WHO/CDS/TB/2000.279

GUIDELINES *for* ESTABLISHING DOTS-PLUS PILOT PROJECTS

FOR THE MANAGEMENT *of* MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB)

WORLD HEALTH ORGANIZATION

WHO/CDS/TB/2000.279
Original: English
Distr: General

GUIDELINES FOR ESTABLISHING DOTS-PLUS PILOT PROJECTS FOR THE MANAGEMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB)

Scientific Panel of the Working Group on DOTS-Plus for MDR-TB

World Health Organization
2000

Scientific Panel of the Working Group on DOTS-Plus for MDR-TB

Thuridur Arnadottir, Nancy Binkin, Peter Cegielski, Marcos Espinal, Paul Farmer, Alex Goldfarb, Rajesh Gupta, Jim Kim, Michael Kimerling, Kitty Lambregts-van Weezenbeek, Albert Laszlo, Mario Raviglione, Lee Reichman, Hans Rieder, Max Salfinger, Pedro Suarez.

This document was edited by Rajesh Gupta and Thuridur Arnadottir

CONTENTS

Note: *Annex 1-8 are provided as examples from potential DOTS-Plus pilot projects and should not be considered official recommendations by the World Health Organization or the Working Group on DOTS-Plus for MDR-TB.*

PREFACE

Worldwide, tuberculosis (TB), a disease caused by *Mycobacterium tuberculosis*, is the second greatest contributor among infectious diseases to adult mortality. The World Health Organization (WHO) estimates that two million deaths occur each year from the disease. Of equal note, one third of the world's population is infected with *Mycobacterium tuberculosis*. The WHO recommended strategy to combat TB, directly observed treatment, short-course (DOTS), can cure over 85% of patients with TB. Of concern, however, is the rise in drug-resistant TB and multidrug-resistant TB (MDR-TB). Several geographical settings with a prevalence of greater than 3% of MDR-TB among newly diagnosed cases have been identified by the WHO/International Union Against Tuberculosis and Lung Disease (IUATLD) Global Project on Drug Resistance Surveillance. In some countries, drug resistance threatens the success of TB control.

In order to address drug-resistant TB in general and MDR-TB in particular, WHO (1999) created the Working Group on DOTS-Plus for MDR-TB (hereafter referred to as the "Working Group"). The Working Group was formed to tackle a number of issues. One of these was to develop guidelines for DOTS-Plus pilot projects based on a consensus of expert advice. Such pilot projects, in turn, would generate the evidence to guide the creation of specific policy for the management of MDR-TB that could be used by WHO Member States. The DOTS-Plus concept includes the five tenets of the DOTS strategy and additionally takes into account specific issues that need to be addressed in areas where MDR-TB is a problem. **The goal of DOTS-Plus is to prevent further development and spread of MDR-TB**.

These Guidelines are based upon consensus of the Scientific Panel of the Working Group. In addition to explaining the DOTS-Plus concept, the Guidelines specifically define the minimum requirements in five areas to be considered when launching DOTS-Plus pilot projects. These five areas are:

- **Political commitment.**
- **Coordination.**
- **Laboratory aspects.**
- **Treatment strategy.**
- **Information system and data management.**

Each category is explicitly defined within the Guidelines. Commitment to the Guidelines, as determined by the Green Light Committee, is required for a project to be included among those supported by the Working Group. These projects will gain the **advantages** of being able to purchase concessionally priced second-line anti-TB drugs negotiated by the Working Group and technical support from the Working Group. Projects adhering to the Guidelines should have a great chance of programmatic success and the least chance of creating resistance to the last line of defence against TB.

FOREWORD

The expanding conflagration of the HIV/AIDS epidemic has combined with the millennial burden of TB to produce what WHO has rightly assessed as a global emergency. Thanks to the collaborative effort by WHO and many national and international bodies, encouraging initial progress has been made in establishing increasingly effective national TB programmes in many countries, though this progress has still been all too slow.

