB	Acid-fast bacilli
AG	Aminoglycosides
AMK	Amikacin
AMX/CLV	Amoxicillin/Clavulanate
ART	Antiretroviral therapy
AUC	Area under the curve
BCG	Bacille Calmette Guérin
BID or bid	Twice a day
CBC	Complete blood count
CDC	Centers for Disease Control and Prevention (U.S.)
CFZ	Clofazimine
CLR	Clarithromycin
CM	Capreomycin
CNS	Central nervous system
CPX	Ciprofloxacin
CrCl	Creatinine clearance
CS	Cycloserine
CT	Computerized tomography
D_5W	5% dextrose in water
DM	Diabetes mellitus
DOT	Directly Observed Therapy
DOTS	Directly Observed Therapy, Short-course
DS	Double strength
DST	Drug-sensitivity testing
E	Ethambutol
EEG	Electroencephalogram
EKG	Electrocardiogram
Ethio	Ethionamide
FEV_1	Forced expiratory volume in one second
FQ	Fluoroquinolones
Gati	Gatifloxacin
GFR	Glomerular filtration rate

GI	Gastrointestinal
H	Isoniazid
HAART	Highly Active Antiretroviral Therapy
HbA_{1C}	Hemoglobin A_{1C}
HCT	Hematocrit
Hg	Hemoglobin
IDU	Injection drug user
IgG	Immunoglobulin G
IM	Intramuscularly
ITR	Individualized treatment regimen
IV	Intravenous
KCI	Potassium chloride
KM	Kanamycin
LFX	Levofloxacin
MAC	*Mycrobacterium avium* complex
mcg	microgram
MDR TB	Multidrug-resistant tuberculosis
meq	milliequivalent
mg	milligram
MIC	Minimum inhibitory concentration
Moxi	Moxifloxacin
$MgSO_4$	Magnesium sulfate
NNRTI	Nonnucleoside reverse transcriptase inhibitor
NSAID	Nonsteroidal anti-inflammatory drug
NaCl	Sodium chloride
O_2Sat	Oxygen saturation
OFX	Ofloxacin
OI	Opportunistic Infection
PARTNERS	Partnership Against Resistant Tuberculosis; A Network for Equity and Resource Strengthening
PAS	Para-aminosalicylic acid
PCP	*Pneumocystic carinii* pneumonia
PI	Protease inhibitor
PIH	Partners In Health
PNCT	Peruvian National TB Program
PO	Orally

PO_2	Partial pressure of oxygen
PPD	Purified protein derivative
PR	By rectum
PRN	As needed
Prothio	Prothionamide
Q	Every (as in "Q 3 months")
QD or qd	Once a day
QHS	At night
QID or qid	Four times a day
R	Rifampin
RFB	Rifabutin
RNA	Ribonucleic acid
S	Streptomycin
SC	Subcutaneous
SCC	Short-course chemotherapy
SPX	Sparfloxacin
SS	Single strength
TB	Tuberculosis
THA	Thiamides (ethionamide and prothionamide)
THZ	Thiacetazone
TID or tid	Three times a day
TMP-SMX	Trimethoprim/sulfamethoxazole
TSH	Thyroid stimulating hormone
WHO	World Health Organization
Z	Pyrazinamide

Introduction

Although the large majority of tuberculosis cases worldwide are drug susceptible, multidrug-resistant tuberculosis (MDR TB) presents an emerging threat to global tuberculosis control. Strains of MDR TB are, by definition, those resistant to the two most potent antituberculosis medications, isoniazid and rifampin. The loss of susceptibility to isoniazid and rifampin makes such strains of tuberculosis more difficult to treat.

Directly observed therapy, short-course (DOTS), is an excellent means of *preventing* acquired resistance but is not an effective means of treating patients with resistant TB. "Acquired resistance" is defined as a form of MDR TB and is caused by previous incomplete or inadequate treatment of tuberculosis. Patients with "primary resistance" are those who have contracted a strain of tuberculosis that has already acquired resistance. Like patients with acquired resistance, patients with primary resistance are unlikely to be cured simply by the DOTS strategy.

The function of tuberculosis (TB) control programs is to cure patients infected with *Mycobacterium tuberculosis* and to prevent the emergence of drug-resistant strains. Nevertheless, drug-resistant tuberculosis is bound to appear in even the best-run programs. There is considerable evidence that drug resistance is increasing in prevalence and complexity in many parts of the world.[2]

In clinical practice, the development of significant drug resistance is almost always due to inadequate therapy. The inadequate therapy may be due to a number of reasons including:

- Patient noncompliance
- Physician error
- Lack of drug availability

- Malabsorption
- Organizational failure of the tuberculosis control program

It is often thought that patient nonadherence is the most common cause of acquired drug resistance.[3] However, it has been argued elsewhere by the authors of this manual that the contribution of the noncompliant patient to acquired resistance is not great when adequate support and medicines are available.[4,5,6] In fact, the authors of this manual believe that the organizational failure of many TB programs, lack of available drugs, and physician error have been the causes of much of the acquired resistance that exists in the world today.

Once patients acquire resistance to a single drug, they are more vulnerable to the acquisition of further resistance. (In this manner, strains can become sequentially resistant to several agents.) When drug resistance has been introduced within individuals, these patients may transmit those strains to others who then present with pre-formed or "primary" drug resistance.

While this manual focuses on the medical care and management of the patient with MDR TB, it is equally important to prevent the formation of new resistance. Thoughtful and adequate treatment of the patient with tuberculosis can minimize the selection of resistance in both patients being treated for the first time and in patients undergoing re-treatment.[7] In addition to appropriate regimens, prompt identification of MDR TB will further decrease transmission of drug-resistant strains by decreasing the time the patient is infectious to susceptible contacts. Moreover, the assurance of adherence, usually through directly observed therapy (DOT), is essential for decreasing the formation of new resistance. Finally, prevention of the transmission of MDR TB by using strict infection control practices for those exposed or likely to be exposed to MDR TB can substantially help prevent new cases of MDR TB. The authors of this guide strongly recommend that all four of

these preventive measures (appropriate regimens, prompt diagnosis, assurance of adherence through DOT, and infection control measures) be in place in programs that embark on a strategy to treat MDR TB.

As mentioned in the Preface, further discussion on addressing the problem of MDR TB can be found in the *DOTS-Plus Handbook*.[1]

1: Diagnosis of Multidrug-Resistant Tuberculosis

The diagnosis of MDR TB is often suspected clinically when a patient has a persistently positive acid-fast bacilli smear or culture or clinical progression of tuberculosis while on standard therapy. MDR TB may also be suspected epidemiologically when a patient is known to have had exposure to a person with MDR TB. The only way to confirm the diagnosis of MDR TB is to perform drug-susceptibility testing (DST) on the patient's TB culture and demonstrate resistance to at least isoniazid and rifampin.

1.1 Selecting patients to undergo drug-sensitivity testing

In countries where resources are available, all patients with TB have DST performed at the start of therapy. However, in resource-limited countries, a targeted approach to decide which patients should have DST is often more practical. In such an approach, only patients in whom MDR TB is suspected have sputum sent for culture and susceptibility testing. Table 1 lists the types of patients for whom this targeted approach is beneficial.

Table 1 Selecting patients for drug-sensitivity testing

Candidates for DST
• Patients who remain or turn positive after 4 months of TB treatment. • Patients previously treated for TB. • Patients who have a contact with known MDR TB. • Patients who have a contact who died while on directly observed therapy for TB. • Hospital and health care workers. • Patients with HIV. • Prisoners from facilities with high rates of MDR TB.

1.2 Laboratory confirmation of MDR TB

The ability to do cultures and DST for at least isoniazid (H), rifampin (R), ethambutol (E), and streptomycin (S) should be part of all TB control programs. In countries where there is no ability to perform cultures or DST, the infrastructure to do these basic laboratory tests should be built along side DOTS expansion. Regular quality control must be set up with a proficient laboratory or supranational laboratory for all tests. Kanamycin (KM), capreomycin (CM), fluoroquinolones (FQ), ethionamide (Ethio), cycloserine (CS), para-aminosalicylic acid (PAS), and other reserve antituberculosis drugs are most appropriately tested at specialized centers within the country or at supranational reference laboratories. The international standardization and discussion of the significance of DST for some second-line antituberculosis agents is presently ongoing. DST for pyrazinamide (Z) requires special techniques.

2: Treatment of MDR TB

2.1 Principles used in the treatment of MDR TB

The following describes the principles used for patients treated for MDR TB:

- Treatment regimens consist of preferably five drugs believed to be sensitive to the strain. Often more than five drugs may be started when the susceptibility pattern is not yet known or if extensive bilateral pulmonary disease is present.
- The drugs are administered six days per week, usually two times per day (To lessen side effects, some drugs can be given three times a day.)
- High-end doses are used. (See Table 2.)
- An injectable agent (an aminoglycoside or capreomycin) is used for at least six months after culture conversion.
- An 18- to 24-month regimen is given at least 18 months after culture conversion.
- Each dose is given as directly observed therapy (DOT) throughout the course of treatment. A treatment card is marked for each dose observed.
- A "Consent to Treatment" should be signed prior to initiating treatment. A sample form can be obtained on the PIH website at http://www.pih.org.
- All patients should be registered in a database specifically for MDR TB patients. Final outcomes should also be recorded here.

Table 2 Weight-based dosing of antituberculosis medications for adults

Medication (Presentation)	< 33 kg	33 – 50 kg	51 – 60 kg	> 60 kg
Isoniazid (100, 300 mg)	4–6 mg/kg/day or high-dose: 15 mg/kg 2x/wk	200–300 mg daily or high-dose: 600–900 mg 2x/wk	300 mg daily or high-dose: 900 mg 2x/wk	300 mg daily or high-dose: 900 mg 2x/wk
Rifampin (150, 300 mg)	10–20 mg/kg/day	450–600 mg	600 mg	600 mg
Ethambutol (100, 400 mg)	25 mg/kg/day	800–1200 mg	1200–1600 mg	1600–2000 mg
Pyrazinamide (500 mg)	30–40 mg/kg/day	1000–1750 mg	1750–2000 mg	2000–2500 mg
Streptomycin (1 gram vial)	15–20 mg/kg/day	500–750 mg	1000 mg	1000 mg
Kanamycin (1 gram vial)	15–20 mg/kg/day	500–750 mg	1000 mg	1000 mg
Amikacin (1 gram vial)	15–20 mg/kg/day	500–750 mg	1000 mg	1000 mg
Capreomycin (1 gram vial)	15–20 mg/kg/day	500–750 mg	1000 mg	1000 mg
Ciprofloxacin (250, 500, 750 mg)	20–30 mg/kg/day	1500 mg	1500 mg	1500 mg
Ofloxacin (200, 300, 400 mg)	Usual adult dose for MDR TB is 800 mg	800 mg	800 mg	800 mg
Levofloxacin (250, 500 mg)	Usual adult dose for MDR TB is 750 mg	750 mg	750 mg	750 mg
Moxifloxacin (400 mg)	Usual adult dose for MDR TB is 400 mg	400 mg	400 mg	400 mg

Table 2 Weight-based dosing of antituberculosis medications for adults, continued

Medication (Presentation)	< 33 kg	33 – 50 kg	51 – 60 kg	> 60 kg
Gatifloxacin (400 mg)	Usual adult dose for MDR TB is 400 mg	400 mg	400 mg	400 mg
Ethionamide (250 mg)	15–20 mg/kg/day	500 mg	750 mg	1000 mg
Prothionamide (250 mg)	15–20 mg/kg/day	500 mg	750 mg	1000 mg
Cycloserine (250 mg)	15 mg/kg/day	500 mg	750 mg	1000 mg
PAS (4 gram sachets, Jacobus PASER®)	150 mg/kg/day	8 grams	8 grams	8 grams
Clofazimine (50, 100 mg)	3-5 mg/kg/day	200-300 mg	200-300 mg	200-300 mg
Amoxicillin/clavulanate (500/125 mg or 875/125 mg)	45 mg/kg/day (based on the amoxicillin component)	2 grams or 1.65 grams	2 grams or 1.65 grams	2 grams or 1.65 grams
Clarithromycin (500 mg)	15 mg/kg/day	1000 mg	1000 mg	1000 mg
Rifabutin (150 mg)	5 mg/kg/day	200–300 mg	300 mg	300 mg
Pyridoxine/B_6 (25, 50, 100, 300 mg)	Dose at least 50 mg per 250 mg of CS	100-150 mg	150 mg	200 mg

Note: The above doses are given as the total daily doses. The following medications are usually given twice daily: ciprofloxacin, ofloxacin, ethionamide, prothionamide, cycloserine, PAS, amoxicillin/clavulanate and clarithromycin. For example, ethionamide (750 mg) is usually given 500 mg for the morning and 250 mg for the evening.

A further description of these medications is offered below and in Appendix 1. The management of side effects is discussed in Chapter 7 and in Appendices 4 and 5.

2.2 Empiric treatment regimens

Any patient suspected of having MDR TB or failing a standardized regimen using Category I treatment should be placed on an empiric regimen while awaiting DST. The empiric regimen should be based on the patient's previous drug exposure, the sensitivity pattern of known MDR TB contacts, or the surveillance data of other patients in a similar setting who have failed therapy.

Empiric regimens can vary, since they are based on different situations. Each tuberculosis program should set guidelines for the use of empiric regimens, but these guidelines must provide enough flexibility so that certain sets of patients are not forced into inappropriate empiric regimens. For example, patients who have received repeated cycles of WHO Category I and II regimens* and have continued to fail are unlikely to have strains sensitive to any of the first-line drugs; an empiric regimen could be based on all second-line drugs. In other settings, patient strains may have retained sensitivity to some of the first-line drugs, and these drugs should be included in the regimen. The guidelines for empiric regimens should be updated periodically. The empiric regimen should be used until the DST results are available, at which point the definitive regimen can be designed. Most empiric regimens will consist of five to seven drugs so that the patient has a high probability of receiving at least four medications that are sensitive to the strain.

* The WHO-recommended standardized regimen for new cases of tuberculosis is referred to as Category I and consists of two months of isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) followed by four months of H-R. The standardized re-treatment regimen is referred to as Category II and in most countries consists of two months of H-R-E-Z and streptomycin (S), followed by one month of H-R-E-Z, followed by five months of H-R-E.

The following are some suggested empiric regimens. Note that in areas of high KM resistance, CM should be used.

Example 1: An empiric regimen for failures of Category I from a program where the majority do *not* have MDR TB or in cases where the suspicion of MDR TB is not very high:

H, R, E, Z, CM (or KM), FQ, Ethio (CS can be used in place of Ethio).

Example 2: An empiric regimen for failures of Category I from a program where the majority *do* have MDR TB or in cases where suspicion of MDR TB is high:

E, Z, CM (or KM), FQ, Ethio, CS (if there is high resistance to FQ or Ethio, consider the addition of PAS to the regimen).

Example 3: For chronically ill patients who have received multiple courses of WHO Category I and II regimens:

Z, CM, FQ, Ethio, CS, PAS (if there is high resistance to FQ or Ethio in the area, consider the addition of clofazimine or amoxicillin/clavulanate to the regimen).

Example 4: For contacts of MDR TB patients with active disease:

If DST of the patient's MDR TB contact is known, the patient's empiric regimen should be based on the DST of the contact.

2.3 Standardized regimens for MDR TB

Standardized regimens for MDR TB are regimens designed to treat MDR TB when the DST pattern is not going to be determined. Data on effectiveness and the amount of amplification that takes place on standardized regimens are limited, and much depends on the DST patterns of the group being treated and the regimen being used. One study from Peru of 466 patients used a standardized treatment that included three months of KM and 18 months of E, Z, CPX, Ethio after patients failed the WHO Category I and II regimens. The regimen was not adjusted based on DST. The study did not have high success, reporting a cure rate of 48.3%.[8] Furthermore, the amount of amplification of resistance to the drugs used in this regimen was not examined. If standardized regimens are used, they should be based on surveillance DST from the patient group to which they will be applied. The regimens should be well designed to cover adequately the possible resistance patterns. Patients should be placed on them early, before extensive parenchymal damage occurs to the lungs. If a patient does fail a standardized regimen designed for the treatment of MDR TB, DST should be performed and the patient placed on an individualized regimen. More studies are needed to determine the role of standardized regimens, and at this time caution is warranted.

2.4 Definitive regimen

When the results of DST are available, the definitive individualized treatment regimen (ITR) can be designed. If the resistance pattern does not demonstrate MDR TB, Appendix 2 can be used to design a regimen. If the DST does reveal MDR TB, the regimen can be designed using the approach described below. While such an approach has been referred to as individualized, there is a basic algorithm that confers uniformity of treatment regimens.

The drug-susceptibility test is interpreted and the regimen is designed using a hierarchical algorithm of drug classes based

on the bactericidal or bacteriostatic properties of the groups of drugs known to be effective against *Mycobacterium tuberculosis*. This hierarchical algorithm was developed so that given any resistance pattern, the treatment regimens suggested by two independent physicians in the program would be highly concordant.

a. Tailoring MDR TB therapy to the drug-susceptibility pattern

Antituberculosis medications can be placed in one of five groups described on the following pages. The five groups are ordered by potency and evidence of efficacy. Based on the drug-susceptibility pattern, all medications from Group 1 to which a strain is susceptible are used. In addition, all patients receive an injectable agent (Group 2) and a quinolone (Group 3) to which the isolate is susceptible.

Generally, five drugs to which an isolate is susceptible are used. Drugs from Group 4 are added based on susceptibility. If five medicines to which the isolate is susceptible cannot be obtained from the first four groups because of resistance or severe allergies, the regimen is reinforced with medicines from the fifth group. In the case of partial resistance or inconsistent results, physicians should follow the general dictum of "use the medication, but do not depend on it for success."[9]

b. Accounting for amplification in regimen design

If there is a high probability of amplification to a drug during the time after the culture for DST was collected, this drug should not be counted as one of the five drugs needed to make the foundation regimen. However, the drug can be added to the regimen as a reinforcing agent until new DST

results arrive and the regimen can be adjusted accordingly.

Each group of antituberculosis medications is discussed below.

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

- All first-line drugs to which a patient's isolate is sensitive should be used.

First-line agents should be used whenever possible, since they are more potent and better tolerated than second-line drugs. They should be used at maximal doses (25mg/kg for ethambutol and 30mg/kg for pyrazinamide).

- In patients sick with strains demonstrating *in vitro* susceptibility to high-dose isoniazid, twice weekly isoniazid at 900 mg PO can exceed the mean inhibitory concentration (MIC) for strains resistant to this drug at conventional doses. However, due to the paucity of data regarding its use against partially resistant strains, high-dose isoniazid should be considered a reinforcing agent (from Group 5) rather than a first-line agent.

Group 2: Injectables (S, KM, CM, AMK)

- Injectable agents are bactericidal, and there is a wealth of data supporting their use. This class of drugs constitutes a critical component of the MDR TB regimen.
- All patients are given an injectable agent until their bacillary burden is demonstrably lower. In Peru, this is defined as a minimum of six months of documented negative cultures.

The history of previous treatment, drug-susceptibility data, relative efficacy, and cross-resistance between parenteral drugs should influence the choice of parenteral therapy.

- Injectables are used according to a hierarchical order based on efficacy, side effects, and cost. If the strain is susceptible, streptomycin is the usual injectable of choice. If resistance is to streptomycin, kanamycin is the second choice. If an isolate is resistant to both streptomycin and kanamycin, then capreomycin should be used.
- If an isolate is resistant to S, KM, CM, DST to amikacin can be performed.
- Empiric choice of the injectable should be based on both the history of what drugs the patient has received and the local resistance surveillance data.
- For patients with renal insufficiency, hearing loss, or peripheral neuropathy, capreomycin should be considered. Although the side effect profile of capreomycin is similar to the aminoglycosides, adverse events are reported to be less frequent.
- If creatinine clearance is significantly reduced, the dose of the injectable agent should be lowered. (See Section 5.4 for more detail on adjusting medications in patients with renal insufficiency.)

Group 3: Fluoroquinolones (CPX, OFX, LFX, Moxi, Gati)

- Quinolones are the only oral, bactericidal second-line agents.
- This class of drugs has excellent *in vitro* activity and has been shown to be effective in several clinical studies.
- All patients sensitive to this class of drugs are given a quinolone.

The fluoroquinolones are bactericidal against *M. tuberculosis*. Because this is the only class of second-line drugs that is oral and bactericidal, a fluoroquinolone should be included in the regimen whenever possible. The choice of a fluoroquinolone depends largely on economic and dosing considerations. Levofloxacin is the active moiety of ofloxacin and has better bioavailability. Other newer, higher-generation quinolones such as gatifloxacin and moxifloxacin also have potent mycobacterial activity.

- Resistance to quinolones is conferred by a mutation or mutations in the mycobacterial gene that codes for DNA gyrase. It is thought by many researchers that cross-resistance between drugs of this class is high.
- At the writing of this manual, a group of patients with strains resistant to ciprofloxacin preserved susceptibility to the newer quinolones *in vitro*, but this has unclear clinical significance.

Group 4: Other second-line drugs (Ethio, Prothio, CS, PAS)

- These second-line agents have a long history of use in the treatment of MDR TB but are bacteriostatic.
- These agents are not as well tolerated as first-line drugs and quinolones.

Traditional second-line drugs – ethionamide (or prothionamide), cycloserine, and PAS – are bacteriostatic and have a long and proven track record in the treatment of tuberculosis. These agents are added to MDR TB regimens based on efficacy, tolerability, resistance pattern, and cost.

- Ethionamide is the most widely available and is often the first of these agents added. Prothionamide is a similar drug; both ethionamide and prothionamide are in the thiamide (THA) family.
- Cycloserine is a potent and proven antituberculosis drug with neuropsychiatric side effects, which, although manageable, require careful monitoring.
- Para-aminosalicylic acid is a potent bacteriostatic antituberculosis agent[10] that is historically poorly tolerated. A newer formulation, PASER® granules, has made it more tolerable. Unfortunately, this formulation is costly and requires cold chain for delivery and storage. It is added last due to these factors. At the writing of this document, several newer formulations of PAS are becoming available.

Group 5: Possible reinforcing agents (High-dose H, AMX/CLV, CFZ, CLR, THZ)

- Drugs in Group 5 have some *in vitro* data or animal data, but there is minimal clinical data supporting their use for the treatment of MDR TB.

If a TB isolate is susceptible to five or more standard antituberculosis medications from Groups 1-4, the use of additional drugs is not warranted. However, in clinically advanced cases or in cases with suspected or confirmed high-grade drug-resistance, drugs from Group 5 may be added to a regimen. The clinical benefit of adding agents from Group 5 has not been proven.

- Clofazimine and amoxicillin/clavulanate have antimycobacterial activity *in vitro*. However, because their contribution to the efficacy of multidrug regimens is unclear, they are considered reinforcing agents. Given the low cost of clofazimine, it is often the first drug chosen from this group.
- Susceptibility to clarithromycin is present in only 15% of *M. tuberculosis* isolates. Because of the low probability of susceptibility to this agent, it is the last choice from this group. DST should be done if this agent is used.
- High-dose isoniazid (900 mg twice a week) can be used if the strain demonstrates *in vitro* susceptibility.
- Thiacetazone is infrequently used in the treatment of MDR TB due to its significant adverse effect profile, weak antituberculosis activity, and possible cross-resistance with ethionamide.

2.5 Partial and intermediate sensitivity

Strains of TB may demonstrate intermediate sensitivity to some drugs. For example, when the proportion method of drug-sensitivity testing is used, if the strain exhibits greater than 1% bacterial growth, the strain is considered resistant. However, if the colony count is less than the control, there is some antituberculosis activity (or intermediate sensitivity). (See Appendix 3 for more on drug-sensitivity testing methods.)

In general, when strains are only intermediately sensitive to a drug, the drug should not be used in the regimen. In strains with high-grade resistance, however, it may be necessary to use any drug that can inhibit antibacterial growth, though this drug should not be relied upon in the regimen for success.

2.6 Summary of cross-resistance

There is well-known cross-resistance between some of the antibiotics used in treating tuberculosis. Resistance mutations to one antituberculosis drug may confer resistance to some or all of the members of the drug family and, less commonly, to members of different antibiotic families. For example, resistance to the aminoglycoside kanamycin is associated with cross-resistance to amikacin. In contrast, cross-resistance between the aminoglycosides, kanamycin, and streptomycin is generally low. Moreover, TB isolates that are resistant to kanamycin at high doses may be resistant to capreomycin, a non-aminoglycoside (peptide antibiotic). Table 3 is a summary of the available literature on cross-resistance and an analysis of isolates from the Massachusetts State Laboratory Institute, 1999-2002.