These programmes, using the "DOTS" criteria for diagnosis and treatment, have been very effective in curing a high proportion of new patients with bacilli sensitive to all, or most, of the standard first-line anti-TB drugs. But it was soon realised that many patients, owing to previous ignorant or careless treatment, had developed disease resistant to standard chemotherapy. Two extensive, but still partial, global surveys by WHO have already shown that this is an important problem. Those resistant cases to at least the most effective anti-TB drugs, isoniazid and rifampicin (so-called MDR-TB), are much less likely to be cured by standard multidrug therapy. Moreover, they can spread their menacing bacilli to others, a particularly horrific scenario where HIV has created a population exquisitely susceptible to TB.

Studies have shown that many patients with MDR-TB can be cured by combinations of reserve second-line anti-TB drugs. Unfortunately, these drugs are weaker than standard therapy, cause adverse reactions difficult for patients to tolerate, have to be taken for prolonged periods to prevent relapse, and are very expensive. Supervising the treatment and the side effects of that treatment requires considerable clinical, managerial personal, and social skills. Reliable laboratory support is essential. It is not surprising that cure rates in most series are much lower than in new patients with drug-sensitive bacilli.

Initially, the great potential cost and high technical skills required to treat patients with MDR-TB seemed to put mass treatment of such cases beyond the reach of many poor countries, most of which still had programmes inadequate for treating even new patients by standard methods (DOTS strategy). Understandably, priority was given to establishing effective TB programmes that use the DOTS strategy. If these were efficiently implemented, little MDR-TB would be created.

However, it was soon realised, and has now been established by the WHO surveys, that in some countries, owing to poor previous programmes, there is an appreciable MDR-TB problem. Both the tragedy for individual patients and the major future threat to the global public health have become increasingly appreciated. There has been much international discussion as to the best way forward. Providing reserve drugs to inefficient national TB programmes, which allow mistreatment and consequent MDR-TB, might create an untreatable epidemic through additional misuse of reserve drugs. It was agreed that the funds becoming available should provide these reserve drugs only to areas where there is a well-established successful DOTS-based TB control programme and an assurance that the reserve drugs will be well used.

It is important to establish, by pilot projects, the most cost-effective organization for comparatively large scale treatment of MDR-TB patients, resulting from previous poor programmes and perhaps a very few resulting from failures of standard treatment (probably mostly due to individual errors in programme implementation). The ideal is individualised treatment for each patient according to his or her exact pattern of resistance. Some consider this, at least in certain countries, to pose considerable operational difficulties. They believe that, in these countries, a standard regimen, geared to the commonest local pattern of resistance, would be more practical. It has been agreed that both approaches should be tried out in pilot studies.

The present publication has been prepared after much expert discussion. It provides guidelines as to how such a "DOTS-Plus" pilot project might be implemented. It lays down criteria that must be met before the pilot project can be supported by international provision of reserve second-line anti-TB drugs at favourable cost and by help from international expertise and monitoring. I am much impressed by the care that has gone into the publication. We have much to learn about the operational problems of implementing effective programmes to deal with it. This guide is a splendid start. It must be followed by urgent action.

Sir John Crofton
Professor Emeritus of Respiratory Diseases and Tuberculosis,
University of Edimburgh, Scotland

1 INTRODUCTION

1.1 Objectives of the Guidelines

A high prevalence of MDR-TB is mostly due to poor TB case management under inappropriate programme conditions. Any intervention to treat and/or control MDR-TB must place highest priority in correcting such errors within the national TB programme (NTP) or corresponding entity.

As there is not yet a standardised DOTS-Plus strategy, projects currently being implemented or in the planning stages should be considered pilot projects and should be subject to rigorous quality assurance, monitoring and evaluation. Setting minimum standards for these pilot projects should ensure the following: protection of individual patients and communities; prevention of increasing trends of MDR-TB; and systematic collection of comparable data in order to develop an evidence-based approach for global policy recommendations for the management of MDR-TB.

The Scientific Panel of the Working Group has prepared these Guidelines with two objectives. The first is to set criteria and technical standards before launching a DOTS-Plus pilot project to manage MDR-TB. The second is to provide an international standard for the structure and function of pilot projects. Adherence to these standards will enable such pilot projects to participate in a global pooled procurement of second-line anti-TB drugs. In addition, conformity with these standards will enable outcomes to be compared across pilot projects so that empirical evidence can guide the expansion of efforts to control MDR-TB. The overall aim is to preserve the integrity of TB control through an evidence-based approach to reduce the burden of MDR-TB.

The Guidelines are directed at NTPs, governmental, and non-governmental organizations (NGOs) embarking upon TB control efforts in areas where MDR-TB is a serious concern, and at donors and other international organisations that may provide financial or technical support for such efforts. They are organised with the intent of presenting a framework of issues that should be addressed when establishing a DOTS-Plus pilot project in order to foster a high probability of programme success. The first chapter lays out the foundation of DOTS-Plus. The next five chapters are devoted to providing a detailed description of the programmatic elements that need to be in place in order for a pilot project to have the greatest chance of programmatic success. The Guidelines close with an Annex section comprised of various strategies to be used in potential DOTS-Plus pilot projects.

Policy development is a dynamic process. The criteria set forward in these Guidelines will need to be evaluated and developed as further experience is gained.[1]

1.2 Magnitude of the MDR-TB Problem

Given the nature of antibiotics, clinical resistance to anti-TB drugs emerged almost simultaneously with the introduction of those very drugs. The most recent report of

[1] These Guidelines will undergo periodic revision to reflect the most recent data analysed from DOTS-Plus pilot projects.

the WHO/IUATLD Global Project on Drug Resistance Surveillance, which surveyed fifty-eight different countries and geographical areas between 1996 and 1999, revealed the presence of new "hot spots" for MDR-TB in addition to those reported in the first phase of the WHO/IUATLD Global Project on Drug Resistance Surveillance. MDR-TB was shown to range from 0% to 14.1% among new TB cases. Another review (1999) compiled by Harvard Medical School has shown that drug-resistant TB exists in 104 countries in recent years.

1.3 Prevention of MDR-TB

MDR-TB arises when TB is improperly managed with incorrect treatment regimens or under inappropriate programme conditions. Prevention of MDR-TB is achieved through the implementation and/or expansion of TB control under adequately structured programmes. This implies political commitment in order to guarantee correct operation of the programme, diagnosis based on bacteriological examination, standard short-course chemotherapy provided under directly observed treatment (DOT) at least during the intensive phase of treatment, uninterrupted supply of drugs, and proper recording and reporting of cases and treatment results. These principles form the basis of the DOTS strategy recommended by WHO for TB control. The use of fixed-dose combination drugs of proven quality and bioavailability should also be considered as a means to prevent drug resistance.

Because MDR-TB arises from improper TB control, priority must be placed on improving the faulty TB control programme before a DOTS-Plus pilot project can be established in an area. However, such a pilot project may be necessary in order to manage MDR-TB cases in the area.

1.4 Basic Principles for the Management of MDR-TB

DOTS-Plus pilot projects for the management of MDR-TB should address the following basic principles:

- Securing political commitment for the treatment of TB, including MDR-TB.
- Acquiring long-term investment of staff and resources.
- Coordinating efforts between and within the community, local government, and international agencies.
- Creating a project manual detailing all the aspects of the pilot project and outlining every participating institution's roles and responsibilities.
- Forming a specialised unit for managing MDR-TB patients.
- Guaranteeing the availability of specific laboratory services [including reliable drug-susceptibility testing (DST)].
- Designing an appropriate treatment strategy that utilises second-line anti-TB drugs.
- Establishing a reliable supply of high-quality second-line anti-TB drugs.
- Instituting parameters to promote patient adherence to treatment.
- Implementing an information system to allow proper management of data, monitoring of performance, and evaluation of the intervention.