Table 3 Cross-resistance

Drug 1	Drug 2	Qualitative description of cross-resistance
Streptomycin	Kanamycin	Low[11,12,13]
Streptomycin	Capreomycin	Low[11,13]
Kanamycin	Amikacin	High, (89-100%) as it is associated with the same A1400G mutation[13,14,15]
Kanamycin	Capreomycin	Some cross-resistance exists: highly kanamycin-R strains can be R to capreomycin yet low-dose kanamycin-R strains retain susceptibility to capreomycin. Capreomycin-R strains were as susceptible as the parent strains to kanamycin.[16,17,18]
Capreomycin	Viomycin	All capreomycin-R strains are R to viomycin, yet not all viomycin-R strains are R to capreomycin.[19]
Ciprofloxacin	Ofloxacin	Variable *in vitro* cross-resistance (17%-100%); yet most studies report >50%. Clinical significance is not fully understood, as the mechanism of resistance is the same (gyrA mutation).[20,21,22,23]
Ciprofloxacin	Levofloxacin	Variable *in vitro* cross-resistance (>47.5%). As achievable blood levels are higher, further study is needed to determine if levofloxacin has clinical activity in ciprofloxacin-R strains, as the mechanism of resistance is the same (gyrA mutation).[13,21]

Table 3 Cross-resistance, continued

Drug 1	Drug 2	Qualitative description of cross-resistance
Ciprofloxacin	Gatifloxacin, moxifloxacin, and other higher generation fluoroquinolones	Lower cross-resistance (<55%). Two step-wise DNA gyrase mutations are required to achieve high-level resistance. No human studies have been done confirming *in vivo* activity of these higher generation fluoroquinolones against ciprofloxacin-R strains. [13,24,25,26]
Isoniazid	Thiacetazone	Cross-resistance has been reported. [27,28]
Isoniazid	Ethionamide	Cross-resistance has been reported among 86% of strains with low-dose H resistance due to inhA mutations. [29,30,31,32,33]
Thiacetazone	Ethionamide	Variable (29-79%) – associated with EtaA mutations. Most studies report >68%. Few studies have looked at the reverse situation. [13,28,34,35]
Thiacetazone	PAS	Cross-resistance has been reported, but it is generally considered low. [36]
Rifampin	Rifabutin	High, 82-94%. [13,37,38,39,40]

2.7 Completion of the injectable

The decision to stop the injectable should be made upon review of the cultures, smears, X-rays, and clinical status of the patient. The following criteria are used to consider cessation of the injectable agent:

- Patient has completed a minimum of six months of documented culture-negativity.
- Surgery is not planned.
- There are four remaining drugs to which the isolate has documented sensitivity.

When the regimen contains only four drugs including the injectable, the injectable is used for a minimum of 12 months of documented culture negativity and may be used for the entire course of treatment in patients with extensive lung damage or high-grade resistance.

2.8 Recurrence/persistence of positive cultures after four months of treatment

For cultures or smears that remain positive or become positive after conversion, the clinical evidence must be weighed to determine the course of action.

- DST should be compared to determine if the newly positive culture has the same susceptibility pattern as the initial strain or whether amplification of the resistance pattern has occurred.
- Re-appearance of single or multiple smears or cultures should be considered as possible evidence for treatment failure, and the patient should in all cases be evaluated for the possibility of changing therapy or of surgery.
- If the culture(s) or smear(s) are thought to reflect active disease, then the treatment should be adjusted and extended for 18 months of consecutive negative cultures. Preferably two or more drugs can be added while waiting for DST results.

- If the resistance pattern is completely different, it may represent either contamination or, less likely, a new infection.
- A culture that has fewer than 10 colonies may represent a contaminant; a repeated culture should be performed two or three times and documented to be negative before it is determined to be a contamination.

2.9 Completion of therapy

Bacteriological, clinical, and radiological data are all considered when determining the duration of therapy for MDR TB. The guidelines are:

- A minimum of 18 months of negative cultures past conversion.
- For patients with extensive damage on chest X-ray, therapy may be extended to 24 months negative cultures past conversion.

The final outcome of treatment should be recorded in the MDR TB registry. Final outcomes consist of cure, treatment completed, death, treatment default, treatment failure, and transfer out. An international consensus on treatment outcome definitions for MDR TB established by the WHO/CDC/PARTNERS is expected to be published in 2004.

2.10 Follow-up after completion of therapy

Treatment follow-up should be done for a minimum of two years after cure. The following are guidelines for surveillance of the cured MDR TB patient:

- Follow-up visits (months 6, 12, and 24) to assess for symptoms and signs of relapse.
- Smear and culture every three months for the first year, and then every six months for the second year.
- Clinical and radiographic evaluation as needed for development of respiratory symptoms.

Due to the high prevalence of residual lung disease, it may be helpful to continue ancillary medicines, such as bronchodilaters, in patients after antituberculosis therapy is completed.

3: Evaluation and Monitoring of Patients on Treatment

The initial evaluation is very important in determining the clinical state of the patient and whether ancillary treatments will be needed (steroids, bronchodilators, or supplemental nutrition). Additionally, the promt detection of co-morbidities such as renal insufficiency, HIV, diabetes, and depression is helpful in planning the treatment program for the patient.

3.1 Initial evaluation

Most programs have an intake form for patients with MDR TB to ensure that all appropriate data are collected. An example of an intake form is included in *A DOTS-Plus Handbook*[1] and is also available for download at http://www.pih.org. The minimal information collected on the intake form should include the following:

I. History
   1. Demographic data
      a. Name, age, sex
      b. Address
      c. Patient Type: new, failure, treatment after interruption, relapse, transfer in, or other (which includes chronic case)
   2. TB history
      a. Date of initial diagnosis
      b. Start and end date of all previous treatments; compliance with treatment regimens; outcomes
      c. Microscopy and culture results
      d. DST results
      e. Adverse effects and allergies
      f. Surgical treatments (resections, chest tubes)
      g. Complications (pneumothorax, empyema, massive hemoptysis)

   h. Type of TB: pulmonary, extrapulmonary, or both (if extrapulmonary, indicate site)
3. Past medical and social history
   a. Chronic medical conditions, including HIV, diabetes, renal insufficiency, chronic liver disease, chronic heart disease
   b. Prior psychiatric history
   c. Current non antituberculosis medications
   d. Allergies
   e. Alcohol, drug, and tobacco use
   f. Incarceration history
   g. Last menstural period and method of contraception
4. Documented and suspected MDR TB contacts
   a. Treatment history of contacts
   b. Current status
   c. DST data
   d. Assessment of how closely the patient interacted with the contact
5. Review of systems: cough, sputum production, fever, night sweats, weight loss (include previous weight when healthy, with date), dyspnea, appetite, abdominal pain, nausea, vomiting, diarrhea, constipation, headache, peripheral leg pain, hearing loss, depression, anxiety

II. Physical Examination
1. Vital signs
2. Heart rate
3. Blood pressure
4. Respiratory rate
5. Height and weight

6. Examination of skin, head, neck, oropharynx, cardiovascular system, pulmonary system, abdominal organs, extremities, and nervous system

III. Laboratory and ancillary tests
1. Baseline chest radiograph
2. Lab tests
    a. Urine pregnancy test
    b. Electrolytes
    c. Urea and creatinine (for elevated creatinine, consider performing a 24-hour creatinine clearance)
    d. Complete blood count
    e. HIV-ELISA
    f. Urine protein
    g. Serum liver tests
3. Sputum for smear, culture, and drug-sensitivity testing
4. Psychiatric evaluation
5. Baseline audiometry

3.2 Monitoring treatment

The patient should be seen as often as needed. The timely and appropriate management of side effects is critical to treatment adherence. In addition, monthly follow-up visits are required while the patient is on the injectable agent. After cessation of the injectable agent, control visits may be done less frequently, such as every two or three months.

Capreomycin is more associated with electrolyte disturbances than other injectable agents.

A directed review of systems should be done at each visit to evaluate for respiratory distress, GI intolerance of medications, progression of hearing loss or tinnitus, and neuropsychiatric effects. A physical exam should be performed, as well as routine monitoring lab tests or any tests that are indicated at the time

of the visit. Table 4 outlines the routine monitoring labs that are recommended; other tests can be done as needed.

Table 4 Routine monitoring of patients on second-line antituberculosis medications

Test	Frequency	Comments
Chest X-ray	Every 6 months	
Creatinine and potassium	Patients without risk factors for renal disease: Monthly while on the injectable if resources are available. Patients with DM, HIV, renal insufficiency, or patients >50 years old: Creatinine and potassium should be measured weekly for the first month and then at least monthly thereafter.	If the creatinine increases, drugs should be adjusted according to Table 9. (Once the dose is adjusted, the creatinine should be checked weekly until it has stabilized.)
TSH	Every 6 to 9 months	At baseline in patients > 50 years old

3.3 The irregular and noncompliant patient

The use of directly observed therapy (DOT) in the treatment of MDR TB is required. Even with DOT, however, there are still patients who are irregular or noncompliant. Such patients present a challenge to the DOT worker, nurse, and physician. At the first sign that a patient is not complying with the treatment regimen, the medical team should analyze the problems resulting in the patient's noncompliance.

- Arrange a doctor's visit with the patient, DOT worker, and nurse to discuss in detail why the patient is missing doses. If the missed doses are due to a scheduling problem, often accommodations can be made (e.g., delivering a dose at work).
- Careful attention must be paid to the development of psychiatric symptoms. Psychological support is often helpful, either in the form of an appointment

with a psychiatrist or counselor or through participation in group therapy. If patients have severe symptoms of depression or psychosis and a psychiatrist is not available, the doctor taking care of the patient may need to start psychiatric medicines until a psychiatrist is available. Often doses are missed because side effects are not being adequately addressed. If this is the case, more aggressive side-effect control is indicated.

- Patients should be assessed for alcohol and drug abuse. Although such behaviors are difficult to modify, education and counseling on addiction may be helpful. In addition, support groups and twelve-step programs, such as Alcoholics Anonymous, have a proven record of helping such patients and should be used in smear-negative patients when available.
- Enablers and incentives may be used to improve adherence. The difference between an enabler and an incentive is that an enabler allows the patient to comply with treatment (for example, money for a bus to come to the clinic) while an incentive rewards the patient for being compliant. Incentives might include such things as extra transport vouchers, a food basket at the end of a week of regular treatment, clothing, stipends, or a meal at the place where the patients come to take their medications. The distinction between an enabler and an incentive is often blurred. For example, a food basket might serve as an incentive to a patient to stay on therapy, but it might also be an enabler for the patient to build nutrition and make the therapy effective. Other incentives and enablers include education on tuberculosis to the patient and family members, referrals to social workers, comprehensive medical care, assignment of the case to a community health care worker, substance abuse

therapy, shelter for homeless patients, delivery of medicines to school, home, or work to accommodate schedule conflicts, and culturally appropriate delivery of care.[41]

- Finally, when all means of facilitating adherence have been exhausted, the patient is asked to sign a contract with rules regarding adherence (e.g., no more than two missed doses in a one-month period). An example of an adherence contract may be found on the Partners In Health website (www.pih.org). If this contract is broken, treatment is suspended permanently.

3.4 Abandoning or defaulting on treatment

When a patient wants to abandon therapy early, every effort should be made to explain the importance of completing the full therapeutic regimen. Discuss fully the reasons for the patient's wanting to stop treatment, and, if possible, try to improve any difficult situations that may be contributing to the patient's desire to stop therapy. Oftentimes more aggressive control of side effects is needed or changes in scheduling time of doses. Try to avoid changing the regimen, if possible, as this can undermine the importance of taking all the medicines and may cause other patients to request similar changes. As with the irregular patient, an evaluation should be done that includes an assessment of the patient for depression and/or substance abuse. Enablers and new incentives can be considered. Finally, if the patient refuses all interventions and insists on abandoning therapy, the patient should sign a refusal of care form. (A sample of this form is provided on the PIH website: http://www.pih.org.)

3.5 Reinitiation of treatment

On rare occasions, the clinician may decide to reinitiate treatment in patients for whom therapy has been suspended due to noncompliance or in patients who have defaulted during therapy. There are no concrete guidelines for the reinitiation of MDR

TB therapy following treatment interruption. The following is a reasonable protocol that has been reached by consensus:

- Have the patient sign a new adherence contract (see above).
- Perform a full history and physical exam.
- Obtain a smear and culture.
- If positive, culture should be sent for DST.
- Obtain a radiograph and repeat the initial laboratory data.
- The treatment regimen and duration to be used for patients restarting therapy depends on the month at which the patient abandoned therapy and the clinical state at which the patient returns to therapy (see Table 5).

Patients who have been off therapy for longer than six months should be evaluated for active disease, and, if it is present, the patient should be started on a completely new course of treatment. If no active disease is present, clinical judgment should be used to decide whether to reinitiate therapy. If therapy is not restarted, the patient should be followed regularly for signs of relapse.

Table 5 Suggested algorithm for reinitiating therapy after default

Length of treatment received prior to abandoning therapy	Result of last culture prior to abandoning therapy -OR- result of smear upon return to therapy	Action
Less than 3 months	Positive or negative	All patients with less than three months of treatment are restarted on a new course of treatment using their previous DST.
Between 3 and 12 months	Positive	Restart treatment and send for DST. Adjust regimen when DST arrives. (If patient was a suspected failure at time of abandonment, consider designing a new regimen instead of restarting original regimen.)
	Negative	Restart the patient with the injectable until two cultures return. All patients in this category should get a minimum of 24 months of therapy total past initial conversion.
Greater than 12 months	Positive	Send for DST and start a completely new course of treatment.
	Negative	If the patient was off the injectable at the time of interruption and has no evidence of clinical deterioration, then all oral medications can be restarted without restarting the injectable.

4: Adjuvant Therapies and Strategies

4.1 Corticosteroids

In patients who are receiving treatment for MDR TB, the adjuvant use of corticosteroids has been shown not to increase mortality and can help alleviate symptoms in the following conditions:

- severe respiratory insufficiency
- central nervous system involvement
- laryngeal TB

There is no evidence that one corticosteroid is better than another. Prednisone is commonly used, starting at approximately 1 mg/kg and gradually decreasing the dose 10 mg per week. In patients dependent on corticosteroids, stopping the prednisone abruptly can be dangerous.

Corticosteroids may also alleviate symptoms in patients with an exacerbation of obstructive pulmonary disease. In these cases, prednisone may be given in a short taper over one to two weeks, starting at approximately 1 mg/kg and decreasing the dose by 5–10 mg per day.

4.2 Surgery

Surgery as an adjunct to chemotherapy for patients with localized disease can significantly improve outcomes where skilled thoracic surgeons and excellent postoperative care are available.[42,43,44,45,46]

When resectable disease is present, surgery should be considered for the following cases:

- Failure to demonstrate clinical or bacteriologic response to chemotherapy after three to six months of treatment.
- High likelihood of failure or relapse, due to high degree of resistance or extensive parenchymal involvement, regardless of smear and culture status.

- Morbid complications of parenchymal disease, e.g., hemoptysis, bronchiectasis, bronchopleural fistula, or empyema.
- Recurrence of positive culture status during DOTS-Plus therapy.
- Relapse after completion of DOTS-Plus therapy and under consideration for further individualized chemotherapy.

There are often restrictions on the number of surgeries a certain country can perform, based on financial resources or available surgeons and facilities. The following lists the priority of cases that should be considered:

1. Persistent or severe hemoptysis.
2. Patients who have high levels of resistance.
   - Patients with strains of bacteria demonstrating high levels of resistance should undergo an evaluation to determine the possibility of resection of their diseased lung.
   - Resection should occur as quickly as possible in these patients.
   - They should be continued on their regimens for their full course of treatment.
   - Even if the patient converts and becomes bacteriologically negative, given the high resistance they are at high risk for eventual failure and therefore should be considered for surgery.
3. Localized surgical disease (i.e., cavities or destroyed lung tissue) in patients who remain culture-positive.
   - All patients with what appears to be localized cavities or damaged lung on chest X-ray should undergo an evaluation for surgical resection of the damaged lung or cavity.
4. Localized surgical disease (i.e., cavities or destroyed lung tissue) in culture-negative patients.

Timing of surgery

Although smear conversion prior to intervention is ideal, the timing of surgery should occur early in therapy and is normally undertaken in the first two to six months of therapy. If it is not possible to achieve conversion prior to surgery, then at least three months of chemotherapy is recommended.[47]

Evaluating patients for surgery

Patients should receive antituberculosis drugs based on documented or presumptive drug sensitivities, both prior to and after surgery. The work-up of the surgical candidate is described below.

- Evaluation should begin with a computed tomography scan of the chest to evaluate the extent of disease. If there is localized disease or a question as to whether the disease is sufficiently localized to be resected, the patient's history and tomography should be evaluated by a thoracic surgeon experienced in operating on patients with tuberculosis.

- When a patient is thought to be an acceptable surgical candidate, the patient should have pulmonary function tests and, in some cases, ventilation perfusion scans to evaluate his predicted postoperative forced expiratory volume in one second (FEV1). Patients should have a predicted postoperative FEV1> 0.8 to be considered candidates for surgery.

- If a patient's predicted postoperative FEV1 is acceptable, analysis of blood for HCT, ABG, electrolytes, urea, and creatinine should be performed preoperatively. A preoperative EKG should be performed on patients older than 50 and on patients with diabetes.

Length of treatment after surgery

In all patients, therapy should continue for 18 to 24 months of consecutive negative cultures. In patients receiving adjunctive surgery, therapy may be prolonged in the postoperative period.[48]

- In patients who are smear- or culture-positive at the time of surgery, treatment is continued for a minimum of 18 months of documented culture-negativity.
- 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 6 months after surgery.
- If pathology reveals viable bacilli on culture, it may be reasonable to continue therapy for 18 to 24 months after the surgery rather than 18 months after the culture conversion of sputum.

5: Special Situations in the Treatment of MDR TB

5.1 MDR TB and pediatrics

Children with MDR TB generally have primary resistance transmitted from an adult contact with MDR TB. When DST is available, it should be used to guide therapy; however, because children have paucibacillary tuberculosis, they are often culture-negative. In culture-negative children who have clinical evidence of active TB and a contact with documented MDR TB, the child's treatment should be guided by results of DST of the contact.[49]

There is limited reported experience using the second-line antituberculosis medications for extended periods in children. Careful consideration of the risks and benefits of each drug should be made in designing a regimen. Frank discussion with the patient and family members is critical, especially at the outset of therapy. Given the life-threatening aspects of MDR TB, there are no drugs that are absolutely contraindicated in children. Children who have received treatment for MDR TB have generally tolerated the second-line drugs, including the aminoglycosides, cycloserine, and ethionamide.[49]

It should be noted that while fluoroquinolones have been shown to retard cartilage development in beagle puppies,[50] experience in the treatment of children with cystic fibrosis has failed to demonstrate similar effects in humans.[51,52] Additionally, ethionamide and cycloserine have been used effectively in children and are tolerated well. In general, drugs should be dosed according to weight (see Table 6). Monitoring monthly weights is therefore especially important in pediatric cases, with adjustment of doses as the child gains weight.[53]

Table 6 Pediatric dosing of second-line antituberculosis medications[49,54]

Drugs	Dosage forms	Daily dose mg/kg/day	Frequency	Maximum daily dose
Kanamycin	Vials: 37.5, 250, 333, 500 mg/ml	15–30	QD	1 g
Amikacin	Vials: 50, 250 mg/ml	15-30	QD	1 g
Capreomycin	Vials: 1g/ml	15–30	QD	1 g
Ciprofloxacin	Tabs: 100, 250, 500, 750 mg Oral suspension: 250 mg, 500 mg/5ml	20–40	BID	1.5 g
Ethionamide	Tabs: 250 mg	15–20	BID	1 g
Prothionamide	Tabs: 250 mg	15–20	BID	1 g
Cycloserine	Capsules: 250 mg	15	QD or BID	1 g
PAS	PASER® 4 g packets	150	BID or TID	12 g
Clofazimine	Tabs: 50 mg	3–5	BID	300 mg
Amoxicillin/ clavulanate	Tabs: 500/125 mg	25–45 (based on amoxicillin component)	BID	2 g

Note: The optimal doses of ofloxacin, levofloxacin, moxifloxacin, and gatifloxacin have not yet been determined in children.

5.2 MDR TB and pregnancy

All female patients of childbearing age should be tested for pregnancy upon initial evaluation; birth control is strongly recommended for all women receiving MDR TB therapy. Since oral contraceptives may have decreased efficacy due to potential drug interactions, other options include the use of medroxyprogesterone (Depo-Provera) intramuscular every 13 weeks or barrier methods (e.g., diaphragm or condom) throughout the course of treatment. All patients are encouraged to use condoms to protect against sexually transmitted diseases.

The table below lists the antituberculosis medications commonly used in the treatment of MDR TB. Pregnancy is not a contraindication to the treatment of active MDR TB, since active, untreated TB and MDR TB pose great risks to the life of the mother and fetus.[55,56]

Table 7 Safety of antituberculosis medications during pregnancy

Medication	Safety class *	Comments
First-line medications		
Isoniazid (H)	C	Experience in gravid patients suggests safety.[57,58] Pyridoxine (vitamin B_6) should be used during pregnancy.[59]
Rifampin (R)	C	Experience in gravid patients suggests safety.[58]
Ethambutol (E)	B	Experience in gravid patients suggests safety.[60,61]
Pyrazinamide (Z)	C	Use with caution when essential. Most references suggest it is safe to use.
Streptomycin (S)	D	Avoid use when possible. Documented toxicity to developing fetal ear. Risks and benefits must be carefully considered. Avoid use when possible.[58]
Second-line medications		
Kanamycin (KM), *Amikacin* (AMK)	D	Avoid use when possible. Documented toxicity to developing fetal ear.[62] Risks and benefits must be carefully considered. Avoid use when possible.
Capreomycin (CM)	C	Avoid use when possible. 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.)[63,64]
Fluoroquinolones (FQ)	C	Use with caution when essential. No teratogenic effects seen in humans when used for short periods of time (2–4 weeks). Experience with long-term use in gravid patients is limited, but given bactericidal activity, benefits may outweigh risks.[65]

Table 7 Safety of antituberculosis medications during pregnancy, continued

Medication	Safety class *	Comments
Ethionamide (Ethio)	C	Avoid use if possible.[66,67] Teratogenic effects observed in animal studies;[68,69,70,71] significantly worsens nausea associated with pregnancy.
Cycloserine (CS)	C	No significant experience in gravid patients; animal studies have not documented toxicity.[72,73]
PAS (PAS)	C	Use with caution when essential.[74] Considered not to be teratogenic.[75,76,77,78]
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.[79]
Clarithromycin (CLR)	C	Avoid use if possible. May be teratogenic.[80,81]
Rifabutin (RFB)	B	Experience in gravid patients suggests safety.[82]
Amoxicillin/ Clavulanate (AMX/CLV)	B	Experience in gravid patients suggests safety.[80]

* *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.

Gravid patients should be carefully evaluated, taking into consideration gestational age and severity of MDR TB. The risks and benefits of MDR TB treatment should be considered carefully, with the primary goal being smear conversion in order to protect the health of the mother and child, both before and after birth.

- Since the majority of teratogenic effects occur in the first trimester, therapy may be delayed until the second trimester unless life-threatening symptoms occur.
- Patients in the third trimester have reduced risk of teratogenicity, although aminoglycosides may still damage the fetal ear. For the most part, aminoglycosides are not used in the regimens of pregnant patients.
- If possible, begin treatment in the second or third trimester with three or four oral drugs with demonstrated efficacy against the infecting strain, and then reinforce the regimen with an injectable agent and possibly other drugs immediately postpartum.[83]

Newborn infants are at high risk of developing disseminated tuberculosis. If possible, smear-positive mothers should avoid close contact with infants, leaving the care of the infant to a family member until the mother is smear-negative. Alternatively, N-95 respirators may be used by the mother; the degree of protection conferred in this setting, however, has not been studied.

Effects of antituberculosis medications on the nursing infant have not been fully studied. Therefore, the use of infant formula is a reasonable way to avoid any unknown adverse effects. However, the use of infant formula will depend on multiple factors, including the petient's resources, safety of water supply, and bacteriological status of the mother. If the setting is not appropriate for infant formula, then breast-feeding may be considered. Table 8 gives a summary of information concerning breast-feeding and antituberculosis medications.