1.5 Concept of DOTS-Plus for MDR-TB

MDR-TB possesses two important characteristics that pose a challenge for its management: strategies to manage MDR-TB are more complex and require more resources, logistically and economically, than the usual management of TB, and treatment of MDR-TB requires multiple drugs (with potential adverse reactions) administered for up to two years. Given the variation in approaches to managing MDR-TB, an evidence-based approach that supplements the DOTS strategy is needed.

DOTS can prevent the emergence of drug resistance where there is little or no drug resistance. In areas where the prevalence of MDR-TB is sufficiently high to threaten the success of TB control[2], the WHO formally recognises the need for the specific management of MDR-TB with the use of second-line anti-TB drugs[3], provided that DOTS is in place and the factors leading to MDR-TB are addressed. DOTS-Plus for MDR-TB is designed to manage MDR-TB in areas where it has emerged and needs to be addressed in conjunction with the treatment of drug-susceptible TB patients. In this instance a DOTS-Plus pilot project should be an integral part of a framework for comprehensive TB control because inadequate TB control generates MDR-TB patients faster than a DOTS-Plus pilot project can treat them. Thus, an effective DOTS-based TB control programme must be in place in an area before investing the considerable resources necessary for the treatment of MDR-TB.

DOTS-Plus pilot projects should contain a number of measures (detailed within this document) to ensure proper management of MDR-TB. These measures should be accurately addressed in a practical project manual to be used for the implementation of the pilot project. In order for members of the Working Group to support potential pilot projects, such pilot projects require:

- A review by a co-ordinating expert body, known as the Green Light Committee, ideally before the pilot project is implemented.
- Continuous monitoring using standardised methods and indicators.
- Periodic evaluation and, if necessary, prompt measures for adaptation or discontinuation of the pilot project depending on performance.

---

2 "Sufficiently high prevalence of MDR-TB" must be interpreted with some flexibility, due to a complex set of variables that may determine the threshold at which a DOTS-Plus approach is warranted. In general, a prevalence of MDR-TB, among cases never treated previously, **above 3%,** may constitute a reasonable level to consider the necessity of a DOTS-Plus approach. It is important to acknowledge that a threshold is not the only issue to be considered when taking a decision to implement a DOTS-Plus pilot project. Economical issues, status of current TB control efforts, and TB case-management priorities also need to be considered.

3 The available formulations and combinations of second-line anti-TB drugs within each country should adhere to the WHO Model List of Essential Drugs as indicated in Annex 10.

1.6 Green Light Committee

The Working Group has identified access, in terms of high cost and limited availability, to second-line anti-TB drugs as one of the obstacles for providing treatment for MDR-TB patients. The Working Group recognises that, while access to second-line drugs must increase, such drugs should only be used in DOTS-Plus pilot projects which meet the standards set forth in these Guidelines. This is to avoid, as much as possible, the rapid development of resistance to these second-line anti-TB drugs and the rise in an incurable form of TB.

Accordingly, the Working Group has developed a way of promoting access to quality-assured second-line anti-TB drugs at preferential low prices to those pilot projects that should have the greatest chance of success. These drugs will only be available to pilot projects that are found to meet the standards set forth in these Guidelines. Therefore, WHO has appointed a "Green Light Committee" (consisting of selected institutional members of the Working Group) that will meet on a periodic basis to review and approve applications in light of these Guidelines.

DOTS-Plus pilot projects approved by the Green Light Committee will benefit from technical support from the Working Group in addition to the option of procuring quality-assured, concessionally priced second-line anti-TB drugs. More importantly, the setting of minimum standards should reduce the chance of failure of individual pilot projects. Inclusion among pilot projects supported by the Working Group should enable standard evaluation of various efforts by WHO (in conjunction with project managers) to help develop global policy for the management of MDR-TB in different settings. Additionally, this process will provide a forum whereby projects can exchange the most up-to-date information available regarding MDR-TB management.