Table 8 Breast-feeding and antituberculosis medications

Drug	Compatible with breast-feeding (according to AAP)[84]	% concentration in breast milk compared with therapeutic doses for infants[84,85]
H	Yes. Nursing infants were reported to have seizures that responded to pyridoxine.[86] Neonates with G6PD deficiency may have susceptibility (hemolysis) to isoniazid.[87] Recommend pyrodixine (vitamin B_6) to prevent peripheral neuropathy and seizures in infant.	6.4–25%
R	Yes.	0.57–7.3%
E	Yes.	2.8–6.9%
Z	Not known.	0.75–1.5%
S	Yes. Poorly absorbed by GI tract.	0.95–22.5%
AMK	Yes. Poorly absorbed by GI tract.	Not reported.
KM	Yes. Poorly absorbed by GI tract.	0.95–18%
CM	Unknown. Concentrations in breast milk unknown.[84]	Not reported.
CS	Yes.	11–28%
CPX	CPX levels in amniotic fluid and breast milk almost as high as serum.[80]	Not reported.
PAS	Unknown.	0.05–0.95%[84]
Ethio/ Prothio	No data on breast milk concentrations.[84]	
CFZ	Present in breast milk.	Not reported.
AMX/ CLV	Amoxicillin excreted in breast milk in low concentrations. Clavulanate excretion in breast milk unknown.	Not reported.
CLR	Likely excreted in breast milk. Safe experience with other macrolides.	Not reported.

5.3 MDR TB and diabetes

The treatment of TB in the diabetic will result in poorer outcomes if glucose is not well controlled. The responsibility often falls on the physician treating the patient for tuberculosis to ensure proper diabetic care. In addition, diabetes may potentiate adverse effects, especially renal dysfunction and peripheral neuropathy. The following guidelines are suggested to assist in the management of the diabetic with MDR TB:[88]

1. Medical follow-up
   - Diabetes must be managed closely throughout DOTS-Plus treatment. The TB physician should be in close communication with a physician who manages the patient's diabetes.
2. Education for the patients
   - Diabetic diet—all nurses and promoters with diabetic patients should be familiar with the basics of the diabetic diet. (Information packets are available, written by National Institute of Diabetes and Digestive and Kidney Diseases.)
   - Weight control
   - Exercise
   - Foot care
   - Symptoms of hypo- and hyperglycemia
3. Glucose monitoring
   - Goals for capillary blood testing: 80–120 mg/dl before meals; 100–140 mg/dl before bedtime; the range should be higher if patient has a history of hypoglycemia.
   - Patients may need a period of intensive glucose monitoring until these goals are met.
   - Once a patient is on a stable dose of insulin, his or her blood sugar may be monitored four times weekly to ensure that targets are being maintained.
   - If a patient is on oral antidiabetic agents, his or her blood sugars may be monitored twice weekly.

4. Regular monitoring
   - Creatinine and potassium should be monitored weekly for the first month and then at least monthly thereafter.
   - If the creatinine rises, a creatinine clearance should be checked and antituberculosis medications should be adjusted according to Table 9. Once the dose is adjusted, the creatinine should be checked weekly until it has stabilized.
   - HbA_{1C} every three months if treatment changes or patient is not meeting goals; every 6 months if stable.
   - Goal for $HbA_{1C} < 7$.
   - Retinal examination annually.
5. Screening and treatment for hypertension
   - Blood pressure checks every month.
   - Hypertensive patients with diabetes should be started on an ACE-inhibitor.
6. Prevention of diabetic nephropathy
   - Injectable dosing according to the renal protocol.
   - Consider using an ACE-inhibitor for patients with albuminuria (>300 mg/24 h).

5.4 MDR TB and renal insufficiency

Renal insufficiency due to longstanding tuberculosis disease is not uncommon. Great care should be taken in the administration of second-line drugs in patients with renal insufficiency, and the dose and/or the interval between dosing should be adjusted according to Table 9. The formula to calculate the creatinine clearance (CrCl) or the glomerular filtration rate (GFR) is:

Estimated Glomerular Filtration Rate (GFR) =

$$\frac{(140\text{-age})(\text{ideal body weight in kg})}{(72)(\text{serum creatinine, mg/dl})}$$ for men (x 0.85 for women)

Normal values for the creatinine clearance are:

Men: 97 to 137 ml/min

Women: 88 to 128 ml/min

Table 9 Dosing of selected antituberculosis drugs in renal failure*

Drug	Change in frequency?	Recommended dose and frequency for patients with creatinine clearance < 30 ml/min or for patients receiving hemodialysis†‡§¶
Isoniazid	No change	300 mg once daily, or 900 mg 3 x wk
Rifampin	No change	600 mg once daily, or 600 mg 3 x wk
Pyrazinamide	Yes	25-35 mg/kg/dose 3 x wk
Ethambutol	Yes	15-25 mg/kg/dose 3 x wk
Ciprofloxacin	Yes	1000-1500 mg/kg/dose 3 x wk
Ofloxacin	Yes	600-800 mg/kg/dose 3 x wk
Levofloxacin	Yes	750-1000 mg/kg/dose 3 x wk
Moxifloxacin	No change	400 mg once daily
Gatifloxacin	Yes	400 mg/dose 3 x wk
Cycloserine	Yes	250 mg once daily, or 500 mg/dose 3 x wk‖
Ethionamide	No change	250-500 mg/dose daily
p-Aminosalicylic acid	No change	4 g/dose, twice daily
Streptomycin	Yes	12-15 mg/kg/dose 2 or 3 x wk**
Capreomycin[89]	Yes	12-15 mg/kg/dose 2 or 3 x wk **
Kanamycin	Yes	12-15 mg/kg/dose 2 or 3 x wk**
Amikacin	Yes	12-15 mg/kg/dose 2 or 3 x wk**
Clofazimine	No change	200-300 mg daily
Amoxicillin/ clavulanate	Yes	1g based on amoxicillin component daily

Notes:

* Adapted from American Thoracic Society/Centers for Disease Control and Prevention/Infectious Disease Society of America. Treatment of Tuberculosis. *Am J Respir Crit Care Med* 2003;167: 603-662.

† To take advantage of the concentration-dependent bactericidal effect of many antituberculosis drugs, standard doses are given unless there is intolerance.

‡ The medications should be given after hemodialysis on the day of hemodialysis (this also allows for the easy administration of DOT three times per week).

§ Monitoring of serum drug concentrations should be considered to ensure adequate drug absorption, without excessive accumulation, and to assist in avoiding toxicity.

¶ Data are currently not available for patients receiving peritoneal dialysis. Until data become available, begin with doses recommended for patients receiving hemodialysis and verify adequacy of dosing using serum concentration monitoring.

|| The appropriateness of 250 mg daily doses has not been established. There should be careful monitoring for evidence of neurotoxicity (if possible, measure serum concentrations and adjust accordingly).

** Caution should be used with the injectable agents in patients with renal function impairment because of the increased risk of both ototoxicity and nephrotoxicity.

Note also that:

Para-aminosalicylic acid (PAS) may worsen renal acidosis. Sodium salt formulations of PAS may result in an excessive sodium load; these should be avoided. Formulations of PAS that do not use the sodium salt (e.g., Jacobus PASER®) can be used without the hazard of sodium retention.[9]

Ciprofloxacin has less renal excretion than levofloxacin or ofloxacin and is preferred in cases of chronic renal failure.[9]

Below is an example of adjusting the dose of a medication in renal insufficiency:

A male patient has a serum creatinine = 2.4, age = 59, ideal body weight = 53 kg. What should be the dose of capreomycin (CM)?

Step 1: Calculate the Glomerular Filtration Rate (GFR)=

$$\frac{(140\text{-age})(\text{ideal body weight in kg})}{(72)(\text{serum creatinine, mg/dl})} = \frac{(140\text{-}59)(53)}{(72)(2.4)} = 24.8 \text{ ml/min}$$

Step 2: Refer to Table 9 and make the appropriate adjustment in dose. In this case the 24.8 ml/min falls below 30 ml/min. The dose of CM given from Table 9 is 12-15 mg/kg. The dose to prescribe would be between (12)(53) = 636 mg and (15)(53) = 795 mg. It is reasonable to choose a dose between these two that is relatively easy to draw up from the vial. In this case, 750 mg three times a week is the logical choice.

Step 3: Check creatinine periodically (often weekly or more frequently in the patient with severe renal insufficiency) and readjust medications for any change.

Note: For this patient, every drug in the regimen should be examined and adjusted if necessary. If this were a woman, the GFR = 24.8 x 0.85 = 21.1 ml/min.

5.5 MDR TB and central nervous system infections

If the patient has symptoms suggestive of central nervous system (CNS) involvement with MDR TB, the regimen used should have adequate penetration into the CNS. In the MDR TB patient, cycloserine at maximum doses should be used as it has the best CNS penetration of all the second-line antituberculosis medications.

Table 10 CNS penetration of antituberculosis medications

Drug	CNS penetration[90,91]
Isoniazid	Good penetration. Equal to serum.
Rifampin	Adequate penetration in the presence of inflammation (10–20%).
Pyrazinamide	Good penetration.
Ethambutol	Generally low. In presence of inflammation, 4–64%.
Streptomycin	Low. In setting of meningeal inflammation, approximately 10% of drug crosses the blood-brain barrier.
Kanamycin	Penetrates inflamed meninges only.
Amikacin	Penetrates inflamed meninges only.
Capreomycin	Penetrates inflamed meninges only.
Quinolones	Fair. For ciprofloxacin and ofloxacin, the penetration is 5-10% and with inflamed meninges 50-90%.
Ethionamide	Good penetration.
Cycloserine	Extremely good penetration.
p-Aminosalicylic Acid	Poor.

5.6 The psychiatric patient and substance dependency

It is prudent to have a psychiatric evaluation before the start of treatment for all patients with MDR TB. The initial evaluation serves to document any preexisting psychiatric condition and establishes a baseline for comparison if new psychiatric symptoms develop while on treatment. Any psychiatric illness identified at the start of or during treatment should be addressed fully. There is a high baseline incidence of depression and anxiety in patients with MDR TB, often connected to the chronicity and socioeconomic stressors related to the disease.

Treatment should not be delayed while waiting for a psychiatric evaluation. If a psychiatrist is not available, the treating physician should do an initial psychiatric evaluation. It is also acceptable to wait until the patient is smear-negative prior to a full psychiatric evaluation, in order to decrease MDR TB exposure to the psychiatrist, other health care workers, and patients at the psychiatric clinic.

Treatment with psychiatric medications, individual counseling, and/or group therapy may be needed to manage the patient suffering from a psychiatric condition or adverse reaction. The physician treating tuberculosis should be involved in all management modalities. Group therapy has been very successful in providing a supportive environment for the MDR TB patient and may be helpful for patients with or without psychiatric conditions.

The patient with a substance dependency poses a difficult challenge. Treatment for addiction should be offered in such cases. Complete abstinence from alcohol or drugs should be strongly encouraged. However, active alcohol or drug use is not an absolute contraindication to treatment. If treatment is repeatedly interrupted due to the patient's addiction, MDR TB therapy should be suspended until treatment for the addiction is suc-

cessful. Good DOT gives the patient contact with and support from health care providers that often aids greatly in being successful in reducing substance dependency.

Cycloserine will have a higher incidence of side effects in both the psychiatric patient and the alcohol or drug dependent patient. However, if cycloserine is considered important to the regimen, it should be used in these patients and the patients closely observed for side effects.

All physicians treating MDR TB should work closely with a psychiatrist and have a system in place for psychiatric emergencies, including psychosis, suicidal ideation, and any situation that involves the patient posing a danger to himself or to others. Psychiatric hospital admissions should be available 24 hours a day. Proper infection-control measures must be taken for the smear-positive patient requiring hospitalization.

Protocols and specific strategies to address psychiatric side effects are discussed in Chapter 7 and Appendix 4.

6: Management of Failures

6.1 Definition of failure

There is no simple definition to determine whether a patient's treatment is a failure. Individualized treatment plans often follow a cycle and, if no response is seen, the regimen and treatment plan are reassessed and a new plan of action formulated. Often new drugs are added and adjunctive options – most commonly surgery – are entertained. A change in treatment should be initiated if the patient has not converted by month four or if a new positive smear or culture occurs after month four in a previously converted patient.

One drug only is never added to a failing regimen; at least two additional, and, if possible, three or more new antituberculosis medications to which the strain is likely to be susceptible should be added.

Despite there being no simple definition for failures, there often comes a time in the treatment when it is clear that the patient is not going to improve. The signs that indicate treatment failure include:

- Persistent positive smears or cultures past the 8th month of treatment.
- Extensive and bilateral lung disease with no option for surgery.
- High-grade resistance with no option to add two additional agents.
- Overall deteriorating clinical condition that usually includes weight loss and respiratory insufficiency.

While not all of these signs necessarily have to be present to declare a patient's treatment a failure, cure is unlikely if they exist.

The health care worker should always investigate whether the patient has taken all the medication prescribed; this also

includes interviewing the DOT worker. If medical personnel are confident that all the medicines have been ingested and there is no possibility of adding medicines or performing surgery, therapy should be suspended.

6.2 Suspending therapy

There are two important reasons for suspending therapy. The first is the patient's quality of life. The medicines used in the treatment of MDR TB have considerable side effects. Continuing them while the patient is failing may cause added suffering for the patient. The second reason is that continuing treatment in a patient who is failing treatment can amplify resistance in the patient's strain, which can go on to infect others.

The clinical team—including all physicians, nurses, and DOT workers involved in the patient's care—should discuss suspension of therapy. Once this is decided, a clear plan should be determined for how to approach the family and patient. In some circumstances, it may be better to start discussion with family members first, so that they can understand and support the decision before the patient is approached. In other circumstances, the team may start discussion with the patient and later include the family. This process usually takes a number of visits over the course of weeks. Home visits offer an excellent opportunity to talk to all family members in a familiar environment.

6.3 Supportive care of failures

Once the decision to suspend therapy has been made, there are a number of supportive measures that can be used. It is important that medical visits continue and the patient does not feel abandoned. Supportive measures include:

- **Pain control.** Codeine with acetaminophen gives relief to moderate pain and helps control cough. If possible, stronger analgesics should be used when appropriate.

- **Relief of respiratory insufficiency.** Oxygen can be used to alleviate shortness of breath. Generally, it is indicated in patients with a pO_2 <55 mmHg or O_2Sat <89% and should be titrated to raise the O_2Sat >90%. Oxygen is usually started at 2–4 L/min via nasal cannula. If more than 5 L/min is needed, the oxygen should be delivered through a mask. Retention of CO_2 can occur in some patients and should be checked when starting oxygen or increasing oxygen delivery. Morphine also provides significant relief from respiratory insufficiency and should be offered if available.
- **Nutritional support.**
- **Regular medical visits.** Once therapy stops, regular visits by the treating physician and support team should still continue.
- **Continuation of ancillary medicines.** All necessary ancillary medications should be continued.
- **Hospitalization, hospice care or nursing home care.** Having a family member die at home can be difficult. Hospice care should be offered to families who want to keep the patient at home, and inpatient end of life care should be available for those for whom home care is not available.
- **Infection control measures.** The patient taken off treatment for reasons of failure often remains infectious for long periods of time, frequently with a strain resistant to many drugs. Infection control measures are very important in such patients and should be implemented in either home settings or institutions.

7: Management of Adverse Effects to Antituberculosis Agents

The timely and aggressive management of adverse effects of second-line antituberculosis medicines facilitates patient adherence. The DOT worker should be familiar with the common side effects of antituberculosis therapy. Patients experiencing side effects should be referred to nurses and physicians as needed. The discussion and protocols below may be used to guide the management of adverse effects. Table 11 lists the common side effects, the likely agents responsible, and suggested management strategies. Appendix 4 presents flow diagrams of side-effect management, and Appendix 5 lists the doses of medications often used to treat side effects.

Table 11 Adverse effects, suspected agents, and management strategies[92]

Adverse reaction	Suspected agent(s)	Suggested management strategies	Comments
Seizures	CS H FQ	1) Suspend suspected agent pending resolution of seizures. 2) Initiate anticonvulsant therapy (e.g., phenytoin, valproic acid). 3) Consider increasing pyridoxine to maximum daily dose (200 mg per day). 4) Restart suspected agent or reinitiate suspected agent at lower dose, if essential to the regimen.	1) Anticonvulsant is generally continued unil MDR TB treatment is completed or suspected agent discontinued. 2) History of prior seizure disorder is not a contraindication to the use of agents listed here if a patient's seizures are well controlled and/or the patient is receiving anticonvulsant therapy. 3) Patients with history of prior seizures may be at increased risk for development of seizures during MDR TB therapy.
Peripheral neuropathy	CS H FQ S KM AMK CM E Ethio	1) Consider increasing pyridoxine to maximum daily dose (200 mg per day). 2) Change parenteral to CM if patient has documented susceptibility to CM. 3) Initiate therapy with tricyclic antidepressants such as amitriptylene. NSAIDS or acetaminophen may help alleviate symptoms. 4) Lower dose of suspected agent, if this can be done without compromising regimen. 5) Discontinue suspected agent if this can be done without compromising regimen.	1) Patients with co-morbid disease (e.g., diabetes, HIV, alcoholism) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the agents listed here. 2) Neuropathy may be irreversible; however, some patients may experience improvement when offending agents are suspended.

Table 11 Adverse effects, suspected agents, and management strategies,[92] continued

Adverse reaction	Suspected agent(s)	Suggested management strategies	Comments
Hearing loss	S KM AMK CM CLR	1) Document hearing loss and compare to baseline audiometry. 2) Change parenteral to CM if patient has documented susceptibility to CM. 3) Lower dose of suspected agent, if this can be done without compromising regimen. More common, consider administration three times a week. 4) Discontinue suspected agent if this can be done without compromising regimen.	1) Patients with prior exposure to aminoglycosides may have baseline hearing loss. In such patients, it may be helpful to obtain audiometry at the initiation of MDR TB therapy. 2) Hearing loss is generally not reversible. 3) The risk of further hearing loss must be weighed with the risks of stopping the injectable in the treatment regimen.
Psychotic symptoms	CS H FQ Ethio	1) Hold suspected agent for a short period of time (one to four weeks) while psychotic symptoms are brought under control. 2) Initiate anti-psychotic drugs. 3) Lower dose of suspected agent, if this can be done without compromising regimen. 4) Discontinue suspected agent if this can be done without compromising regimen.	1) Some patients will need to continue anti-psychotic treatment throughout MDR TB therapy. 2) Prior history of psychiatric disease is not a contraindication to the use of agents listed here but may increase the likelihood of development of psychotic symptoms. 3) Psychotic symptoms are generally reversible upon completion of MDR TB treatment or cessation of the offending agent.

Table 11 Adverse effects, suspected agents, and management strategies,[92] continued

Adverse reaction	Suspected agent(s)	Suggested management strategies	Comments
Depression	Socio-economic circum-stances, chronic disease, CS, FQ H Ethio	1) Improve socioeconomic conditions. 2) Group or individual counseling. 3) Initiate antidepressant drugs. 4) Lower dose of suspected agent, if this can be done without compromising the regimen. 5) Discontinue suspected agent if this can be done without compromising regimen.	1) Socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression. 2) Depressive symptoms may fluctuate during therapy and may improve as illness is successfully treated. 3) History of prior depression is not a contraindication to the use of the agents listed here; however, these patients may be at increased risk for developing depression during MDR TB treatment.
Hypo-thyroid-ism	PAS Ethio espe-cially when given in combina-tion	1) Initiate thyroxine therapy. 2) Follow TSH and adjust thyroxine periodically.	1) Completely reversible upon discontinuation of PAS or Ethio. 2) Generally, no need to suspend suspected agents.

Table 11 Adverse effects, suspected agents, and management strategies,[92] continued

Adverse reaction	Suspected agent(s)	Suggested management strategies	Comments
Nausea and vomiting	Ethio PAS H E CFZ Z	1) Assess for dehydration. Initiate rehydration if indicated. 2) Initiate anti-emetic therapy. 3) Lower dose of suspected agent, if this can be done without compromising regimen. 4) Discontinue suspected agent if this can be done without compromising regimen, rarely necessary.	1) Nausea and vomiting are ubiquitous in early weeks of therapy and usually abate with time on treatment and supportive therapy. 2) Electrolytes should be monitored and repleted if vomiting is severe. 3) Reversible upon discontinuation of suspected agent. 4) 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.
Gastritis	PAS Ethio H E CFZ Z	1) Antacids (e.g., calcium carbonate, H2-blockers, proton-pump inhibitors). 2) Hold suspected agent(s) for short periods of time (e.g., one to seven days). 3) Lower dose of suspected agent, if this can be done without compromising regimen. 4) Discontinue suspected agent if this can be done without compromising regimen.	1) Severe gastritis, as manifested by hematemesis, melena, or hematechezia, is rare. 2) Dosing of antacids should be carefully timed so as to not interfere with the absorption of anti-TB drugs (take two hours before or after anti-TB medications). 3) Reversible upon discontinuation of suspected agent(s).

Table 11 Adverse effects, suspected agents, and management strategies,[92] continued

Adverse reaction	Suspected agent(s)	Suggested management strategies	Comments
Hepatitis	Z R H Ethio PAS E FQ	1) Stop all therapy pending resolution of hepatitis. 2) Rule out other potential causes of hepatitis. 3) Consider suspending most likely agent permanently. Re-introduce remaining drugs, one at a time with the most hepatotoxic agents first, while monitoring liver function.	1) History of prior hepatitis should be carefully analyzed to determine most likely causative agent(s); these should be avoided in future regimens. 2) Generally reversible upon discontinuation of suspected agent.
Renal failure	S KM AMK CM	1) Discontinue suspected agent. 2) Consider using CM if an aminoglycoside had been the prior parenteral in regimen. 3) Adjust all TB medications according to the creatinine clearance. (See Table 9.)	1) History of diabetes or renal disease is not a contraindication to the use of the agents listed here, although patients with these co-morbidities may be at increased risk for developing renal failure. 2) Renal impairment may be permanent.

Table 11 Adverse effects, suspected agents, and management strategies,[92] continued

Adverse reaction	Suspected agent(s)	Suggested management strategies	Comments
Electrolyte disturbances (hypokalemia and hypomagnesemia)	CM KM AMK S	1) Check potassium. 2) If potassium is low, also check magnesium (and calcium if hypocalcemia is suspected). 3) Replace electrolytes as needed. (See Tables 13, 14, and 15.)	1) If severe hypokalemia is present, consider hospitalization. 2) Amiloride 5-10 mg QD or spironolactone 25 mg QD may decrease potassium and magnesium wasting and is useful in refractory cases. 3) Electrolyte disturbances most commonly observed with capreomycin.
Optic neuritis	E	1) Stop E. 2) Refer patient to an ophthalmologist.	1) Usually reverses with cessation of E. 2) Rare case reports of optic neuritis have been attributed to streptomycin.
Arthralgias	Z FQ	1) Initiate therapy with nonsteroidal anti-inflammatory drugs. 2) Initiate exercise regimen. 3) Lower dose of suspected agent, if this can be done without compromising regimen. 4) Discontinue suspected agent if this can be done without compromising regimen.	1) Symptoms of arthralgia generally diminish over time, even without intervention. 2) Uric acid levels may be elevated in patients on pyrazinamide. Allopurinol appears not to remediate uric acid levels.

These common side effects, as well as more important adverse effects, are discussed in the sections below. Please see Appendix 1 for a list of all drugs used in the treatment of MDR TB and their common and rare side effects.

7.1 Anaphylaxis and allergic reaction

Anaphylaxis, although exceedingly rare, is one of the most severe manifestations of a drug allergy. The identification and management of anaphylaxis is an essential skill for all caregivers of patients receiving MDR TB therapy. Anaphylaxis presents within minutes of administration of the offending agent, classically presenting with signs of airway obstruction such as stridor, wheezing, swelling of the tongue, sensation of a "lump" in the throat, and hoarseness. Accompanying symptoms such as shock, pruritis, and urticaria (with or without angioedema), nausea, vomiting, cramps, and diarrhea may or may not be present. Acute stabilization of anaphylaxis requires basic life support, i.e., maintaining airway, breathing, and circulation (see Protocol 12). Epinephrine should be administered, and the patient should be hospitalized as soon as possible.