For more information and the procedure for applying to the Green Light Committee, consult the WHO document *Instructions for Applying to the Green Light Committee for Access to Second-line Anti-tuberculosis Drugs*. WHO/CDS/TB/2001.286.

Chapter 1: Summary

- MDR-TB arises in areas of poor TB control.
- DOTS-Plus addresses both TB and MDR-TB.
- DOTS-Plus pilot projects should be conducted in areas with good TB control.
- Basic principles of MDR-TB management include utilising multiple levels of health services to ensure DOT of treatment with second-line anti-TB drugs, establishing the necessary culture-based laboratory network, and building capacity for data collection and analysis.
- A DOTS-Plus pilot project should be conducted using a comprehensive project manual.
- Countries interested in supporting DOTS-Plus pilot projects should apply to the Green Light Committee to benefit from concessionally priced second-line anti-TB drugs and to receive technical support from the Working Group.
- Potential criteria to evaluate the effectiveness of current TB programme:
  Ability to collect and analyse cohort data;
  Combined default and transfer rates of less than 10%;
  Continual supply of first-line anti-TB drugs; and
  Application of DOT in 90% of cases.

2

POLITICAL COMMITMENT

A DOTS-Plus pilot project must demonstrate the existence of local political and administrative support for the planned activities. The first step in this process is to define the pilot project setting, which includes geographic, demographic, administrative and epidemiological characteristics. Identification of appropriate local and national government departments should follow, as should the identification of specific officials empowered to oversee and enforce technical and managerial aspects of the pilot project. This includes the NTP or the corresponding entity. Once appropriate definitions are established and key individuals are identified, formal written endorsement of the pilot project concept (as stated above) by appropriate national and local authorities should be secured. This endorsement must also contain government commitment for regulation of distribution of second-line anti-TB drugs. Also necessary is evidence that the minimum amount of funds required to initiate, monitor, complete and evaluate the pilot project has been obtained from internal or external sources. This can either follow or precede the endorsement step, depending on the necessity of endorsement for securing such funds.

Based upon fulfilment of the above points, a detailed project manual with a work plan (part of which may serve as official guidelines and regulations for mandatory use by local health care systems) should be developed. This manual should state the commitment, responsibilities and contributions of all stakeholders and should, as a minimum, include the following:

- Relation of the pilot project to the present structure of the TB control services.
- Identification of individuals who will be held responsible for completion and monitoring of the pilot project (including a project manager). A local steering committee to coordinate between partners should be considered.
- Centralisation and quality control procedures for laboratories providing DST.
- Administration of treatment regimens under DOT and justification for use of the regimens.
- Plan for management of adverse reactions.
- System of providing supervision of patients and methods to encourage defaulters to return to the health system for care.
- Strategy regarding the regulated distribution and use (within local health care facilities) of the second-line anti-TB drugs.
- Milestones, performance and evaluation standards for monitoring and evaluation of both the treatment of individual patients and of the overall pilot project.
- Information system and data management strategy.
- Detailed description and justification of the budget.

All stakeholders involved in the project should formally endorse the project manual.

Interagency co-operation via local and external agencies should emphasise integration of technical aspects (laboratories and data management), case finding among risk groups (such as close contacts of MDR-TB patients, prisoners, the homeless, beneficiaries of welfare, etc.), and handling of referral and transfers of patients (including post-release care of prisoners).

To ensure sustainability and expansion, proposed DOTS-Plus pilot projects should illustrate their intention to enhance local capacity for executing and evaluating the pilot project.

Finally, the public and private doctors, medical societies, and NGOs managing TB should be informed by the NTP or corresponding entity of the creation of the pilot project and incorporated into the various aspects of the pilot project. This will help to stimulate the referral of potential patients, and prevent continued mismanagement and misuse of second-line anti-TB drugs by private practitioners and institutions active in TB control.