Other severe reactions may occur days to weeks after exposure to the offending agent. Rash, fever, and hepatitis are other severe allergic reactions that can be precipitated by antituberculosis medications. Stevens-Johnson syndrome can also be seen with many of the antituberculosis agents. It is characterized by epidermal sloughing and, in 90% of cases, mucosal lesions.

When any of the severe allergic reactions are present, all antituberculosis medications should be suspended. Treatment of allergic reactions includes the use of epinephrine, as mentioned above, as well as corticosteroids and antihistamines. It is essential to determine which drug caused the reaction. Once the patient has improved, antituberculosis therapy can be reinstated as a "challenge"– a partial dose – in a serial fashion (see Table 12), with the most likely allergen administered first.

The challenge described in Table 12 should not be used for agents that may have caused an anaphylactic reaction. In rare cases, an agent that has caused anaphylaxis can be introduced through a desensitization protocol under careful, hospital-based observation,[93,94,95,96,97] by a physician experienced in allergy or immunology. Desensitization is only done when other therapeutic options are extremely limited.

Table 12 Example of antituberculosis medication challenge

Drug	Day 1 (mg)	Day 2 (mg)	Day 3 (mg)	Day 4
Isoniazid	25	50	100	5 mg/kg
Rifampin	50	100	150	10 mg/kg
Pyrazinamide	125	250	500	25-30 mg/kg
Ethambutol	100	200	400	20-30 mg/kg
Streptomycin, Kanamycin, Capreomycin Amikacin	125	250	500	15-20 mg/kg
Ciprofloxacin	125	250	500	20 mg/kg
Ofloxacin	100	200	400	800 mg
Ethionamide Prothionamide	62.5	125	250	15 mg/kg
Cycloserine	62.5	125	250	15 mg/kg
PAS	100 am 200 pm	500 am 1000 pm	2000 am 2000 pm	150 mg/kg

Note: *The above table is to be used only for challenges to medicines in which reactions were mild to moderate.*

For severe reactions, smaller doses should be used over a longer period of time.

7.2 Depression

Clinical depression refers to a constellation of symptoms, lasting more than two weeks, that interferes with normal social and physiological functioning. Symptoms include depressed mood; loss of interest in previously enjoyed activities; lack of energy; psychomotor retardation (slowing of speech, thought, and movement); appetite and sleep disturbances; feelings of guilt, helplessness or hopelessness; inability to concentrate; and possibly psychosis and/or suicidal ideation. Mood changes have been reported with CS, H, Ethio, and AMX/CLV, while depression has been primarily associated with CS. Other etiologies include psychosocial stressors (including poverty, stigmatization, domestic violence); hypothyroidism; and drug or alcohol dependence (including benzodiazepines).[98] A high baseline prevalence of depression is to be expected in patients suffering from a chronic disease; furthermore, social stigma associated with tuberculosis often exacerbates the patient's feeling of alienation and worthlessness.

In approaching a patient with depression, other causes or contributors should be investigated, including any psychosocial stressors. While formal psychotherapy and support groups can be utilized, the DOT worker plays a crucial role in providing intensive counseling and support to the family and patient.

Evidence of suicidal or homicidal ideation should prompt immediate action with consideration of hospitalization. Antidepressant therapy can also be initiated as needed. The need to discontinue an antituberculosis agent due to refractory depression is extremely rare.[98,99,100] (See Protocol 3 in Appendix 4.)

7.3 Electrolyte abnormalities

Although often asymptomatic, low serum potassium and magnesium may present as fatigue, myalgias, cramps, paresthesias, lower extremity weakness, behavior or mood changes, somnolence, and confusion. More severe disturbances can lead to

tetany, paralysis, and life-threatening cardiac arrhythmias. For this reason, frequent electrolyte surveillance is recommended in patients with significant GI losses and in all patients receiving parenteral therapy (see Table 4 for monitoring schedule). Electrolyte wasting is more often associated with capreomycin than other injectable agents. The magnitude of total body depletion of potassium (K^+) and magnesium (Mg^{++}) may be far lower than that which is reflected in serum levels.

Hypokalemia (defined as a serum potassium less than 3.5 meq/L) and hypomagnesemia (defined as a serum magnesium less than 1.5 meq/L)* are not uncommon in patients receiving MDR TB therapy and are caused by the following:

- Direct renal tubular effect of aminoglycosides and capreomycin.
- Vomiting and diarrhea.

Once hypomagnesemia or hypokalemia is diagnosed:

- Underlying causes such as vomiting and diarrhea should be treated.
- Arrhythmogenic medications (such as digoxin, tricyclic antidepressants) should be discontinued if possible.
- An electrocardiogram should be performed in patients with significant electrolyte disturbances; if the QT segment is prolonged, any drugs contributing to QT prolongation – including certain fluoroquinolones, haloperidol, fluconazole, and cisapride – should be held.[101]

Treatment of hypokalemia and hypomagnesemia:

- May be administered orally if electrolyte disturbance is not severe.

* Normal ranges can vary between reporting laboratories.

- Replacement may be needed during the whole course of the use of the aminoglycoside or capreomycin.
- Hypokalemia will be refractory to treatment unless hypomagnesemia is also treated.

Normal renal function should be confirmed prior to instituting repletion, although even patients with renal failure should receive repletion in smaller doses. Both electrolytes can be supplemented in IV or oral form. When possible, potassium depletion should be corrected orally by increased dietary uptake or supplementation with potassium salts. Intravenous treatment is required for patients with gastrointestinal disorders or severe potassium deficiency. See Protocol 14 in Appendix 4.

Potassium-sparing diuretics (spironolactone, triamterene, or amiloride) may be used as adjuvant therapy in severe renal potassium losses secondary to aminoglycosides and capreomycin. Great caution must be used when potassium-sparing diuretics are given in conjunction with potassium supplements, as hyperkalemia may result.

Of note is that hypomagnesemia often causes hypokalemia and hypocalcemia. Hypokalemia (and hypocalcemia) may be refractory to treatment if hypomagnesemia is present and not addressed.[102, 103] Since serum magnesium levels are not always reflective of total body magnesium content, empiric magnesium replacement is often needed in hypokalemia even if the serum magnesium levels are within normal range.

The frequency and replacement schedules for potassium, magnesium, and calcium are being determined as more and more tuberculosis programs use aminoglycosides and capreomycin long term. Recommendations from the Peruvian DOTS-Plus program include:

Potassium

Oral Supplementation

- May dilute KCl tablets in water or take as pills.
- May split dose and give two or three times per day.
- Supplement diet with banana, orange/tomato/grapefruit juice.

IV Supplementation

- Should NOT exceed more than 20 meq/hr of KCl.
- Normal preparation is 40 meq in 1 liter of NaCl 0.9%, maximum preparation is 60 meq/L.

Table 13 Frequency and replacement table for potassium

Potassium level meq/L	Quantity of KCl	When to do next control (sooner if pt has vomiting or diarrhea)
4.0 or more	None	Monthly
3.7 – 4.0	None	Monthly
3.4 – 3.6	20 - 40 meq	Monthly
3.0 – 3.3	60 meq	Two weeks
2.7 – 2.9	80 meq	One week
2.4 – 2.6	80-120 meq	1 – 6 days
2.0 – 2.3	60 meq IV and 80 meq PO	Every 6 to 24 hrs
<2.0	60 meq IV and 100 meq PO	Every 6 hrs with aggressive IV replacement. Consider holding injectable until >2.4

Magnesium

Oral Supplementation

- Presentations:
  - Magnesium gluconate
  - Magnesium oxide
- Different preparations have different amounts of elemental magnesium. The following table gives the tablet dosage amount; we assume that a 400 mg tablet will contain 240 mg elemental magnesium. If the preparations you are using have less elemental magnesium, you may have to increase the tablet dosage.
- Quantities greater than 2000 mg are often more easily given IV or IM.

IV Supplementation

- Maximum concentration: 5 g or 40 meq $MgSO_4$ in 1 liter of NaCl 0.9% or dextrose 5%
- Do NOT exceed 150 mg per minute.
- If not emergency:
  - 2 g in 100 ml administered over 1–2 hours
  - 4 g in 250 ml administered over 2–4 hours

Intramuscular Supplementation

- 1 g (or up to 250 mg/kg) of $MgSO_4$ without dilution IM every 6 hours.
- No advantage over IV magnesium.
- Indicated if supplementation cannot be received PO or IV.

Table 14 Frequency and replacement table for magnesium

Magnesium level meq/L	Quantity of mg (total daily dose)	When to do next control
1.5 or more	None	Monthly
1.1 – 1.4	1000 mg – 1200 mg	Monthly
0.8 – 1.0	2000 mg (consider IM)	1–2 weeks
<0.8	3000 mg – 6000 mg (give IV or IM)	1–6 days

Calcium

- Symptomatic hypocalcemia should be treated on an emergency basis with 2 grams of calcium gluconate (180 mg elemental calcium or 20 ml 10% calcium gluconate) IV over 10 minutes, followed by infusion of 6 grams calcium gluconate in 500 ml D5W over 4–6 hrs. The IV infusion should be tapered. The initial oral dose during the transition from IV to oral therapy is 1–2 g elemental calcium three times a day.
- For long-term therapy the typical dose is 0.5–1.0 g PO TID.
- Hypomagnesemia must be treated if present.
- Total serum calcium levels need to be adjusted for low albumin (ionized levels of calcium do not need to be adjusted). The total serum calcium can be corrected by adding 0.8 mg/dL for every 1 g/dL decrease of serum albumin below 4 g/dL. By doing this calculation one can determine if true hypocalcemia is present:[103]

Corrected calcium for hypoalbuminemia =
0.8(4.0-measured albumin) + reported calcium

Table 15 Frequency and replacement table for calcium

Calcium level (total calcium adjusted for low albumin)	Dose of calcium	When to do next control
>8.5 mg/dL (>4.2 meq/L)	None	
7.5 – 8.4	500 mg TID	Monthly
7.0 – 7.4	1000 mg TID	1–2 weeks
<7.0	Consider IV and taper to 1000 mg TID	1–4 days

Use of potassium-sparing diuretics in the treatment of hypokalemia and hypomagnesemia

- Certain diuretics decrease renal loss of K and Mg:
  - amiloride 5–10 mg per day
  - spironolactone 25–50 mg per day
- Often must continue with K and Mg supplement but in lesser quantity.
- Side effects of potassium-sparing diuretics: increased urination, dehydration, gynecomastia (not seen with amiloride), gastric intolerance.

Additional points

- Always treat vomiting and diarrhea which may contribute to electrolyte abnormalities.
- Preliminary anecdotal observations indicate that capreomycin may cause electrolyte abnormalities more frequently than other injectables. Consider changing CM to AMK or KM if the strain is susceptible.
- Continue electrolyte monitoring and replacement until injectable course is completed.

- The electrolyte abnormalities seen in our patients have always corrected after suspension of the injectable. If electrolyte abnormalities do not correct once the injectable is suspended, suspect another etiology.

7.4 Gastrointestinal intolerance

The wide spectrum of gastric intolerance ranges from nausea and abdominal bloating to gastric ulcers and refractory abdominal pain. Mild symptoms, including nausea, loose stools, and abdominal bloating, are common, especially in the initial months of therapy. Gastritis is also frequently observed, especially in those patients having received multiple previous treatments. Symptoms associated with gastritis include epigastric burning or discomfort, a sour taste in the mouth, and exacerbation of symptoms in the morning and prior to eating. Signs of gastric ulcers include severe postprandial pain, as well as hematemesis and/or melena. Gastric symptoms presenting later into therapy include fat malabsorption and lactose intolerance due to the effects of long-term antibiotics on intestinal flora. Additionally, deposition of clofazimine crystals can lead to abdominal cramping that may be severe.

The agents most likely to induce gastrointestinal intolerance are PAS, Ethio (Prothio), CFZ, H, E, and Z. Severe nausea and vomiting should also raise the suspicion of hepatitis. Workup for infectious causes of diarrhea should include *C. difficile* and be guided by knowledge of regionally endemic pathogens. Alternative causes of gastritis include *H. pylori*, alcohol or tobacco use, and medications (NSAIDs, aspirin, corticosteroids).[104]

Early GI symptoms, while common, can be minimized. Any patient with baseline gastritis should be started on H2-blocker therapy. Also, ethionamide (or prothionamide) is started at lower doses of 250–500 mg, gradually increasing over one to two weeks to achieve the target dose. Initial gastric symptoms

should be aggressively managed; reassurance that these symptoms diminish after the first few weeks of therapy is equally important. Anti-emetics and antacids are commonly used either on a PRN or standing basis. Antacids should be given three hours before or after the administration of tuberculosis medications, because they interfere with the activity of fluoroquinolones. Treatment for gastritis with an H2-blocker or proton pump inhibitor often provides relief.

For patients with significant emesis and/or diarrhea, electrolytes and hydration status should be assessed and corrected as necessary. In patients experiencing refractory GI symptoms, other possible causes should be considered. Only in severe cases should antituberculosis medications be adjusted; in such instances, temporary discontinuation (or dose reduction) of ethionamide or PAS may allow effective control of symptoms before reinstitution of normal dosing is attempted. In cases of severe gastritis and/or suspected gastric ulcer, emergent hospitalization and endoscopy should be considered.[103] (See Protocols 4, 5, and 9 in Appendix 4.)

7.5 Headaches

Often common during the initial months of therapy, headaches may be migraines or cluster headaches, and their relationship to therapy is unclear. Psychosocial stressors often contribute to the severity of headache symptoms. To minimize headaches as well as dizziness and sleep disturbances upon treatment initiation, CS is started at lower doses of 250–500 mg, gradually increasing over one to two weeks to achieve the target dose. Most headaches can be treated with anti-inflammatory agents, although refractory headaches may respond to low-dose tricyclic antidepressants or anti-inflammatory agents with an additional analgesic such as codeine. (See Protocol 6 in Appendix 4.) Meningitis, while rare, requires prompt attention.

7.6 Hepatitis

Hepatitis is characterized by nausea, vomiting, jaundice, scleral icterus, tea-colored urine, pale stool, and diminished appetite. Tuberculosis itself may cause hepatitis. Antituberculosis medications associated with hepatitis include H, R, Z, Ethio, and PAS; other etiologies include infections (e.g., Hepatitis A, B, C, D, E; cytomegalovirus; leptospirosis; Epstein-Barr virus; herpes simplex virus; yellow fever; rubella), alcohol use, and other medications (e.g., anti-epileptics, acetaminophen, sulfa drugs, erythromycin). Routine screening of serum liver tests is recommended, and a mild transient transaminitis may be observed in the first months of therapy. However, clinically significant hepatitis is almost invariably symptomatic, and the diagnosis is confirmed by an elevation in serum transaminases or direct bilirubin. Mild elevation of serum liver tests often can be tolerable. Many clinicians do not suspend therapy until elevation of serum transaminases reaches three to four times what is normal.[105]

Once significant hepatitis is diagnosed, all antituberculosis agents and other hepatotoxic drugs should be suspended immediately. When clinically appropriate, other causes should be explored. Once serum liver tests return to baseline, antituberculosis medications should be resumed in a serial fashion, adding a new medicine every three to four days, while monitoring serum liver tests before adding the next medicine. The most likely agent that caused the hepatitis can be left out of the serial challenge. If an agent is permanently stopped, try to substitute a different, less hepatotoxic agent. The challenge should begin with the agents more likely to cause hepatitis. If the responsible agent is essential to the patient's regimen, the drug may be tolerated at a lower dose. (See Protocol 7 in Appendix 4.)

7.7 Hypothyroidism

Hypothyroidism is caused by inadequate thyroid hormone production or conversion. Symptoms of hypothyroidism include

fatigue, somnolence, cold intolerance, dry skin, coarse hair, and constipation, as well as occasional depression and psychosis. Thyromegaly and delayed deep tendon reflexes may be encountered on exam. In cases of primary hypothyroidism, the diagnosis is confirmed by a serum level of thyroid-stimulating hormone greater than 10.0 mU/L. Both ethionamide (or prothionamide) and PAS interfere with hormone synthesis, and in most cases of hypothyroidism induced by MDR TB treatment the patient is receiving both. Other causes include iodine deficiency, medications (lithium, amiodarone), previous radioiodine treatment, pregnancy-associated thyroid dysfunction, and Hashimoto's disease.[106]

Once other etiologies are excluded, levo-thyroxine should be initiated. Hypothyroidism associated with antituberculosis medications is, in our experience, easily controlled and does not forcibly require discontinuation of the thiamide or PAS. Thyroid dysfunction resolves upon discontinuation of MDR TB therapy; thus, hormone replacement may be discontinued several months after treatment completion.[107,108] (See Protocol 8 in Appendix 4.)

7.8 Musculoskeletal effects

Arthralgias, arthritis, and myalgias are transient symptoms most commonly encountered in the early months of therapy, and are associated with pyrazinamide, fluoroquinolones and thiamides. Similar symptoms may be observed in gout, pseudogout, and degenerative joint conditions. Such symptoms are usually transient and can be treated with anti-inflammatory drugs.

7.9 Nephrotoxicity

Nephrotoxicity is most readily diagnosed by a rise in serum creatinine above baseline. For this reason, routine surveillance of serum creatinine is recommended, especially while patients receive parenteral therapy. While asymptomatic cases may be detected in this manner, symptomatic cases may present with any

of the following findings: oliguria or anuria; evidence of volume overload such as edema, anasarca, or shortness of breath; or uremic symptoms such as mental status changes (confusion, somnolence) or serositis. Aminoglycosides and capreomycin are nephrotoxic agents, while other etiologies of acute renal failure include sepsis, medications (e.g., NSAIDs, ACE-inhibitors, sulfa drugs, diuretics), and vasculitides.[109]

Risk of nephrotoxicity can be minimized by encouraging fluids and avoiding other nephrotoxic drugs in patients receiving parenteral therapy. Additionally, any patient with baseline renal insufficiency requires renal dosing of antituberculosis medications, according to Table 9. Since acid-base and electrolyte disturbances are serious complications of renal failure, serum chemistries should be reviewed once an abnormality in creatinine and/or urea is detected. Other causes should be addressed and any nephrotoxic drugs avoided if possible. In cases of mildly elevated creatinine and/or urea, parenteral therapy may be continued. If the infecting strain is susceptible, CM should replace aminoglycoside therapy. In some cases of renal insufficiency, an option may be to give the injectable three times a week. In cases of severe renal failure, parenteral therapy should be suspended altogether, and hospitalization should be considered. Management involves supportive care with correction of electrolyte and volume imbalances. (See Protocol 10 in Appendix 4.) Involvement of a nephrologist is recommended in such instances.

7.10 Ototoxicity

Ototoxicity refers to damage of cranial nerve VIII, usually manifested by hearing loss and/or tinnitus. Other vestibular symptoms such as nystagmus, ataxia, and disequilibrium can also occur. Presentation is most commonly observed in patients receiving large cumulative doses of aminoglycosides and/or capreomycin, although clarithromycin has been reported to have ototoxic effects as well. Concomitant use of furosemide, par-

ticularly in the setting of renal insufficiency, may exacerbate ototoxic effects of these medications.

Although hearing loss is irreversible, progression can be prevented once the offending agent is discontinued. However, continuation of injectable therapy despite hearing loss may be warranted in patients with significant resistance and/or disease. In such cases, capreomycin may replace an aminoglycoside agent if the infecting strain is susceptible. Using the injectable three times a week can also be considered.

7.11 Peripheral neuropathy

Peripheral neuropathy refers to damage to the nerves located outside of the central nervous system. This side effect has been associated with numerous antituberculosis medications, including the aminoglycosides, H, thiamides, fluoroquinolones, CM, CS, and E. Other etiologies include DM, HIV, alcoholism, hypothyroidism, other drugs (e.g., phenytoin, amiodarone, dapsone, certain cancer chemotherapy agents), and vitamin deficiencies (e.g., B_{12}, folate, thiamine). While nerve conduction studies provide the diagnostic gold standard, the diagnosis can be made on clinical grounds. Findings occur most commonly in the lower extremities, with sensory disturbances (e.g., numbness, tingling, burning, pain, loss of temperature sensation), difficulty walking, weakness, and decreased or absent deep tendon reflexes. At times, sensory changes may occur in upper extremities or elsewhere.[110]

Aside from pyridoxine prophylaxis, other preventive measures include correction of vitamin deficiencies in patients with nutritional compromise. Once peripheral neuropathy is diagnosed, other contributing causes should be addressed. Treatment options include physical therapy and tricyclic antidepressants, if no contraindications exist. Of note, if the patient is receiving a parenteral agent, electrolytes should be checked prior to starting a tricyclic. A low dose, e.g., amitriptyline 25 mg QHS, should be started, observing treatment response for at

least a week. If the patient reports no response, the dose may be increased, up to 75 mg QHS. In patients who fail to respond to a tricyclic, gabapentin (400–1200 mg TID) can be effective.[111,112,113] (See Protocol 11 in Appendix 4.)

7.12 Psychosis

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 psychosis. Caregivers should be familiar with signs of psychosis, since patients are more easily managed when symptoms are mild. CS is the medicine most commonly associated with psychosis; however, H, fluoroquinolones, and thiamides have also been associated with it.[97,114,115] Other etiologies include psychosocial stressors, depression, hypothyroidism, and other medications (benzodiazepines, certain antidepressants), as well as illicit drug and alcohol use.[98]

Pyridoxine prophylaxis may minimize risk of neurological and psychiatric adverse reactions. The usual dose is 150 mg daily for a patient on cycloserine.

Once psychosis has been diagnosed, other possible etiologies should be ruled out. Twenty-four-hour surveillance and possible hospitalization should be considered for all patients with florid psychosis and/or suicidal or homicidal ideation. Antipsychotic therapy, e.g., haloperidol 1–5 mg PRN, should be started at the earliest signs of psychosis. During initial stabilization, CS should be suspended and then resumed once the patient is no longer psychotic, usually at a lower dose. Some patients will not be able to tolerate reinitiation of CS, so the use of other agents should be considered. Once all symptoms have resolved, antipsychotic therapy may often be tapered. If CS is continued, some patients will require antipsychotic therapy throughout treatment. In such patients, antipsychotic ther-

apy may usually be discontinued upon completion of MDR TB therapy.[99,116, 117,118] (See Protocol 13 in Appendix 4.)

7.13 Seizure

Seizure is caused by abnormal electrical activity of the brain. The diagnosis can often be made clinically without the need for EEG testing. Presentation may include a preceding aura, loss of consciousness, involuntary movement or flaccidity, bowel-bladder incontinence, and a postictal state of confusion or somnolence. Once seizure is diagnosed, possible causes should be explored. CS, H, and the fluoroquinolones have been associated with seizure, while other causes include infection (including CNS TB), hypoglycemia, electrolyte abnormalities, hypoxia, alcohol withdrawal, other drugs (e.g., penicillins, tricyclics), uremia, and hepatic failure.[97]

Approaches to seizure prevention include pyridoxine prophylaxis and, in patients previously taking an anti-epileptic, close monitoring of serum levels during MDR TB treatment, given the interactions with certain antituberculosis medications (i.e., H, R, CS, fluoroquinolones). If seizure does occur, other possible causes should be excluded and anti-epileptic therapy initiated. If CS is not essential to the regimen, it should be suspended and another drug added in its place. If CS is essential, after stabilization with anti-epileptic medications, the CS may be restarted and the anti-epileptic therapy continued throughout the duration of MDR TB therapy. The anti-epileptic therapy can be discontinued upon treatment completion.[119,120] (See Protocol 15 in Appendix 4.)

8: Mycobacteriology Laboratory Analysis and Support

Basing treatment regimens on the results of *in vitro* DST is the gold standard of TB therapy in the United States and Europe.[121,122,123] DST should be done only in laboratories staffed by personnel who are proficient at identifying mycobacteria and who perform a sufficient number of susceptibility tests to be aware of the problems associated with the procedures.[124]

There are several conventional methods of DST and thus of diagnosing antituberculosis drug resistance.[125] The most widely used are mentioned in Table 16 (also see Appendix 3).

Table 16 Methods of drug-sensitivity testing

Methods of DST
• Absolute concentration method • Resistance ratio method • Proportion method and its variants • The disc method • BACTEC 460® radiometric method

Susceptibility testing can be performed using the patient's decontaminated sputum specimen *(direct test)* or using growth from a primary culture *(indirect test)*. The latter is superior since the inoculum size is more uniform and bacteria are metabolically active. Since direct tests can only be performed on smear-positive specimens and have several other inherent limitations, the indirect test for DST is more commonly used.