Chapter 2: Checklist for DOTS-Plus Pilot Projects

- Analysis of factors leading to the emergence of MDR-TB and implementation of measures to address these factors.
- Defined pilot project setting.
- Secured commitment from local and national health authorities to assist in monitoring missions.
- Evidence of the financial resources required for the entire duration of the pilot project.
- Detailed project manual with a work-plan stating the commitment (endorsement), responsibilities and contributions of all stakeholders.
- Cooperation between agencies on technical aspects of the pilot project.
- Formal endorsement of the pilot project from national health authorities.
- Plan for long-term sustainability of the pilot project (including building local capacity to evaluate and execute the pilot project).

3 COORDINATION

As organizations and governments in various parts of the world embark on DOTS-Plus pilot projects for the management of MDR-TB, it has become increasingly clear that coordination of activities at all levels is critical. The regulation and control of second-line anti-TB drugs, quality assurance of DST, proper outcome evaluation, and overall project management require extensive cooperation and a high degree of coordination at many levels within the health care systems of regions or countries in which DOTS-Plus pilot projects are conducted. Furthermore, effective screening, early diagnosis and treatment, monitoring, management of adverse reactions, and adherence to therapy require the daily involvement of patients, their families, and community health workers.

Specifically, the Guidelines address coordination at different levels: the community, the local health systems, the NTP, and international collaboration. While tasks are listed under a specific level, each pilot project must determine which level would best suit the task, given the context of that pilot project. Coordination plays a major role in the following aspects of a DOTS-Plus pilot project.

- Outlining the duties and responsibilities of all organizations and individuals involved in the project.
- Reinforcing DOT both as the key component of adherence to and completion of any TB treatment, and as an important tool for preventing drug resistance in general and MDR-TB in particular.
- Developing a technical unit that will be responsible for the monitoring and evaluation of treatment of individual patients and of the overall pilot project.
- Securing a supply of high-quality second-line anti-TB drugs.
- Ensuring the availability of the laboratory services required for DOTS-Plus pilot projects.
- Designing training programmes for health personnel and ensuring training of multi-disciplinary teams comprised of providers at all levels of the health care system.
- Developing and implementing operational research protocols to evaluate the effectiveness, cost-effectiveness, treatment outcomes, limitations, and/or innovations of the pilot project.

3.1 Community Level

At the community level, groups of patients who have successfully completed MDR-TB treatment can be recruited to form a support network for other patients in order to reinforce their adherence to treatment. Therapeutic support groups in which patients, health promoters, nurses, physicians and family members participate can also play an important role in this process.

Community involvement may help satisfy the needs of the population targeted. This may include providing food and housing for MDR-TB patients, and ensuring that adequate transportation is available to get to and from facilities providing treatment. This can also be the responsibility of the local government.

3.2 Local Health Systems / Services Level

DOTS-Plus pilot projects should be tailored to the local infrastructure and ensure that all the key elements of TB control, as defined by the DOTS strategy, are implemented and that all factors responsible for the emergence of MDR-TB are addressed. Thus, a pilot project must take note of the findings of a review of the previous and current TB control efforts, including a systematic analysis of the treatment delivery process to identify the factors responsible for the emergence of MDR-TB in the particular setting. Additionally, the needs and characteristics of population groups who suffer from MDR-TB must be accurately identified and addressed.

A strong DOTS-based TB control programme that functions effectively in the local health units is an important prerequisite for a DOTS-Plus pilot project. Specialised units of physicians and nurses trained in MDR-TB management can establish standard practices in MDR-TB treatment. Nurses can play an important role in most of the teams at the local level. Their training should make it possible for them to keep reliable records, manage minor adverse reactions of anti-TB drugs, supervise and support other workers, and complete the required reports. Physicians familiar with the clinical management of TB should receive training in the management of adverse reactions of the second-line anti-TB drugs used in the pilot project. Nutritional support is warranted to patients identified by health workers as malnourished or at high risk of malnutrition.