The most widely used indirect method is the *proportion method*. In this method, the number of colonies that grow on media containing an antituberculosis drug is reported as a proportion of the number of colonies growing on control media (without antituberculosis medications). When the colony count on the media containing the drug is less than 1% of colonies counted

on the control media, the strain of *M. tuberculosis* is regarded as susceptible to that drug.

The BACTEC 460® rapid method of drug-sensitivity testing is a radiometric method used for the isolation, identification, and susceptibility testing of mycobacteria.[126,127] Growth is measured by the release of radiolabeled carbon-14. Drug-susceptibility results (using a limited number of commercially available drugs) are available in 7 to 14 days.[128]

This book is not meant to serve as a guide on how to do cultures and DST. However, for the reader's knowledge, a more detailed description of the most widely used methods is given in Appendix 3.

9: MDR TB Contacts and Treatment of Latent Infection

The following categories of people are considered at risk for MDR TB:

- Household contacts of patients with MDR TB
- Health care workers
- Prisoners
- Prison employees

9.1 Adult contacts

Of groups at risk for MDR TB, household contacts of patients with MDR TB are the most likely to have MDR TB. Symptomatic contacts of persons with known MDR TB should undergo the following workup:

- An evaluation by a physician
- A chest X-ray
- Sputum smear and culture

If the workup is negative, trial of a broad-spectrum antibiotic which does not have anti-tuberculosis activity can be considered – for example, trimethoprim/sulfamethoxazol for 10 days. If the patient continues to be symptomatic, consider chest computed tomography and/or directed bronchoscopy for smear and culture. If the sputum smear returns positive, the patient can be started on empiric therapy for MDR TB pending the results of DST.

In a contact who remains symptomatic and with no clear diagnosis of tuberculosis, smears and cultures can be performed monthly with frequent physical exams, including chest X-rays, as needed. This close monitoring should be performed until three months of consecutive negative cultures and resolution of symptoms occur.

In symptomatic adults who have HIV or other immune-compromised states, an empiric treatment regimen based on

the contact's DST may be warranted even if bacteriologic and radiologic studies are negative.

9.2 Pediatric contacts

Symptomatic pediatric household contacts should receive a PPD, chest X-ray, and sputum smear and culture. If the child is less than five years old, then gastric aspiration for smear and culture should be performed. Gastric aspiration should be considered in older children if there is any suspicion that the child cannot expectorate sputum. If a smear or culture returns positive, the child should be started on an empiric regimen based on the DST of the contact's strain.

If the results of the gastric aspiration are negative, bronchoscopy can be considered to attempt to obtain a sample. If, after gastric aspiration and bronchoscopy, the smears remain negative, these tests may be repeated.

In symptomatic contacts who have a negative chest X-ray in addition to negative sputum smear and gastric aspirate, a computed tomography of the chest can help greatly with the decision whether or not to initiate empiric therapy. Furthermore, if the tomography shows a lesion, a directed bronchoscopy can be performed to increase the possibility of obtaining a specimen for DST.

If the tomography and gastric aspirate or sputum smear are all negative and the patient is clinically stable, the patient should be followed closely, with monthly evaluations by a pediatrician, gastric aspirates or sputum samples, and chest X-rays, until three months of negative cultures or resolution of the symptoms occurs. If the patient's condition is clinically deteriorating, empiric therapy designed according to the contact's strain should be started.

The efficacy of using antituberculosis medications for prophylaxis or treatment of latent infection of multidrug-resistant

strains is not well established. Until more data are available, our group does not recommend the routine use of prophylaxis for MDR TB contacts.

10: MDR TB and HIV/AIDS Co-infection

The treatment of MDR TB is complicated when patients are co-infected with HIV. Even with appropriate MDR TB therapy, mortality remains high in this population. The presentation, diagnosis, and treatment of TB in the HIV-infected patient represent a significant challenge. This section offers an introduction to some of these challenges and provides clinical guidelines on the treatment of patients who have TB or MDR TB and are co-infected with HIV.

Role of HIV in susceptibility to TB

- Co-infected individuals are 100 times as likely as HIV-negative individuals to develop tuberculosis. The annual risk of developing active tuberculosis is 7–10% in HIV-positive patients with positive tuberculin skin tests.[129,130]
- HIV-infected persons are at increased risk for both reactivation of disease and new infection or reinfection with a new strain of TB.[131,132]

Role of TB in HIV

- *In vitro* studies have shown that tuberculosis increases HIV replication up to 160-fold.[133]
- The risk of death for co-infected patients is twice that of HIV-positive patients without tuberculosis, independent of CD4 count.[132,134]
- The median time of progression to AIDS in patients free of AIDS at baseline was 6 months for co-infected patients, compared to 14.5 months for HIV patients without TB (control group).[135,136]

Because of the interaction between TB and HIV, the authors of these guidelines recommend that all patients with TB be screened for risk factors for HIV. If these factors are present, HIV counseling and testing should be performed. Furthermore, all newly diagnosed HIV-positive individuals should be

screened for TB. HIV-invected patients from countries with a high burden of tuberculosis who do not have active TB should be given prophylaxis with isoniazid for at least 9 months.[137]

Clinical, radiographic, and diagnostic features in TB/HIV co-infection

- Tuberculosis in HIV-positive persons with high CD4 counts may present with the usual signs and symptoms of tuberculosis, including smear-positive disease and cavitations on chest radiograph.[138]
- At lower CD4 counts, the clinical presentations may include: mid or lower lobe disease, a miliary pattern, and extrapulmonary disease (>50% if CD4 count is <100) and mycobacteremia (up to 49% in advanced stages).[139,140] Patients with these presentations may have positive sputum cultures for *M. tuberculosis* even if the chest radiograph is negative.

10.1 The link of MDR TB to HIV/AIDS

The presence of HIV poses a risk for mortality in patients with multidrug-resistant tuberculosis. While the full link between MDR TB and HIV/AIDS is not yet fully understood, there are several reasons that may account for this important association and that need further study:

- Nosocomial transmission has played an important role in the acquisition of MDR TB among AIDS patients due to more frequent hospitalization and longer lengths of stay which allow for more prolonged exposure to circulating strains.
- The underlying immunosuppression in HIV patients leads to an increased likelihood of co-infected patients failing standard regimens and amplifying resistance to antituberculosis medications.
- A larger proportion of recent circulating strains are drug-resistant, and HIV-infected patients with advanced disease are at higher risk for reinfection

which may allow for higher rates of MDR TB in this population.[131,132]

- Rifampin monoresistance, reportedly more common in HIV patients, has been independently associated with nonadherence, severe immunosuppression, positive AFB smear, prior rifabutin use, antifungal therapy, and diarrhea.[141,142]
- Malabsorption of antimycobacterial drugs has also been reported in patients with HIV-enteropathy. Implicated drugs include rifamycins, ethambutol, pyrazinamide, ethionamide, cycloserine, and isoniazid.[143,144,145]

For these reasons, the health care worker should have a high suspicion of MDR TB in all HIV patients. Because MDR TB, if not promptly recognized in the HIV patient, often results in death, and because HIV may be a risk factor for MDR TB, the authors of this manual recommend performing drug-sensitivity testing for all patients with HIV and TB.

10.2 Initial evaluation of TB/HIV patients

As stated above, culture and DST should be carried out for all HIV patients diagnosed with TB. Furthermore, rapid diagnostic techniques for MDR TB may offer improved outcomes by identifying HIV patients with drug resistant tuberculosis earlier.

In addition to the TB history described in previous sections, the evaluation of co-infected patients should also include:

- Details of the patient's HIV history, including opportunistic infections and HIV-related illnesses.
- Available CD4 counts and viral loads.
- Previous antiretroviral therapy.
- History of hospitalization, residence in congregate settings, or known contacts with MDR TB.

The physical exam should focus on determining signs of immune suppression and assessing the patient's underlying nutritional and neurological status, as well as any signs of extrapulmonary disease.

Initial labs in HIV-positive patients should include (if resources are available):

- CD4 count
- Viral load
- Complete blood count and differential
- Full chemistry panel (including renal and hepatic parameters)
- Syphilis screening
- Hepatitis B and C serologies
- Toxoplasma IgG (especially if CD4 count <200)

Although the patient should be under the care of an infectious disease specialist, the TB program should also document, and at times help perform, health care maintenance, as well as supervise the prevention and treatment of opportunistic infections. The health care maintenance tasks that should be performed are listed in Table 17.

10.3 Prevention of opportunistic infections

It may fall upon the TB program to help ensure that prophylactic therapy of opportunistic infections is being adequately addressed while the patient receives TB therapy. (See Table 18.)

The timing of prophylaxis will depend on the patient's HIV and TB status. Given the higher likelihood of sulfa-related adverse reactions in HIV-positive patients (six to eight times greater than in the general population), sulfa-based prophylaxis should ideally be started in a staggered fashion (two to four weeks apart) from MDR TB and/or antiretroviral therapy, depending on the clinical setting.

Table 17 Heath Care Maintenance of HIV-Infected Patients

Intervention	Frequency	Comments
Pneumovax	Every 5 to 6 years	
Influenza vaccine	Yearly	
Hepatitis A vaccine (if HCV +, IDU or if MSM)	A series of two injections, at least six months apart, month 0 and months 6–18	If HepA antibody positive, vaccine is not indicated
Hepatitis B vaccine	A series of three injections, given at month 0, month 1 and month 6	
Pap smear	Yearly	
Cholesterol (if on PIs)	Every 6 months	Only needed for patients taking protease inhibitors
Counseling on on-going risk of transmission	Every visit	
Counseling for social and emotional support	Based on individual need	Formal support systems should be in place for patients with TB/HIV
Contraception use	Document every visit	Free condoms should be provided
Nutritional evaluation	Every 6 months	Nutritional support should be given in those with malnutrition

Table 18 Prophylactic therapy for opportunistic infections in the HIV patient[146]

Pathogen/OI	Indication	Preventive regimens
Pneumocystis carinii pneumonia (PCP)	CD4 count <200 or history of oral thrush or history of prior *PCP*	Trimethoprim-sulfamethoxazole (TMP-SMZ) 1 DS PO QD or TMP-SMZ 1 SS PO QD or Dapsone 100 mg PO QD or Atovaquone 1500 mg PO QD or aerosolized pentamidine 300 mg Q month
Toxoplasma gondii (toxoplasmosis)	CD4 count <100 and Toxoplasma IgG sero-positive	TMP-SMZ 1 DS PO QD or Dapsone 50-200 mg PO QD plus pyrimethamine 50-75 mg plus leukovorin 25 mg q week
Mycobacterium avium (MAC)	CD4 count <50	Azithromycin 1200 mg PO Q week or Clarithromycin 500 mg PO BID or Rifabutin 300 mg PO QD

10.4 Antiretroviral treatment in co-infected patients–overall impact

Antiretroviral therapy (ART) in co-infected patients has been associated with improved survival and decreased progression to AIDS. In a study of 188 co-infected patients, 45% received highly active antiretroviral therapy (HAART) during TB treatment. Treatment with HAART led to significant reductions in mortality and other AIDS-defining illnesses (3.5% vs. 24.5%, RR 0.14).[147] In a study on the effects of HAART in patients from Argentina with MDR TB, the mortality in 48 patients who received antiretroviral therapy was 31.2%, compared to 90.7% mortality in co-infected patients treated for MDR TB but not given antiretroviral therapy.[148]

Though there are distinct benefits to HAART in co-infected patients, the initiation of HAART is also associated with adverse events that may lead to the interruption of both TB and HIV therapy. Thus, the following recommendations have been made weighing the risks and benefits of beginning antiretroviral therapy in co-infected patients: starting HAART within the first 2 months of therapy in patients with advanced AIDS (CD4 <100) and deferring HAART until the continuation phase (after two months) in clinically stable patients with CD4 counts >100.[149] Please refer to Table 19.

In those patients who receive HAART during treatment for tuberculosis, the use of antiretroviral therapy may be associated with immune-reconstitution syndromes in up to 36% of co-infected patients.[150] This syndrome — a paradoxical worsening of tuberculosis — is due to the ability of the treated HIV patient to mount a stronger immune response, resulting in an inflammatory reaction against TB which may lead to a clinical worsening of the patient's condition. This remains a controversial area that requires further study. Following the recommendations in Table 19 will decrease the possibility of immune-reconstitution syndrome.

Table 19 Antiretroviral therapy in co-infected TB/HIV patients[146]

Stratification groups	Must meet all criteria	Recommendations
Group 1	1) Pulmonary TB only. 2) CD4 >200 or total lymphocyte count >1000–1200/mm^3 (if CD4 count is not available). 3) Not on ART.	1) Treat TB. 2) Monitor CD4 counts Q 3–6 months. 3) Consider holding ART unless history of other OI or AIDS-defining illness (e.g., Kaposi's Sarcoma, HIV wasting syndrome).
Group 2	1) CD4 >200 with extrapulmonary disease. 2) CD4 <200 yet >100. 3) Not receiving ART.	1) Treat TB. 2) Begin ART after 2 months of TB therapy.
Group 3	1) CD4 <100 (or total lymphocyte counts <1000–1200/mm^3) or 2)Extrapulmonary disease with CD4 <200 3)Not on ART.	1) Treat TB. 2) Begin ART therapy as soon as TB therapy is tolerated (within 2 months of TB treatment if possible).
Group 4	1) Already receiving ART.	1) Continue ART therapy, yet evaluate for virological failure. Begin TB therapy (evaluate for potential drug interactions and additive toxicities).

10.5 Potential drug interactions in the treatment of HIV/TB:

There are several known interactions between ART and anti-tuberculosis medications. These include:

- *Rifamycins* – inducers of cytochrome P-450. In particular, rifampin leads to lower concentrations of protease inhibitors and NNRTIs. See recommendations regarding the co-administration of rifamycins and ART.[151]
- *Quinolones and didanosine* – nonenteric-coated didanosine contains an aluminum/magnesium-based antacid. If given jointly with quinolones, it may result in decreased absorption of quinolones; it should therefore be given six hours before or two hours after quinolone administration.
- *Clarithromycin and ritonavir-based regimens* – result in increased clarithromycin blood levels; however, only individuals with CrCl <60 ml/min require dose adjustment.
- *Clarithromycin and efavirenz or nevirapine* – induction of clarithromycin metabolism with a decrease in clarithromycin plasma concentration (area under the curve or AUC) by 35-39%, respectively. The efficacy of clarithromycin may be decreased.
- *Clarithromycin's* plasma concentration (AUC) is reduced by 50% if rifabutin is co-administered and may increase rifabutin's plasma concentration (AUC) by up to 77%.

10.6 Potential drug toxicity in the treatment of HIV/TB

HIV patients in general have a higher rate of adverse drug reactions to both TB and non-TB medications. In several studies of co-infected patients, the rates of adverse reactions in HIV-infected patients with TB have been as high as 26-39%, compared to 3-22% in HIV-negative controls.[152,153]

Known adverse effects of increased magnitude in co-infected patients:

- **Peripheral neuropathy.** Peripheral neuropathy may be exacerbated in patients on D4T (stavudine), with one study noting that 55% of 22 patients developed this complication with concomitant use of H and D4T.[154] Peripheral neuropathy has also been associated with the use of aminoglycosides, cycloserine, and pyrazinamide. Careful monitoring for this complication with the use of these drugs should be performed.
- **Cutaneous reactions.** Thiacetazone is an antituberculosis medication with significant toxicity in this population, since HIV patients have up to a 28.6% rate of serious cutaneous reactions with this agent. It should never be used in HIV-infected individuals.[155]
- **GI side effects.** In co-infected patients, one study has shown that up to 50% develop gastrointestinal or neurological adverse effects attributable to TB medications. With the use of PAS and ethionamide in patients with MDR TB, this effect may be potentiated by anti-retroviral agents with similar side-effect profiles.[147]
- **Renal toxicity.** Renal toxicity associated with the long-term use of injectables in MDR TB treatment is another concern in this population and should result in frequent monitoring in HIV-infected patients.
- **Neuropsychiatric effects.** The combination of cycloserine and efavirenz may increase the rate of neuropsychiatric side effects; this has not been formally studied, however.

10.7 HIV treatment

Antiretroviral therapy should be initiated and monitored in conjunction with an infectious-disease specialist. It is beyond

the scope of these guidelines to describe how to design regimens for the treatment of HIV. However, it should be noted that adherence to HIV medications is even more important to the success of HIV therapy than adherence to antituberculosis medications is to the success of TB therapy. Studies have shown that greater than 95% adherence is needed to suppress viral replication.[156] Unlike TB therapy where we often give the patient a day of rest from medication on Sundays, full adherence (7 days per week) is essential in HIV therapy due to the risk of development of resistance.

The appropriate time to initiate ART in the co-infected patient is still a subject of much debate and requires further study. Taking into account the risk of new AIDS-defining illnesses and mortality as stratified primarily by immunological status, Table 19 provides a guideline for when to initiate therapy in co-infected patients.

10.8 Monitoring of TB and HIV therapy in co-infected patients

The complexity of both antiretroviral regimens and TB treatment, each with its own toxicity profiles – some of which may be potentiated in the setting of concomitant therapy – demands rigorous monitoring in this particular group of patients. In addition to the MDR TB treatment monitoring and health care maintenance of HIV-infected individuals described earlier in this manual, the following monitoring is recommended with respect to HIV.

Monitoring of CD4 counts and viral loads[157]

Patients not receiving ART;

- CD4 counts should be performed at the time of diagnosis and every three to four months thereafter (depending on the individual patient and available resources).

Patients receiving ART;

- CD4 counts should be measured every three to six months while on therapy.
- Viral loads should be measured immediately prior to initiation of antiretroviral therapy (baseline) and then two to eight weeks thereafter, followed by testing every three to four months, provided that patients have reached virological goal. At two to eight weeks, patients should have at least a 1 log (10-fold) decrease in viral load. If not, an appropriate evaluation of early virological failure should be done (assessment of adherence, potency, absorption of regimen, or determination of virologic resistance).
- On appropriate therapy, viral load usually becomes below detectable levels (<50 RNA copies/ml) by 16-20 weeks, although this outcome is affected by baseline CD4 count, baseline viral load, regimen

potency, adherence, prior exposure to antiretrovirals, and intercurrent opportunistic infections.

Other important considerations include the following:

- Viral loads should not be measured during or within four weeks of any intercurrent acute infection, immunization, or symptomatic illness.
- A significant decrease in CD4 count is a >30% decrease from baseline.
- A significant change in plasma viral load is a 3-fold or 0.5 log increase or decrease.

Table 20 Monitoring of MDR TB/HIV-positive patients

Group	CD4	Viral load	Additional lab followup
On MDR TB therapy, no ART	Q 3–6 months	Not usually done unless resources are available.	Monthly creatinine while on injectable.
On MDR TB therapy and ART	Q 3–6 months	Baseline (prior to ART), then at 2–8 weeks to assess if >1 log drop. If virological goal has been reached, follow Q 3–6 months thereafter.	Monthly creatinine while on injectable. CBC and serum liver tests Q 3 months. For additional recommendations, see Table 17.

10.9 Summary of treatment guidelines for the TB/HIV-infected patient

The patient co-infected with TB/HIV will require intense medical intervention to decrease the high mortality in these patients. The TB/HIV patient with multidrug-resistance poses an even greater challenge and will require the following:

- Prompt and accurate diagnosis of tuberculosis in the HIV-infected individual.
- Screening for HIV in all patients diagnosed with tuberculosis.
- Adequate and appropriate regimens for the treatment of TB, including DST testing and regimens based on the DST.

- The use of potent combination antiretroviral therapy (at least three drugs) under the supervision of persons experienced with treating HIV.
- Monitoring for drug interactions and additive drug toxicities.
- Monitoring, prophylaxis, and treatment of opportunistic infections.
- Administration of recommended vaccinations and health care maintenance interventions.
- Counseling to provide psychosocial and emotional support and to reinforce prevention of secondary transmission.
- Nutritional support when needed.

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Appendix 1
Descriptions and Side Effects of Antituberculosis Medications

Table 21 Antituberculosis medications – side effects

Drug name	Description	Side effects
Isoniazid	Bactericidal. Nicotinic acid hydrazide. Inhibits mycolic acid synthesis most effectively in dividing cells. Hepatically metabolized.	**Common:** hepatitis (10-20% have elevated transaminases; H discontinuation indicated in symptomatic hepatitis; increased risk with alcohol ingestion), peripheral neuropathy (dose-related; increased risk with malnutrition, alcoholism, diabetes, concurrent use of AG or THA). **Less common:** fever, GI upset, gynecomastia, rash (2%). **Rare:** agranulocytosis, anemia, encephalopathy, eosinophilia, hypersensitivity, memory impairment, optic neuritis, positive anti-nuclear antibodies, psychosis, seizure, thrombocytopenia, vasculitis. **Drug interactions:** increases phenytoin levels.
Rifampin (Rifampicin)	Bactericidal. Produced by *Streptomyces spp.* Inhibits protein synthesis by blocking mRNA transcription and synthesis. Hepatically metabolized.	**Common:** orange-colored bodily secretions; transient transaminitis. **Less common:** GI upset (1.5%), hepatitis. **Rare:** cholestatic jaundice, drowsiness, fatigue, fever (0.5%), gynecomastia, headache, pruritis, rash (0.8%), renal insufficiency, thrombocytopenia (especially in conjunction with E), urticaria. **Drug interactions:** decreased reliability of oral contraceptives, protease inhibitor (PI) levels decreased by R, decreased activity of drugs metabolized by P450 system (e.g., CPX, corticosteroids, dapsone, diazepam, digitoxin, fluconazole, haloperidol, methadone, oral hypoglycemics, phenytoin, quinidine, theophylline, warfarin).

Table 21 Antituberculosis medications – side effects, continued

Drug name	Description	Side effects
Pyrazinamide	Bactericidal. Nicotinamide derivative. Mechanism unknown. Effective in acid milieu (e.g., cavitary disease, intracellular organisms). Hepatically metabolized, renally excreted.	**Common:** arthropathy, hepatotoxicity, hyperuricemia. **Less common:** GI upset, impaired diabetic control, rash. **Rare:** dysuria, fever, hypersensitivity reactions, malaise. **Drug interactions:** none reported.
Ethambutol	Bacteriostatic at conventional dosing (15mg/kg). Inhibits lipid and cell wall metabolism. Renally excreted.	**Less common:** arthralgia, GI upset, headache, malaise. **Rare:** disorientation, dizziness, fever (0.3%), hallucination, peripheral neuropathy, pleuritis, rash (0.5%), retrobulbar neuritis (0.8%, dose-related and reversible, increased risk with renal insufficiency). **Drug interactions:** none reported.
Aminoglycosides *Amikacin* *Kanamycin* *Streptomycin*	Bactericidal. Inhibits protein synthesis through disruption of ribosomal function. Less effective in acid, intracellular environment. Renally excreted. S least nephrotoxic. AMK has been shown to be highly mycobactericidal compared to other aminoglycosides *in vitro*.	**Common:** pain at injection site. **Less common:** cochlear otoxocity (hearing loss, dose-related to cumulative and peak concentrations, increased risk with renal insufficiency, may be irreversible), facial paresthesia, nephrotoxicity (dose-related to cumulative and peak concentrations, increased risk with renal insufficiency, may be irreversible), peripheral neuropathy, rash, vestibular toxicity (nausea, vomiting, and vertigo). **Rare:** anaphylaxis, hemolytic anemia, neuromuscular blockade, pancytopenia. **Drug interactions:** ototoxicity potentiated by certain diuretics.

Table 21 Antituberculosis medications – side effects, continued

Drug name	Description	Side effects
Capreomycin	Bactericidal. Polypeptide isolated from Streptomyces capreolus. Renally excreted.	**Common**: pain at injection site. **Less common**: ototoxicity and nephrotoxicity (dose-related to cumulative and peak concentrations, increased risk with renal insufficiency). **Rarely**: electrolyte abnormalities, eosinophilia, hypersensitivity, neuromuscular blockade. **Drug interactions**: enhanced risk of neuromuscular blockade with ether anesthesia.
Fluoroquinolones *Ciprofloxacin* *Ofloxacin* *Levofloxacin* *Sparfloxacin* *Moxifloxacin* *Gatifloxacin*	Likely bactericidal. DNA-gyrase inhibitor. Not FDA-approved for use during pregnancy—associated with arthropathies in studies with immature animals. Renally excreted. Levofloxacin active moiety and thus possibly the drug of choice.	**Less common**: diarrhea, dizziness, GI upset, headache, insomnia, photosensitivity (8% occurrence with SPX), rash, vaginitis. **Rare**: arthralgia, interstitial nephritis, palpitations, psychosis, seizure, transaminitis (CNS effects seen almost exclusively in elderly). Because of arrythmias and sudden cardiac deaths associated with SPX, this fluoroquinolone has been withdrawn in many countries; its use should be avoided. **Drug interactions**: CPX, OFX prolong half-life of theophylline with increased risk of toxicity; $CaSO_4$ or $FeSO_4$ and antacids with Al, Mg may inhibit GI absorption of fluoroquinolones; altered phenytoin levels (increased and decreased); exacerbated hypoglycemic effect of glyburide; increased coumadin levels reported with CPX, OFX; probenacid increases CPX, OFX levels; use of SPX contraindicated in persons receiving any drug that prolongs the Q-T interval.