3.3 National TB Programme Level

MDR-TB management in areas with a high prevalence of primary MDR-TB could aid NTPs in reaching one of the WHO objectives for TB control, namely, 85% cure rate of patients treated. Thus, NTPs should be able to identify proper sites requiring and prepared to implement DOTS-Plus pilot projects, and maintain a list of clinical staff with MDR-TB management skills.

The Ministry of Health and other relevant bodies (e.g. Ministry of Justice) need to commit the necessary resources (directly or via partnerships) to guarantee ready access to diagnosis and treatment under direct supervision and free of charge to all patients with TB. Drugs for treatment and for managing adverse reactions should be provided free of charge to the patients throughout treatment. A network of laboratories established through the efforts of the NTP and outside donors permits periodic monitoring of (acid-fast bacilli) smears and/or cultures, which are important tools for clinical follow up of the patients. If such a network is not in place, then a network of laboratories (whether on-site or off-site) must be created to satisfy these conditions.

Diagnosis and treatment of MDR-TB should be limited to certain health facilities or special units selected for this purpose. Coordination with the NTP is essential

in order to detect and refer patients from local health care facilities to the sites selected as MDR-TB treatment units in the project.

A public health education programme directed at physicians and nurses to prevent the misuse of any anti-TB drugs, especially second-line anti-TB drugs, is of utmost importance.

3.4 International Level

DOTS-Plus pilot projects are, by necessity, collaborative projects based on mutual assistance between groups. In most resource-limited countries where MDR-TB is a serious problem, supplemental funding is needed to conduct DOTS-Plus pilot projects. NTPs considering the implementation of DOTS-Plus pilot projects should strongly consider the possibility to explore partnership with institutions with experience in the management of MDR-TB such as NGOs, academic institutions, and public health organizations with interest in this matter. This will be helpful for advanced training of local professionals and proper allocation of resources. Capacity must be strengthened and investments should be made through such partnership, including funding elicited from national governments. Involvement in DOTS-Plus pilot projects, during the course of operation, fosters the development and maintenance of skills and "know-how" and may, thus, benefit technical experts and donor(s). However, the main responsibility for sustaining such pilot projects should be with the local government and the NTP.

International efforts should focus on support for strengthening local capacity to execute every aspect of comprehensive TB control, including the elements necessary for diagnosis and treatment of MDR-TB. These include conducting training for health care workers regarding clinical management of such patients.

Capacity building is important in enhancing research and evaluation skills among participants. These include skills in epidemiology and economic analysis that help local researchers to design and analyse future projects.

At the onset of a project, DST may need to be performed in an international reference laboratory. However, training of local professionals and acquisition of necessary technology to allow on-site DST should be built into DOTS-Plus pilot projects if routine use of DST is required for the strategy being piloted.

International cooperation for centralised procurement of second-line anti-TB drugs, via the Working Group, can lead to a significant decrease in prices of these agents. Also, if procurement is performed through a procurement agency, the agency will be responsible for quality assurance of the drugs. Thus, centralised procurement of second-line anti-TB drugs for DOTS-Plus pilot projects is critical for reducing overall costs of these drugs and providing high-quality drugs. It is strongly advised that DOTS-Plus pilot projects consult WHO concerning procurement of second-line anti-TB drugs. WHO will provide information on the concessionally priced second-line anti-TB drugs that are only available to DOTS-Plus pilot projects to be found in line (as determined by the Green Light Committee) with these Guidelines.

Any intervention to treat and control TB must take note of basic human rights. International cooperation should help ensure the adherence to international human rights standards for patients. This includes maintaining the management of MDR-TB patients, if needed, once the pilot project is completed.