Table 21 Antituberculosis medications – side effects, continued

Drug name	Description	Side effects
Thiamides *Ethionamide* *Prothionamide*	May be bacteriostatic or bactericidal depending on concentration attained at the site of infection and the susceptibility of the bacteria. Derivative of isonicotinic acid. Hepatically metabolized, renally excreted.	**Common**: GI upset (nausea, vomiting, abdominal pain, loss of appetite), metallic taste, hypothyroidism (especially when taken with PAS). **Less common**: arthralgia, dermatitis, gynecomastia, hepatitis, impotence, peripheral neuropathy, photosensitivity. **Rare**: optic neuritis, psychosis, seizure (increased risk of CNS effects with concurrent use of ethanol, H, CS, or other centrally acting medications). **Drug interactions**: transiently increased H levels.
Cycloserine	Bacteriostatic. Alanine analogue. Interferes with cell-wall proteoglycan synthesis. Renally excreted.	**Common**: neurologic and psychiatric disturbances including headaches, irritability, tremors. **Less common**: hypersensitivity, psychosis, peripheral neuropathy, seizures (increased risk of CNS effects with concurrent use of ethanol, H, THA, or other centrally acting medications). Neurologic adverse effects may be lessened by pyridoxine coadministration. **Drug interactions**: interacts with phenytoin.
Para-aminosalicylic acid	Bacteriostatic. Hepatic acetylation, renally excreted.	**Common**: GI upset (nausea, vomiting, diarrhea), hypersensitivity (5-10%), hypothyroidism (especially when taken with ethionamide). **Less common**: hepatitis, electrolyte abnormalities. **Rare:** Lupus like reactions. **Drug interactions**: decreased H acetylation, decreased R absorption in non-granular preparation, decreased B12 uptake.

Table 21 Antituberculosis medications – side effects, continued

Drug name	Description	Side effects
Rifabutin *Rifapentine*	Bactericidal. Rifamycin spiropiperidyl derivative.	Similar or lesser side-effect profile and drug interactions compared to R, including reduced activity of drugs metabolized by P450 system. **Drug interactions**: RFB interacts less with PI levels than does R; RFB and RFP decrease PI levels; RFB levels increased by PIs.
Thiacetazone	Weakly bactericidal. Inhibition of mycolic acid synthesis.	**Common**: GI upset (nausea, vomiting), hypersensitivity. **Rare:** cutaneous reactions (including Stevens-Johnson syndrome, increased risk in HIV-infected patients), jaundice, reversible bone-marrow suppression. **Drug interactions:** may potentiate ototoxicity of aminoglycosides.
Amoxicillin-clavulanate	Bactericidal effect demonstrated *in vitro*. Beta-lactam antibiotic with a beta-lactamase inhibitor.	**Common**: GI upset. **Less common:** hypersensitivity. **Drug interactions:** none reported.
Clarithromycin	Demonstrated efficacy against *M. avium* complex; *in vitro* bactericidal effect on susceptible strains of *M. tuberculosis*. Semisynthetic erythromycin derivative.	Well tolerated. **Less common**: GI side effects (abdominal pain, diarrhea, metallic taste). **Rare**: ototoxicity. **Drug interactions**: increased theophylline and carbamazepine levels; use of terfenadine is contraindicated.
Clofazimine	Bacteriostatic. Substituted iminophenazine bright-red dye. Transcription inhibition by binding guanine residues of mycobacterial DNA.	**Common**: discoloration of skin and eyes, GI upset. **Less common:** photosensitivity, malabsorption, severe abdominal distress due to crystal deposition. **Drug interactions**: none reported.

Appendix 2
Regimens for mono- and poly-resistant tuberculosis

Table 22 in this appendix offers suggested regimens for mono- and poly-resistant drug sensitivity patterns. The optimal treatments for many mono- and poly-resistant sensitivity patterns have not been adequately studied. One must always take into account the clinical history, including previous use of antituberculosis drugs, extensiveness of the illness, and reliability of the laboratory when deciding on what regimen to give a patient. Therefore, this table is designed to offer guidance and is not to be followed blindly.

The suggested regimens in Table 22 should not be used if amplification of resistance is suspected in any of the drugs proposed in the regimen. When amplification is suspected, the definitive regimen should be designed based on the principles outlined in section 2.4 of this manual. Amplification can be suspected if the patient has received two or fewer effective drugs for more than ten days. Also, all drugs in the failing regimen should be suspected of having acquired resistance.

If clinical history suggests that a drug could be resistant yet the laboratory data shows it to be sensitive, it should be included in the regimen but additional agents should be added. For example, in a chronically ill patient who has failed multiple courses with HREZS, a DST that reveals only HEZS resistance may not be accurate given the previous TB treatment history. Rifampin should be included in the regimen, but other antituberculosis agents should be added, as the history suggests this patient may have MDR TB. The design of the regimen in this case should follow the principles put forth in Section 2.4 of the manual. A reasonable regimen would be R, KM, FQ, Ethio, CS, PAS. A repeat culture for DST should also be performed. (As an aside, the patient in this example may have remained sensitive because of malabsorption of rifampin, so obtaining serum levels of the drug is suggested to document

whether the patient is adequately absorbing rifampin. If the levels are low, the dose of rifampin can be increased to obtain adequate levels.)

The regimens in Table 22 are designed under the assumption that there is documented sensitivity to the drugs being used in the suggested regimen. The efficacy of the regimens may be over estimated if only DST for first-line drugs is available. In situations where DST is not routinely available to second-line drugs, the prevalence of resistance to second-line drugs in the area must be considered. The proposed regimens in Table 22 may need to be adjusted or strengthened if DST to second-line drugs is not known, or if there is a high prevalence of resistance in the area to any of the drugs being used in the regimen.

Isolated resistance to R, E, or Z is not very common and may prove to be a laboratory error. Isolated rifampin resistance, however, has recently become more common for reasons possibly related to HIV disease, including malabsorption problems of antituberculosis agents and the use of rifabutin in HIV patients.

In summary, Table 22 contains suggested regimens to help guide physicians in designing regimens for patients with mono- and poly-resistant tuberculosis. Table 22 is based on the consensus from the group of MDR TB treating physicians at PIH, and further study to determine optimal regimens for mono- and poly-drug reistance is encouraged. Previous treatment history, chronicity of disease, possibility of amplification, laboratory error, and the reliability of the DST should all be considered when the definitive regimen is designed.

Table 22 Suggested regimens for mono- and poly-drug-resistance

Resistance pattern	Suggested regimen
H	Option 1: 9R-E-Z Option 2: 9R-E-Z-FQ Option 3: 6S-R-E-Z/3R-E-Z
E	Option 1: 2S-H-R-Z/4H_3R_3 Option 2: 3S-H-R-Z/6H_3R_3
Z	6S-H-R-E/6$H_3R_3E_3$
HE	6S-R-Z-FQ/6R-Z-FQ
HZ	6S-R-E-FQ/6R-E-FQ
EZ	6S-H-R-FQ/6H-R-FQ
HEZ	6S-R-FQ-Ethio-CS/12R-FQ-Ethio-CS
R	Option 1: 9S-H-Z-E (regimen not proven for other aminoglycosides or capreomycin) Option 2: 6S-H-E-Z/12S_3-H-E-Z Option 3: 6S-H-E-Z-FQ/12H-E-Z-FQ
RE	6S-H-Z-FQ-Ethio/12H-Z-FQ-Ethio
RZ	6S-H-E-FQ-Ethio/12H-E-FQ-Ethio
REZ	6S-H-FQ-Ethio-CS/12H-FQ-Ethio-CS

Notes on how to use this chart:

- Some DST patterns have more than one option for treatment. Option 1 should only be used if there is not extensive disease and there is high confidence in the DST results, while options 2 and 3 are more aggressive and should be used for patients with more extensive disease.
- If the strain is resistant to streptomycin, then a sensitive aminoglycoside or capreomycin should be substituted in the regimen.
- Prothionamide can be substituted for ethionamide.

- The length of the injectable phase is designated by the first coefficient and is the time past sputum conversion.
- The second coefficient is the minimum amount of treatment after suspension of the injectable phase. The total length of treatment can be extended in patients that have extensive lung damage.
- The subscript indicates the number of times per week the agent needs to be administered.

Direct observation of every dose should take place throughout the course of therapy. Surgical evaluation should be considered for those who do not respond to therapy, or have localized disease with persistent cavities that may put them at risk for failure or relapse.

Appendix 3
Sensitivity testing methods

Sensitivity testing aims to determine the drugs to which a patient's isolate is susceptible in order to design appropriate therapy. An essential part of any MDR TB treatment program, susceptibility testing should be carried out in an experienced laboratory and performed on a wide panel of drugs. There are several methods of drug-susceptibility testing, but similar principles underpin the various methods. Typically, the patient's isolate is incubated in media impregnated with a given antituberculosis drug. Growth is then compared with that of controls known to be susceptible. Given the slow growth of *Mycobacterium tuberculosis* in culture, there is often a long wait before results become available. Conventional methods include the absolute-concentration, proportion, resistance-ratio, and disc diffusion methods. In addition to methods using conventional media, radiometric methods are also used.

Conventional methods

1. Absolute-concentration method

This method determines the minimum inhibitory concentration (MIC) – the lowest drug concentration required to inhibit mycobacterial growth – by preparing culture media with serial drug concentrations. The plates are then inoculated with the patient's isolate and monitored for growth. The MIC is the drug concentration that allows the growth of no more than two to three colonies. This method is also performed using microplates and broth containing serial drug concentrations. The broth is assayed for turbidity.

2. Proportion method

This method cultures the patient's isolate in drug-free media and in media containing serial drug concentrations. The number of colonies grown on the drug-free plates is compared with those on the plates

containing drugs. The isolate is considered resistant to a given drug if the number of colonies growing on the plate containing the drug is 1% or more of the colonies growing on the drug-free plate.

3. Resistance-ratio method
This method compares the MIC for the patient's strain with the modal average of several control strains. The isolate and controls are grown on drug-free and drug-containing media. The MIC for each strain is determined. The resistance-ratio is the ratio of the patient's MIC to the mean control MIC. Strains with a resistance-ratio of 1 or 2 are considered susceptible.

4. Disc diffusion method
In this method, paper discs impregnated with each drug are placed on culture-media plates containing the patient's isolate and on plates containing control isolates. Growth around the disc is then assessed for both the control and the patient's isolate.

Radiometric method (BACTEC)

This method uses radioisotopes to measure metabolic activity of the mycobacteria, thus providing results more rapidly than the conventional methods discussed above. Radio-labeled liquid media (usually containing Carbon-14) are inoculated with the patient and control isolates. Both drug-containing and drug-free bottles of liquid media are used. The difference in metabolic activity on consecutive days is measured and calculated as a daily growth index. If the strain's growth index in a drug-containing solution is less than the growth in a 1:100 dilution of the control strain, the patient's isolate is deemed susceptible to that drug.

For a more in-depth discussion of testing methods, see:

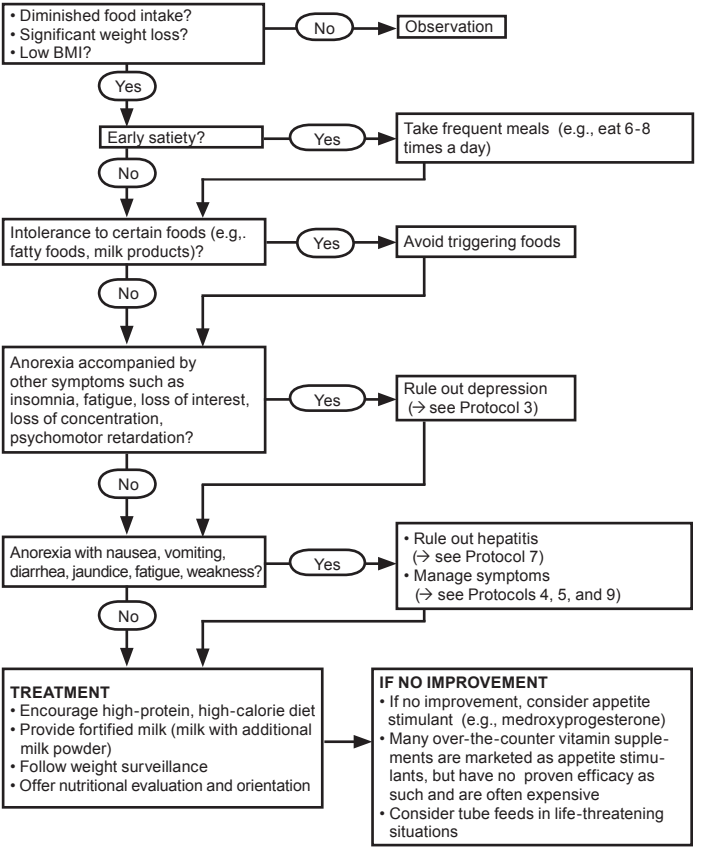
- Collins CH, Grange JM, Yates MD. *Tuberculosis Bacteriology: Organization and Practice*. Boston: Butterworth-Heinemann, 1997.
- Heifets LB, Cynamon MH. *Drug Susceptibility in the Chemotherapy of Mycobacterial Infections*. Boca Raton: CRC Press, 1991.
- Laszlo A. Tuberculosis bacteriology laboratory services and incremental protocols for developing countries. *Clin Lab Med* 1996; 16(3):697-716.

Appendix 4
DOTS-Plus Management Protocols

Protocol 1: Nutritional Surveillance Protocol
Protocol 2: Management of Positive Smear or Culture after Five or More Months of Treatment
Protocol 3: Management of Depression
Protocol 4: Management of Diarrhea
Protocol 5: Management of Gastritis
Protocol 6: Management of Headaches
Protocol 7: Evaluation and Management of Hepatitis
Protocol 8: Management of Hypothyroidism
Protocol 9: Management of Nausea and Vomiting
Protocol 10: Management of Nephrotoxicity
Protocol 11: Management of Peripheral Neuropathy
Protocol 12: Management of Anaphylaxis and Allergic Reaction
Protocol 13: Management of Psychosis
Protocol 14: Management of Hypokalemia
Protocol 15: Management of Seizure, Parts I and II
Protocol 16: Management of Fever, Parts I and II
Protocol 17: Management of Hemoptysis, Parts I and II
Protocol 18: Management of Respiratory Insufficiency, Parts I and II

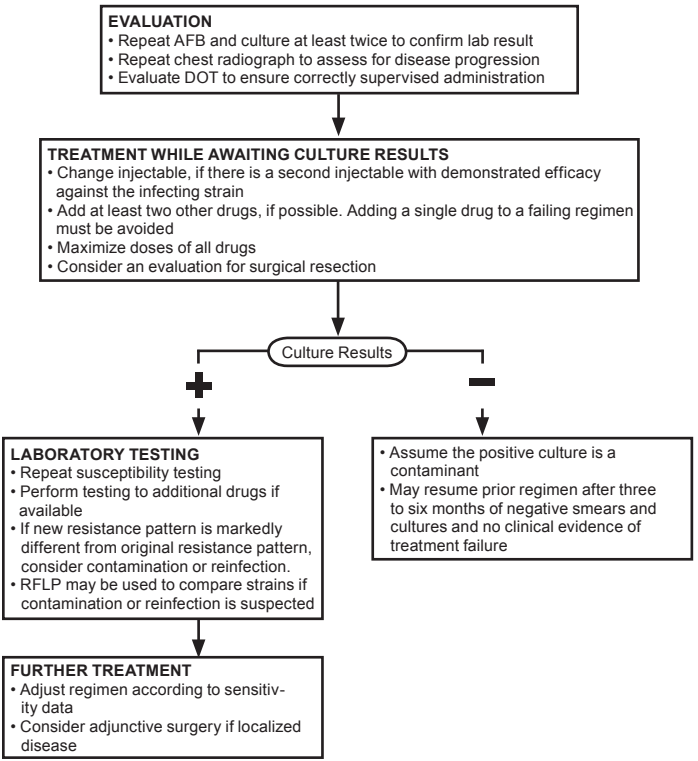
Protocol 1: Nutritional Surveillance Protocol

Anorexia is defined as the lack of appetite or the loss of the desire to eat. It is important to evaluate the duration of anorexia, the amount and rapidity of weight loss, and any symptoms which may suggest an organic etiology (e.g., nausea, vomiting, diarrhea, jaundice). Monthly weights provide one of the most important indicators of clinical response to antituberculosis therapy. Although many patients lose weight during the first few weeks of therapy with second-line drugs, failure to regain weight or continued weight loss during therapy must be considered an urgent management issue.



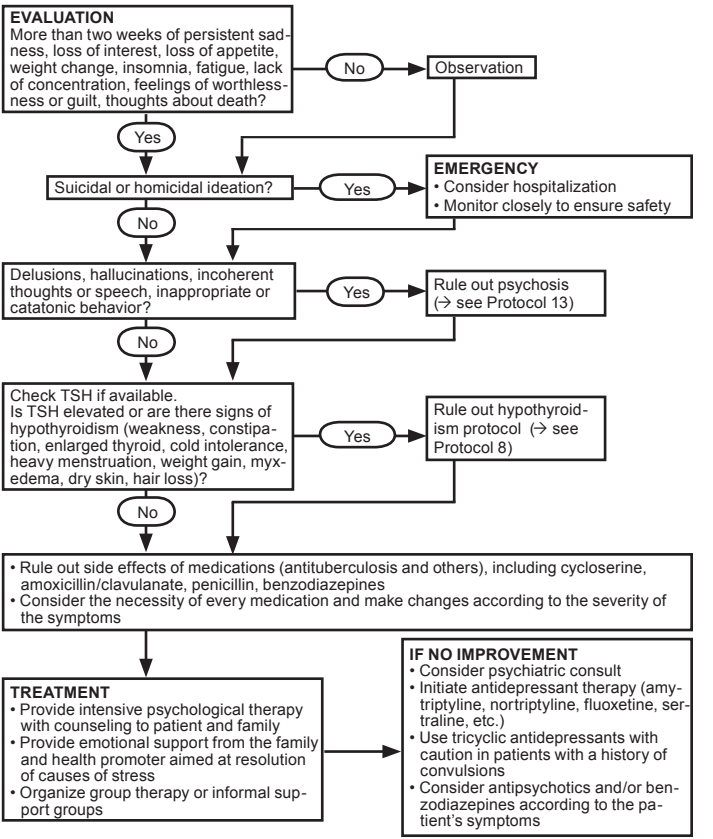
Protocol 2: Management of Positive Smear or Culture after Four or More Months of Treatment

Although a positive smear or culture after four or more months of therapy may not indicate treatment failure, attention to the patient with persistent positive smear or culture is important. First, the possibility of contamination needs to be ruled out. This can be done by obtaining two more samples and examining them for the presence of acid-fast bacilli or growth in culture, comparing the resistance pattern of the new or continued positive specimen with the pattern at treatment initiation, and by using RFLP data to compare the genomes. Second, direct observation of therapy should be confirmed and any irregular therapy promptly corrected. Lastly, the presence of a positive smear or culture may indicate failure of therapy. Regimen changes and possible surgical intervention should be considered at this time as outlined below.



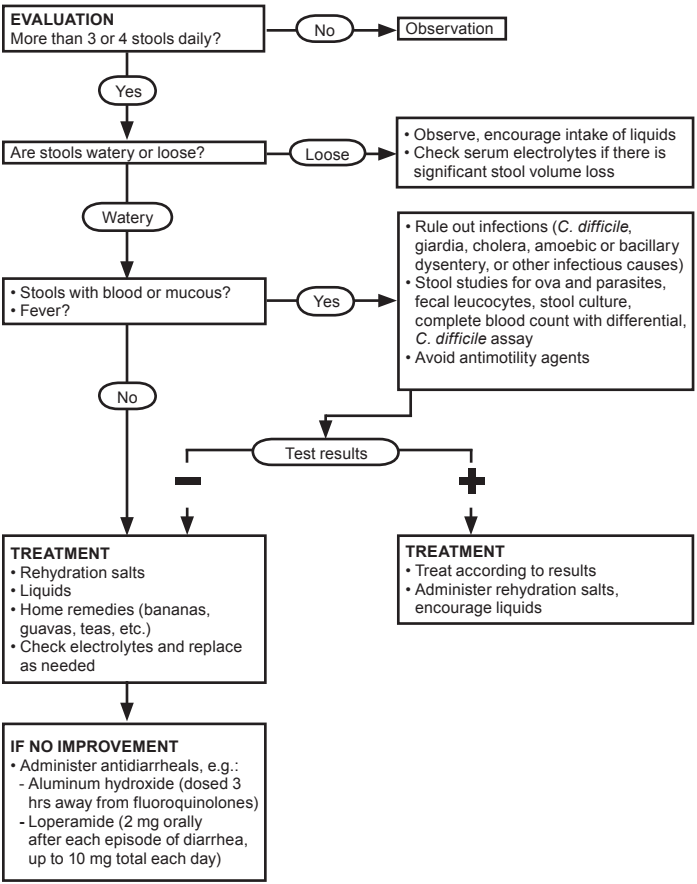
Protocol 3: Management of Depression

Although the word "depressed" is often used to describe sadness, clinical depression refers to a specific psychiatric diagnosis. Symptoms of major depressive disorder can include changes in sleep pattern, loss of interest in usual activities, feelings of guilt, diminished energy, decreased concentration, lack of appetite, psychomotor retardation (slowed movement and thought), and suicidal ideation. Sadness may be considered a normal reaction for a patient with a chronic illness such as TB; however, additional factors (including antituberculosis drug side effects, loss of work or social factors associated with TB) may exacerbate this condition and result in clinical depression. If a patient presents with significant changes in behavior or mood that affect his or her daily activities, he or she should be evaluated for depression.



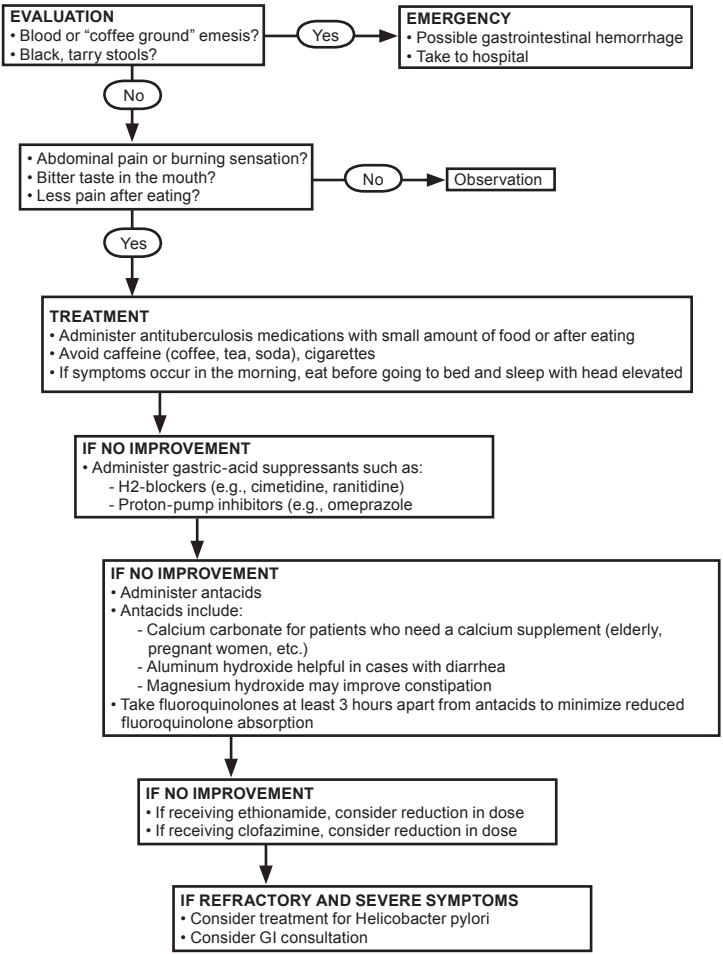
Protocol 4: Management of Diarrhea

Diarrhea is characterized by frequent watery bowel movements. Since many patients use the term diarrhea to describe bowel movements that are more frequent or loose than normal, it is important to note whether the stool is truly watery and more than three or four times a day. Both loose stool and diarrhea are frequent side effects of many antituberculosis medications. Avoid antimotility agents in patients with fever or if blood is present in the stool.



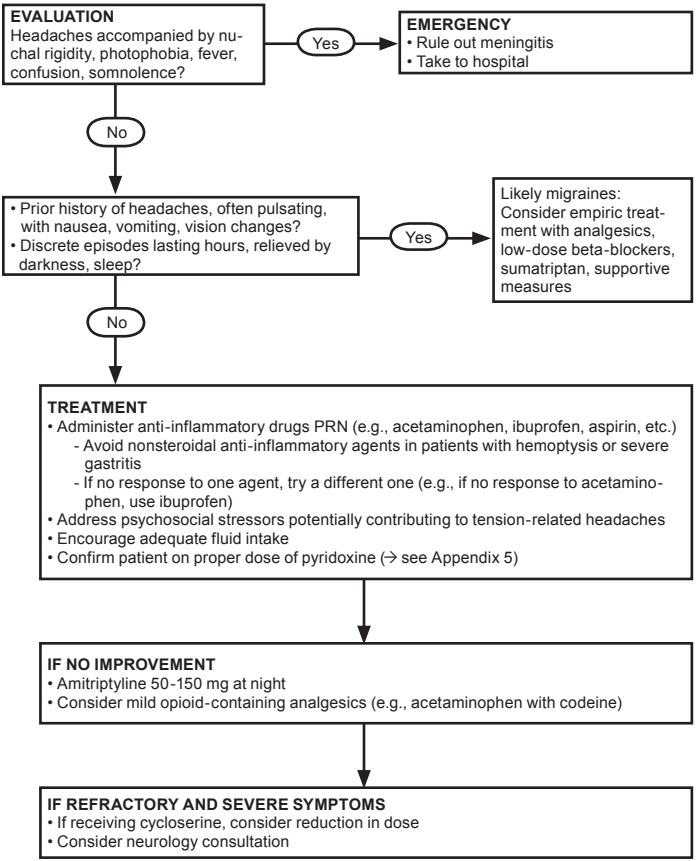
Protocol 5: Gastritis

Gastritis refers to the inflammation of the stomach. Multiple causes (including infection, alcohol, diet, and medications, including nonsteroidal anti-inflammatory drugs and antituberculosis medications) should be considered. If left untreated, gastritis can progress to ulcers and gastrointestinal bleeding. Emesis that has the appearance of coffee grounds can represent coagulated blood from a bleeding gastrointestinal source.



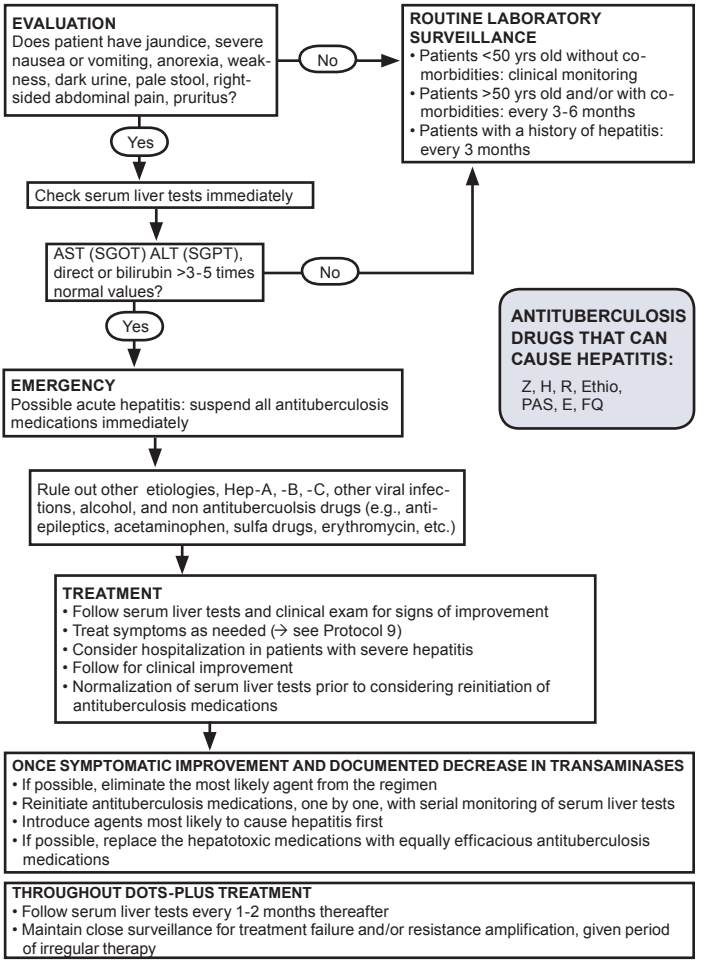
Protocol 6: Management of Headaches

Although headaches are often a side effect of anti-tuberculosis treatment, it is important to rule out other causes of headaches, including meningitis or migraines.



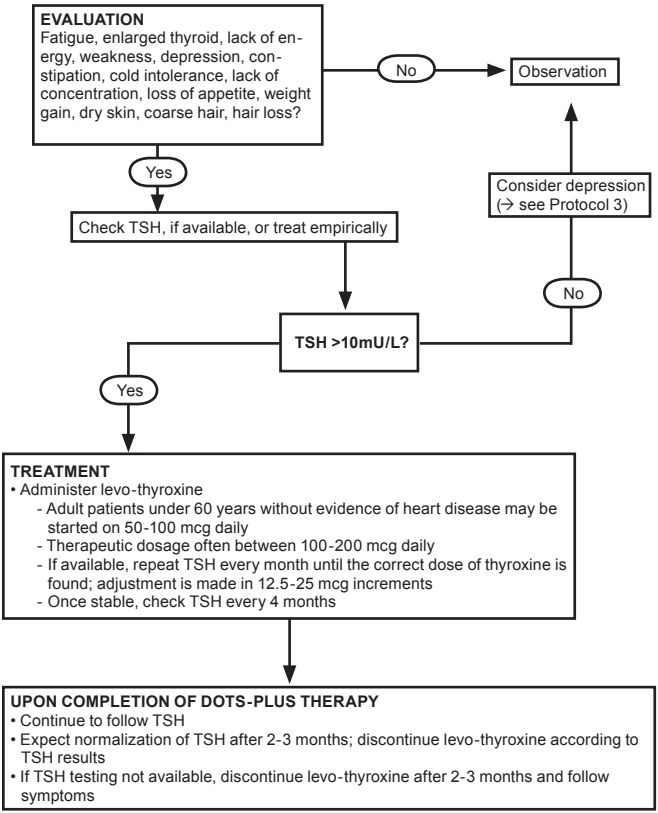
Protocol 7: Evaluation and Management of Hepatitis

Hepatitis refers to inflammation of the liver. Diverse causes include infections (e.g., viral, amoebic, etc.), autoimmune disease, alcoholism, and medications, including antituberculosis drugs. For this reason, it is important to obtain serum liver tests at the beginning of treatment and at intervals during the course of therapy for patients at risk for liver problems. Any signs or symptoms of hepatitis (including nausea, severe vomiting, scleral icterus, jaundice, dark urine, pale stool) merit immediate evaluation of serum liver tests.



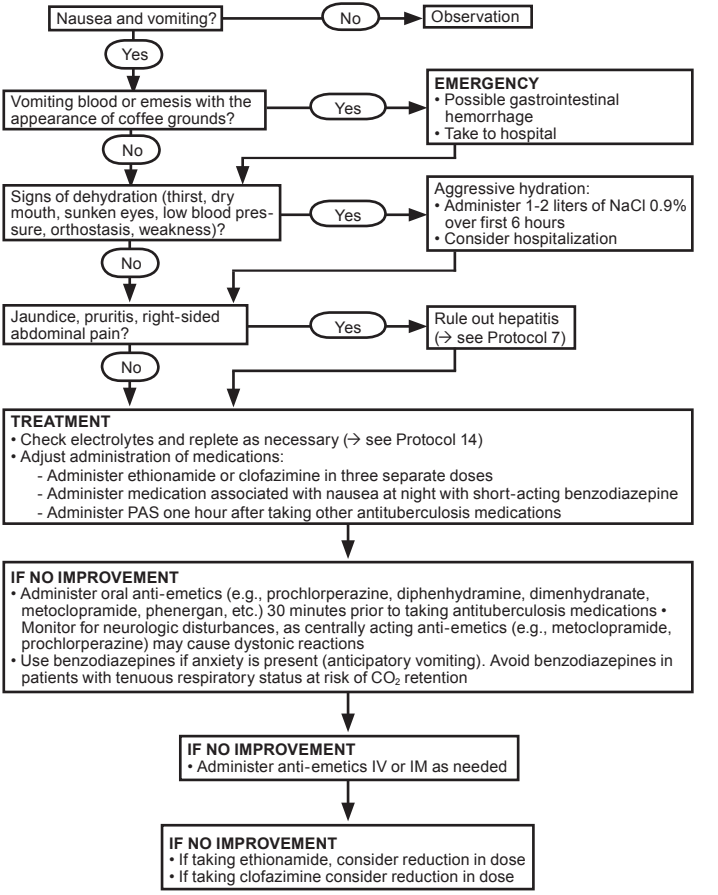
Protocol 8: Management of Hypothyroidism

Hypothyroidism, caused by suppression of the thyroid gland, can be diagnosed by serum thyroid stimulating hormone (TSH) above 10mU/L. Chief among causes of hypothyroidism in patients with MDR TB is ethionamide and PAS when used in combination. Hypothyroidism can be managed with levo-thyroxine replacement while the offending medicines are continued. The hypothyroidism will improve once the patient has completed MDR TB treatment.



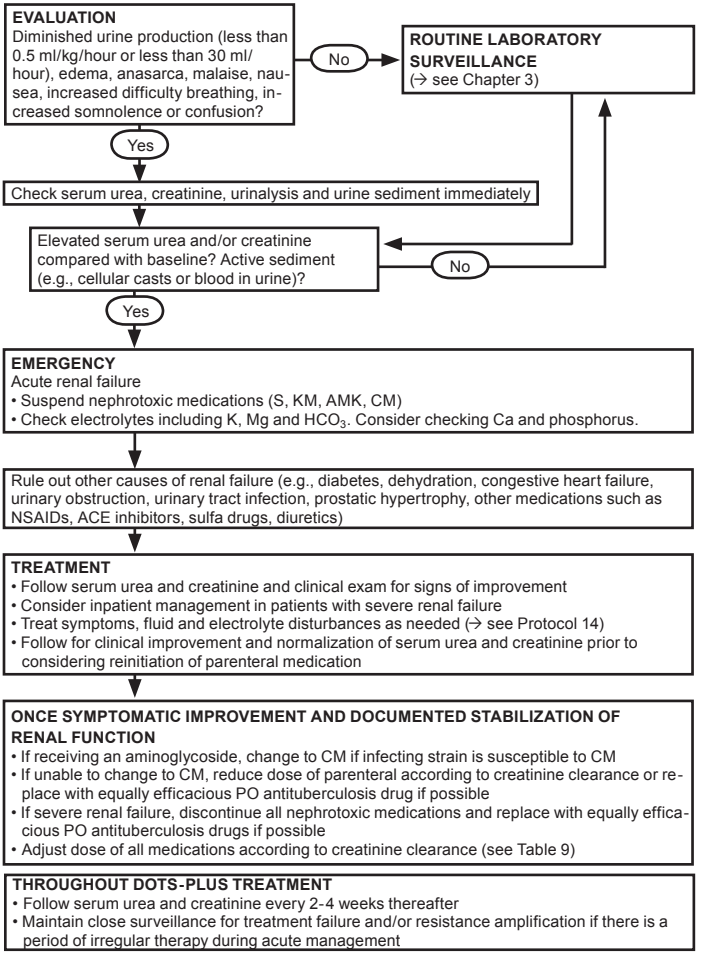
Protocol 9: Management of Nausea and Vomiting

While the majority of patients experiences nausea and/or vomiting as an adverse effect during MDR TB therapy, these symptoms rarely prevent delivery of adequate therapy. Symptoms should be controlled, and any medications lost due to emesis recuperated. Volume and electrolyte management is also essential if emesis is significant. Refractory nausea and vomiting may suggest the need for further investigation, including addressing the possibility of hepatitis.



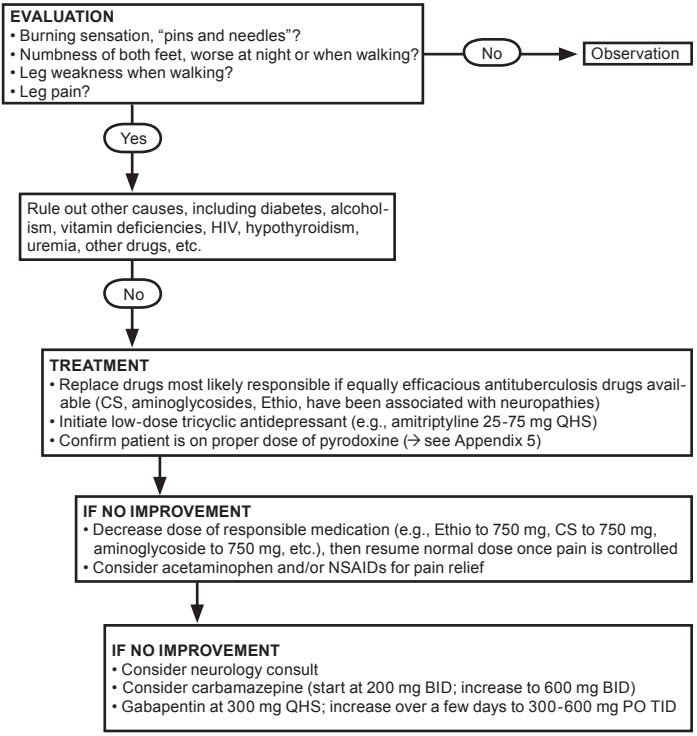
Protocol 10: Management of Nephrotoxicity

While many recommend a six-month maximum of parenteral administration and maximum cumulative aminoglycoside doses of ≤150 grams, a cohort of relatively young patients in Peru with few co-morbidities has demonstrated remarkable tolerance to far larger cumulative doses of injectable agents. Serum urea and creatinine should be documented at the beginning of therapy and followed regularly throughout DOTS-Plus treatment.



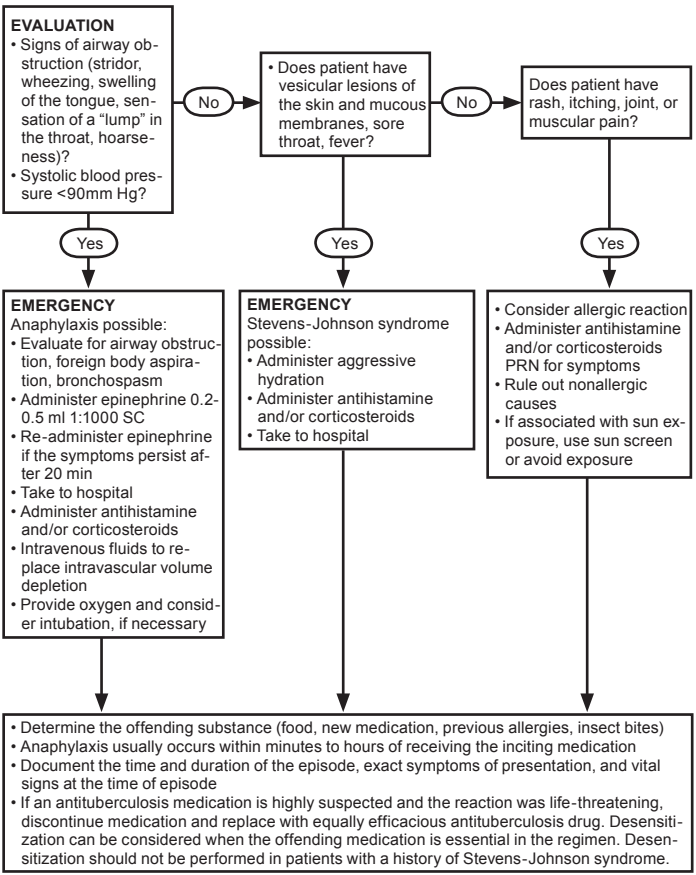
Protocol 11: Management of Peripheral Neuropathy

The term neuropathy refers to a degenerative, infectious, or inflammatory process that causes damage to the nerves. Peripheral neuropathy refers to those neuropathies located outside of the central nervous system. In a patient presenting with symptoms of peripheral neuropathy, it is important to consider causes other than antituberculosis drugs (e.g., alcoholism, diabetes, other medications, etc.).



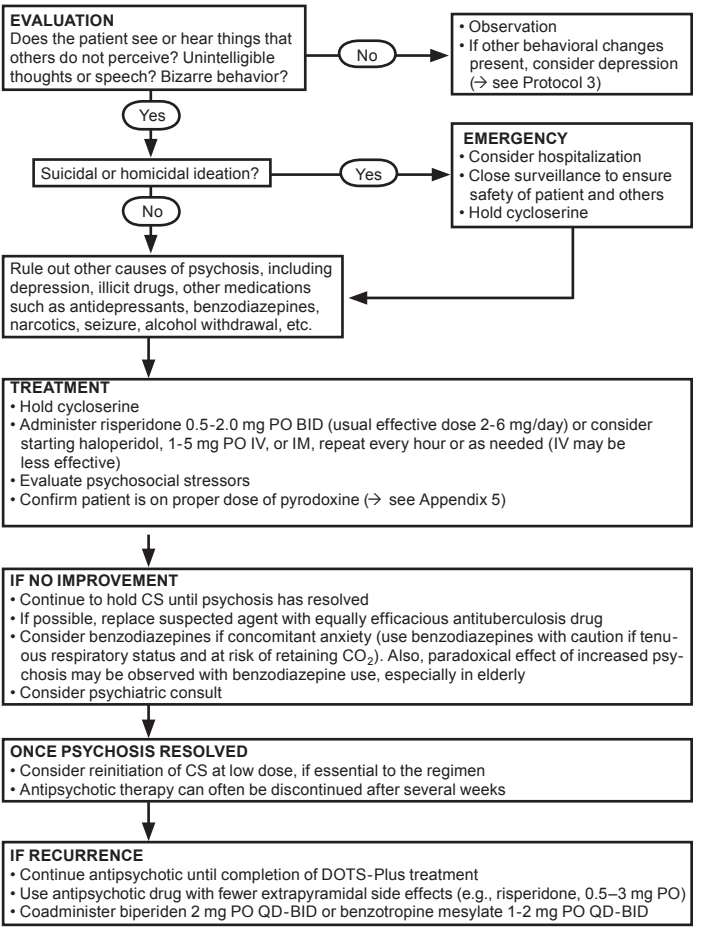
Protocol 12: Management of Anaphylaxis and Allergic Reaction

There are many types of adverse reactions, but it is important to be able to promptly identify anaphylaxis. The anaphylactic response can be fatal and appears within minutes of the administration of the offending medication. Symptoms include: difficulty breathing (often with wheezing), shock, pruritis, urticaria (with or without angioedema), nausea, vomiting, cramps, and diarrhea. At times, the patient can also present with fever, arthralgia (joint pain), and myalgias (muscle pain).



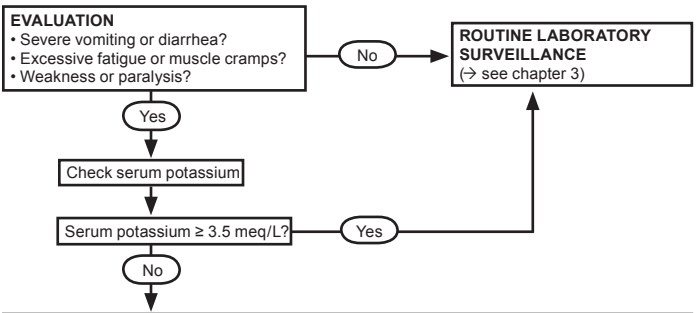
Protocol 13: Management of Psychosis

Psychotic symptoms refer to a constellation of symptoms that indicate a disintegration of personality or a loss of contact with reality. Patients tend to present with hallucinations or delusions. The causes of psychotic symptoms in patients with MDR TB may be related to underlying psychiatric disorders, antituberculosis medications (especially cycloserine), and other medications. Decompensation may occur in the context of stressors such as socioeconomic problems, additional medications, substance abuse, etc.



Protocol 14: Management of Hypokalemia

Hypokalemia signifies a low level of potassium in the blood (<3.5 meq/L). It can also be associated with other electrolyte abnormalities, such as hypomagnesemia. Persistent vomiting and diarrhea is a common cause of hypokalemia. Some of the antituberculosis medications–-in particular the aminoglycosides and capreomycin-–cause renal wasting of potassium and magnesium. Because hypokalemia can occur without clinical signs or symptoms and because it can be life-threatening, we recommend checking potassium levels frequently while the patient is receiving injectable therapy. For this protocol, normal values for potassium = 3.5-5.0 meq/L and for magnesium, 1.5-2.5 meq/L.

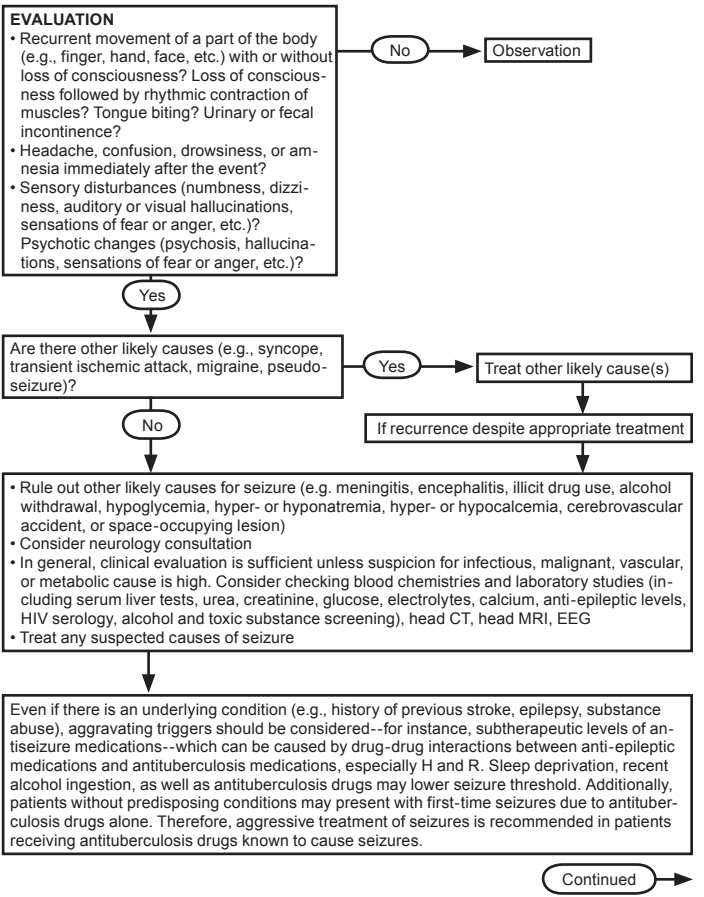


Potassium level Normal value (3.5-5.0 meq/L)	Quantity of KCl
3.7 or more	None
3.4 – 3.6	40 meq
3.0 – 3.3	60 meq
2.7 – 2.9	80 meq
2.4 – 2.6	80-120 meq
2.0 – 2.3	60 meq IV and 80 meq PO
<2.0	60 meq IV and 100 meq PO

Magnesium level Normal value (1.5-2.5 meq/L)	Quantity of Magnesium (Total daily dose)
1.5 or more	None
1.1 – 1.4	1000 mg – 1200 mg
0.8 – 1.0	2000 mg (consider IM)
<0.8	3000 mg – 6000 mg (give IV or IM)

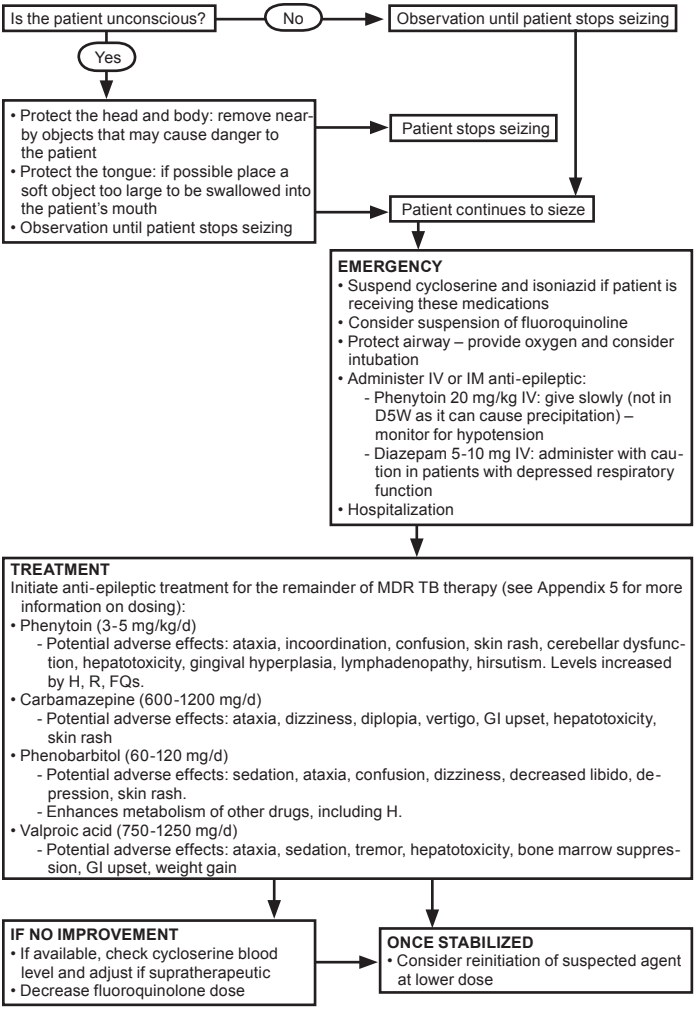
Protocol 15: Management of Seizure, Part I

The term seizure applies to a paroxysmal neurological dysfunction caused by abnormal electrical activity of the brain. While epilepsy describes the syndrome of recurrent episodes, a seizure may also occur as an isolated episode. Prompt identification of a seizure is essential for timely management; however, the spectrum of presentations is diverse and, at times, subtle. While convulsive seizures present with motor activity disturbances, other seizures may manifest as mere sensory or cognitive changes. Along with many other etiologies, certain antituberculosis drugs have been associated with seizures, as has TB of the central nervous system.



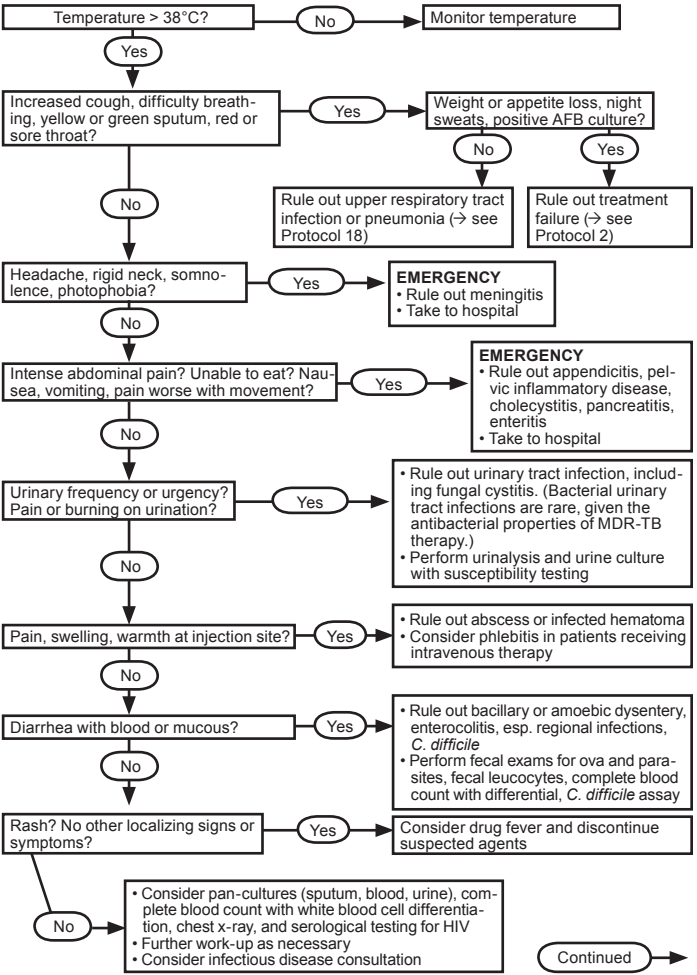
Protocol 15: Management of Seizure, Part II

The goals of seizure management are the stabilization of the patient during an acute episode and the prevention of seizure recurrence.



Protocol 16: Management of Fever, Part I

Fever is defined as an elevation in body temperature in excess of normal range, although temperatures within 1 degree of normal (37°C) are not generally considered significant. When a patient receiving MDR TB treatment has a fever, various sources must be ruled out.

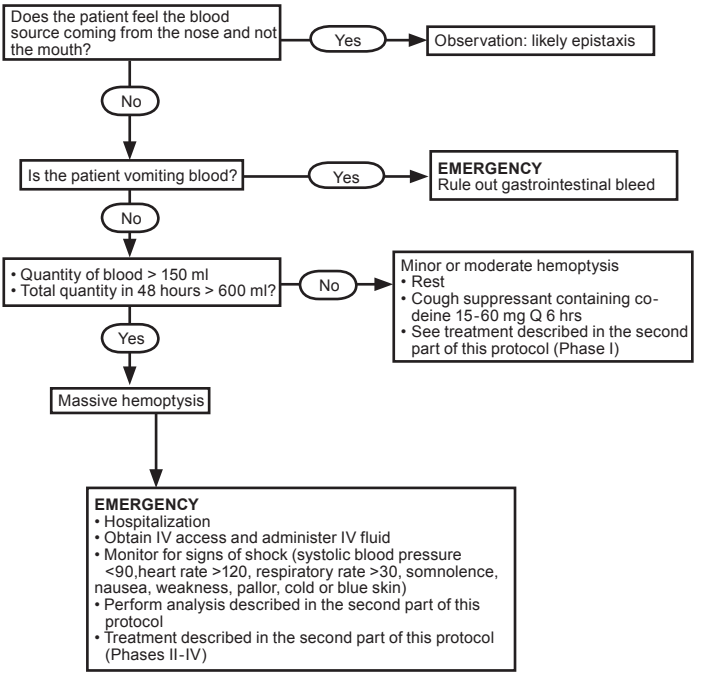


Protocol 16: Management of Fever, Part II

POSSIBLE CAUSE	PRESENTATION	TREATMENT
URINARY TRACT INFECTION		
Bacterial	• Urine leucocytes • Positive Gram stain • Positive urine culture	• Treat according to susceptibility testing
Fungal	• Urine leucocytes • Negative bacterial urine culture	• Treat with fluconazole 200 mg QD first dose, then 100 mg QD for 4 days
ABSCESS, HEMATOMA	Injection site: • Pain • Warmth • Swelling • Fluctuance	• Aspirate with 18-gauge needle or incise and drain • If abscess, treat with dicloxacillin 500 mg four times a day (or other antistaphylococcal therapy)
GASTROENTERITIS, ENTEROCOLITIS		
Viral	• Diarrhea, usually without mucous or blood • Negative fecal studies	• Oral rehydration therapy
Bacterial/Parasitic	• Diarrhea, can be with mucous or blood • Positive fecal leukocytes	• Oral rehydration therapy • Treat according to fecal study results
	• Possible *C. difficile* if positive fecal leucocytes, elevated white blood count, fever	• If *C. difficile* suspected or confirmed, treat with metronidazole 500 mg TID for 10-14 days

Protocol 17: Management of Hemoptysis, Part I

Hemoptysis is the expectoration of blood originating from the larynx, trachea, bronchi, or lungs. Because hemoptysis may present as anything from blood-streaked sputum to a large quantity of blood, it is essential to specify the quantity of blood loss and the period of time over which the loss occurred. During an episode of hemoptysis, the blood pressure, heart rate, and respiratory rate should be quickly obtained and documented. All patients who have a history of hemoptysis should have their blood type identified on initiation of DOTS-Plus therapy, as blood transfusion may be required.



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Protocol 17: Management of Hemoptysis, Part II

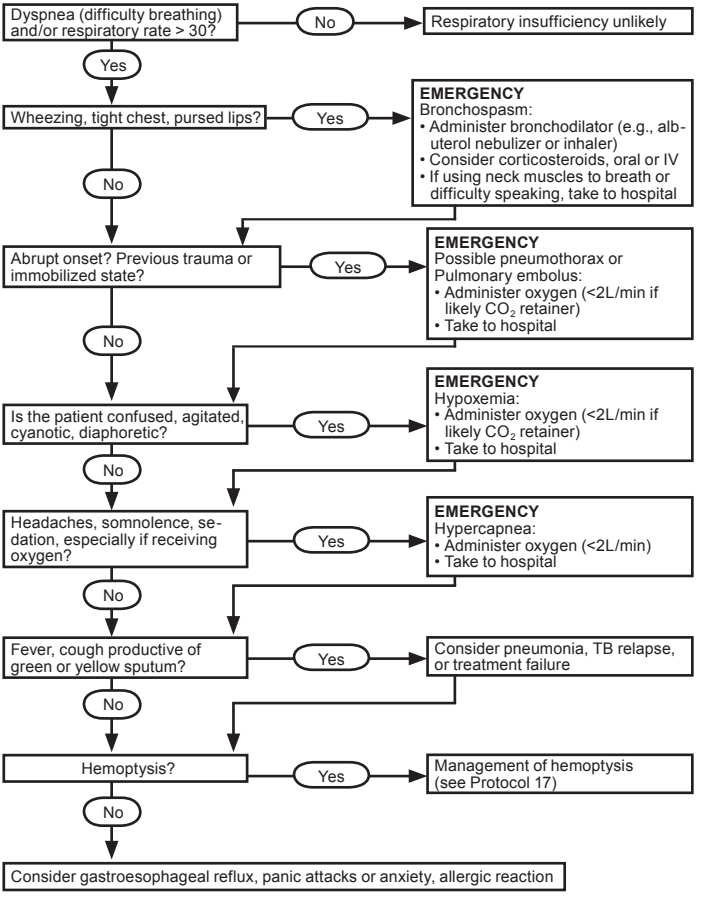
ANALYSIS

- Chest radiograph
- Hematocrit (Hct)
- Type and crossmatch blood for possible transfusion
- If fever and productive sputum: AFB and culture, sputum Gram stain and culture

TREATMENT

Phase I Minor or moderate hemoptysis	• Prescribe bed rest • Monitor patient closely • Avoid NSAIDs and aspirin • If evidence of respiratory superinfection, initiate appropriate antibiotic treatment • Use cough suppressant containing codeine, 15-60 mg Q 6 hrs
Phase II For massive hemoptysis	• Place large bore IV and resuscitate with 1-2 liters of normal saline within the first hour • Thereafter, maintain fluid (normal saline 0.9%) • Lay patient with likely source of hemorrhage in dependent position • Provide oxygen, if needed • Check vital signs frequently • Administer vitamin K 5 mg SC QD for three days if malnutrition or coagulopathy present
Phase III If Hct < 30%	• Transfuse with matched blood • Follow Hct closely
Phase IV If recurrent episodes without improvement	• Consider bronchoscopy to localize the bleeding site • Consider surgical evaluation: bronchiectasis, cavities, or coin-shaped lesions may be hemorrhagic sources (e.g., tuberculous destruction, erosion of blood vessels, aspergilloma) and may require surgical resection

Protocol 18: Management of Respiratory Insufficiency, Part I



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Protocol 18: Management of Respiratory Insufficiency, Part II

ANALYSIS

- Chest radiograph
- Complete blood count with differential
- Sputum AFB and culture, Gram stain and culture
- Pulse oximetry, if available
- If severe symptoms, arterial blood gas, if available

POSSIBLE CAUSE	PRESENTATION	TREATMENT
Bronchospasm	• Wheezing, prolonged expiration • May be associated with respiratory superinfection	**Phase I** • Inhaled bronchodilators • Treat for infection, if suspected **Phase II** • Administer oral or intravenous steroids **Phase III** • Consider long-term use of inhaled bronchodilators and/or inhaled steroids **Phase IV** • Nebulized bronchodilators
Pneumothorax	• Sharp pain, sudden onset of respiratory insufficiency, previous trauma • Positive chest x-ray	• Administer O_2 • Take to hospital • Thoracic surgery consult and chest-tube placement
Pulmonary embolus	• May have fever, chest pain, tachycardia, positive EKG, positive chest x-ray and/or diminished O_2 sat/pO_2	• Administer O_2 • Take to hospital • Perform V/Q scan, if available • Anticoagulation, if no contraindication
Respiratory infection	• Fever, productive cough • May have bronchospasm • Infiltrate on chest x-ray • Leucocytosis, positive sputum	• Treat with antibiotics according to sputum Gram stain/culture results • Administer O_2 as needed
Tuberculosis relapse	• Productive cough, fever, night sweats, weight loss, diminished appetite • Chest radiograph may reveal new infiltrate • Positive AFB and/or culture	• Confirm positive AFB and/or culture • → see Protocol 2 for positive AFB and/or culture

Appendix 5

Ancillary drugs for the management of side effects and complications

NOTE: Table 23 contains ancillary medicines commonly used to treat side effects due to MDR TB therapy and to manage complications of tuberculosis. This list does not represent the only medicines that may be needed in an MDR TB treatment program. Doses are for adults. The physician should also be aware of the side effects that can occur with these ancillary medications; only the more serious ones are mentioned here.

Not all side effects due to the treatment of MDR TB need to be treated with medications. Often reassurance, emotional support, or a behavioral intervention can result in the avoidance of adding yet another medication to the high burden of medications the patient is already receiving.

Table 23 Ancillary drugs for the management of side effects and complications

Gastrointestinal agents			
Anti-emetics	Miscel-laneous anti-emetic agents	Metoclopramide (*Reglan*) - 10 mg PO/IM/IV TID-QID or PRN, usually given 30 minutes prior to meals or medications. OR Dimenhydrinate (*Gravol, Dramamine*) - 50–100 mg PO/IM/IV Q 4–6 hrs. OR Prochlorperazine (*Compazine*) - 5–10 mg PO/IM/PR TID-QID. OR Promethazine (*Phenergan*) - 12.5–25 mg PO/IM/PR Q 4–6 hrs.	Metoclopramide, prochloperazine, and promo-ethazine can cause extrapyramidal reactions and dystonias. Other side effects include urinary frequency or incontinence. Can be sedating, which can be beneficial at night for patients with insomnia and/or nausea.
	Medications for anticipatory vomiting	Lorazepam (*Ativan*) - 0.5–2.0 mg PO used 30 to 60 minutes prior to antituberculosis medi-cations. OR Diazepam (*Valium*) - 2.0–10 mg PO used 30 to 60 minutes prior to antituberculosis medi-cations.	Because of the shorter half-life, lorazepam is preferable over diazepam. Warning: potential for addiction.
Anti-ulcer	Antacids	CaHCO3, MgSO4, Aluminum Hydroxide; most commonly given as Magal (combination of Magnesium and Aluminum hydroxide) - 15–30 ml TID PRN PO.	Must be taken three hours before or two hours after taking antituberculosis medications. Magnesium-containing antacids can cause di-arrhea and aluminum-containing antacids can cause constipation.

Table 23 Ancillary drugs for the management of side effects and complications, continued

Gastrointestinal agents, continued			
Anti-ulcer, continued	H2-blockers	Ranitidine (*Zantac*) - 300 mg PO QHS.	Other alternatives are cimetidine, famotidine, and nizatidine.
	Proton pump inhibitors	Omeprazole - 20 mg PO QHS.	Other alternatives are esomeprazole, lansoprazole, pantoprazole, rabeprazole.
Oral Candidiasis (non-AIDS patient)	Antifungal agents	Fluconazole (*Diflucan*) - 200 mg single dose, or 100 mg/d for 5–14 days. OR Clotrimazole 1 troche (10mg) 5 times daily for 14 days.	Significant drug interactions with rifampicin, oral hypoglycemics, phenytoin, theophylline and other medications.
Antidiarrheals		Loperamide (*Imodium*) - 4 mg initially, then 2 mg PO after each unformed stool for a maximum of 16 mg/day.	Do not use for diarrhea associated with fever or blood in the stool.
Dehydration agents		Oral rehydration packets as needed. OR IV fluids with electrolytes as needed.	IV therapy may be preferred if there is a lot of nausea associated with the dehydration.

Table 23 Ancillary drugs for the management of side effects and complications, continued

Psychiatric agents			
Antidepressants	Tricyclic antidepressants	Amitriptyline *(Elavil)* - Start 25-50 mg PO QHS, gradual increase the dose to usual effective dose 50-300 mg/day.	Avoid in patients with risk of arrhymthmias.
	Selective serotonin reuptake inhibitors	Fluoxetine *(Prozac)* - Start 20 mg PO QD, usual effective dose 20–40 mg/day, maximum dose 80 mg/day. OR Sertraline *(Zoloft)* - Start 25–50 mg PO QD, usual effective dose 50–200 mg/day, maximum dose 200 mg/day	Other alternatives include: citalopram, fluvoxamine, paroxetine.
Anxiolytics	Benzodiazepines	Lorazepam *(Ativan)* - 0.5–2.0 mg PO Q 4–6 hrs or PRN. OR Diazepam *(Valium)* - 2.0–10 mg PO BID-TID or PRN. OR Clonazepam *(Klonapin)* - Start 0.25–0.5 mg PO TID, maximum dose is 20 mg/day, but often doses much less than this are effective.	Warning: all benzodiazepines have potential for addiction
Hypnotics	Antihistiamines	Diphenhydramine *(Benadryl)* - 25-50 mg PO QHS.	

Table 23 Ancillary drugs for the management of side effects and complications, continued

Psychiatric agents, continued			
Hypnotics, continued	Benzodiaz-epines	Lorazepam *(Ativan)* - 0.5-2.0 mg PO QHS	Try to avoid regular use because of potential for addiction. Regular use may cause sleep disturbances in the long term.
Anti-psychotics		Haloperidol - Start 0.5 to 5 mg PO BID-TID. Usual effective dose 2–10 mg/day for cyclo-serine-induced psychosis. OR Risperidone - Start 0.5 to 5 mg PO BID-TID. Usual effective dose 2–10 mg/day for cyclo-serine-induced psychosis.	Consider concomitant use of benzotropine 1-4 mg PO QD/BID or biperiden 2 mg QD/BID to prevent extrapyramidal side effects Respiridone is more expensive, but fewer side effects.
Neurological agents			
Anti-convulsants	Benzodiaz-epines	Diazepam - Active seizing: 0.2-0.4 mg/kg up to 5-30 mg IV.	

Table 23 Ancillary drugs for the management of side effects and complications, continued

Neurological agents, continued		
Anticonvulsant agents, continued	Phenytoin *(Dilantin)* - Load 10-20 mg/kg 1000 mg in typical adult) IV. no faster than 50 mg/min. Oral load: 400 mg initially, then 300 mg in 2h and 4h. Mainenance 5 mg/kg or 100 mg PO TID. OR Carbamazepine *(Tegretol)* - 200–400 mg PO BID-QID. OR Valproic acid *(Depakene, Depakote)* - start 15 mg/kg/day PO QD or divided BID, maximum 60 mg/day. OR Phenobarbital - load 15–20 mg/kg up to 300–800 mg IV at 25-50 mg/min. Maintenance 60 mg PO BID-TID.	
Agents for propylaxis of neurological complications	Pyridoxine (vit. B_6) - use at least 50 mg for every 250 mg of cycloserine.	Consider using high doses in patients with refractory side effects (200 mg max). Paradoxically, very high doses of pyrodoxine can cause peripheral neuropathy.

Table 23 Ancillary drugs for the management of side effects and complications, continued

Neurological agents, continued			
Agents to treat peripheral neuropathy	Tricyclic antidepressants	Amitriptyline (*Elavil*) - Start 25-50mg PO QHS, gradually increase the dose to usual effective dose 50-300 mg/day.	Avoid in patients with risk of arrhythmias.
	Analgesics	Ibuprofen or acetaminophen may also provide relief. See dosing under agents for headaches.	
Agents to treat vestibular symptoms	Antihistamines	Meclizine *(Antivert)* - 25 mg PO Q 6 hrs.	
Agents for headaches	Analgesics	Ibuprofen - 200-800 mg PO TID-QID PRN. OR Acetaminophen - 325-650 mg PO Q 4-6 hrs PRN.	Alternatives include similar non-steroidal anti-inflammatory (NSAID) agents, paracetamol, or aspirin.
	Opiod-containing analgesics	Codeine, often in combination with acetaminophen, for severe refractory headaches can be used: 15-60 mg Q 4-6 hrs.	Warning: potential for addiction.
Agents for cutaneous reactions			
Topical Agents	Corticosteroid creams and ointments	Hydrocortisone - apply to affected area 1-2% BID-QID for one to two weeks.	Avoid prolonged use to facial area.

Table 23 Ancillary drugs for the management of side effects and complications, continued

Agents for cutaneous reactions, continued			
	Anti-pruritus lotion	Calamine, caladryl lotions - apply to affected area BID-QID.	
Systemic Agents	Antihistamines	Diphenhydramine *(Benadryl)* - 25–50 mg PO Q 4-6 hrs. OR Chlorpheniramine - 4 mg PO Q 4–6 hrs. OR Dimenhydrinate *(Gravol, Dramamine)* - 50–100 mg PO/IM/IV Q 4–6 hrs.	
	Corticosteroids	See sections below on agents for systemic hypersensitivity reactions	
Muscoskeletal agents			
Analgesics for arthralgias, non-gouty arthritis		Ibuprofen - 200-800 mg PO TID-QID PRN. OR Acetaminophen - 325-650 mg PO Q 4-6 hrs PRN.	Can also use similar non-steroidal anti-inflammatory (NSAID) agent or aspirin.

Table 23 Ancillary drugs for the management of side effects and complications, continued

Hypothyroidism			
Thyroid replacememnt hormone		Levo-thyroxine *(Synthroid, Levo-thyroid)* 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 at 3–8 week episodes.	Usual maintenance dose is 100-200 mcg/day.
Agents to manage fluids and electrolytes			
Diuretics	Loop diuretics	Furosemide - 20-80 mg IV/IM/PO Q 6-24 hrs.	Added ototoxicity when used with an aminoglycoside.
	Potassium sparing diuretics	Amiloride - 5 mg PO QD, maximum dose 2-mg/day.	Used for uncontrolled potassium wasting.
	Electrolyte replacement	For potassium, magnesium and clacium replacement recommendations, see section on electrolyte abnormalities (Section 7.3).	
Agents for bronchospasms			
Bronchodilators	Beta agonist inhalers	Albuterol Inhaler *(Ventolin, Prventil, Salbutamol)* - 90 mcg per spray, 2 puffs Q 4-6 hrs.	For acute bronchospasm, use 400-500 mcg (4-5 puffs).
	Beta agonist nebulizers	Albuterol Solution for nebulization - 2.5 mg (0.5 ml of 0.5% solution) Q6 hrs.	

Table 23 Ancillary drugs for the management of side effects and complications, continued

Agents for bronchospasms, continued			
Anti-inflammatory	Inhaled corticosteroids	Beclomethasone 2 puffs TID-QID or 4 puffs BID.	
	Oral corticosteroids	Prednisone 1 mg/kg per day then taper dose as indicated.	Injectable steroids can be used for severe cases of bronchospasm and rarely epinephrine is needed (see hypersensisitivy section in this table for dosing).
Agents for systemic hypersensitivity reactions			
	Antihistamines	Diphenydramine *(Benadryl)* - 25 mg PO/IM/IV Q 4-6 hrs.	
	Oral corticosteroids	Prednisone - 1 mg/kg per day then taper dose as indicated.	
	Injectable corticosteroids	Dexamethasone - Doses vary, 4 mg Q 6-12 hrs	Other alternatives are prednislone, Methylprednisolone, and others.
	Other agents	Epinephrine - 0.1-0.5 mg SC (1:1000 solution). Use only in severe reactions. May repeat every 20 mins. as needed.	May repeat after 20 minutes.

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