Chapter 3: Checklist for DOTS-Plus Pilot Projects

- Outlining the various roles and responsibilities of all individuals and organizations involved in the project.
- Addressing patient needs through support groups and provision of services.
- Establishing an effective TB control programme within the local health system.
- Creating a laboratory network to provide laboratory services and to ensure quality control of laboratory tests.
- Using a centralised drug procurement system.
- Providing TB services and medications free of charge to the patients.
- Obtaining commitment of resources from Ministry of Health, Ministry of Justice, etc.
- Strengthening local capacity in all aspects of conducting the DOTS-Plus pilot project.
- Forming a specialised unit(s) of trained nurses and physicians to manage MDR-TB.
- Offering continuing education for clinical management of MDR-TB, economic analysis of projects, epidemiology, and laboratory techniques.

4

LABORATORY ASPECTS

Knowledge of drug susceptibility pattern is a crucial aspect in determining proper treatment for patients in DOTS-Plus pilot projects, whether an individualised or standardised approach to treatment is chosen. Access to a laboratory providing rapid, valid, and reliable DST is a basic requirement in DOTS-Plus pilot projects. New technology that could rapidly identify drug-resistant TB is currently in the testing phase.

At a minimum, there should be local competence in: sputum smear microscopy th-rough a laboratory network; culture of *Mycobacterium tuberculosis*; DST for isonia-zid, rifampicin, streptomycin and ethambutol[4]; information management; and drug resistance surveillance in a representative sample of patients. DST for pyrazinamide is difficult on conventional solid culture media because this drug is active in an acidic environment and growth of *Mycobacterium tuberculosis* is often inhibited under the-se conditions. A reliable radiometric BACTEC 460 pyrazinamide testing procedure using a modified liquid 7H12 medium with a reduced pH of 6.0 has been developed and can be used if resources permit.

There need not be local competence in DST for second-line anti-TB drugs but there should, at a minimum, be access to a qualified laboratory for this purpose. It should be noted that data on the reliability and validity of DST for second-line anti-TB drugs are largely fragmentary or lacking altogether[5], but current knowledge suggests that the accuracy of this kind of testing performed with Middlebrook 7-H10 and 7-H12 media is greatest with kanamycin and ofloxacin, and less so with capreomycin, ethionamide, and rifabutin. DST for cycloserine is not standardised.

Clinical response should be determined by smear and culture results primarily. On the other hand, DST results will help the health care provider determine whether or not the drug in question might be useful in further treatment.

Susceptibility testing can be performed as a *direct* test (inoculation with the de-contaminated sputum specimen) or as an *indirect* test (inoculation with growth from a primary culture). The indirect test for DST is currently recommended. As part of the indirect test, the use of the proportion method (using either Lowenstein-Jensen or Middlebrook 7H10 agar medium) is also recommended. The proportion method uses the seeding of drug-free and drug-containing media with equal quantities of two dilutions of a standardised inoculum, and the number of culture-forming units found on drug-containing media compared with those ob-tained on drug-free media are expressed as a percentage. An indirect test is supe-rior since the inoculum size is more uniform, and the bacteria are metabolically active. Direct tests are limited to smear-positive specimens and have other inhe-rent problems including delayed detection of contaminants. A direct test should not be used unless an indirect test is performed as well.

It is strongly recommended to perform all tests (smear, culture and, if possible, DST) in duplicate (i.e. on two different specimens) to improve the reliability of

4 *Guidelines for Surveillance of Drug-resistant Tuberculosis.* WHO/TB/96.216.

5 *Guidelines for Susceptibility Testing of Second-line Anti-tuberculosis Drugs for DOTS-Plus*. Geneva, 2001.

the results. A mechanism of quality assurance of all laboratory procedures needs to be in place. Quality assurance of the method chosen for DST, for both first- and second-line anti-TB drugs, must be performed on a regular basis. A link to a Supra-national Reference Laboratory is essential for two reasons: to guarantee quality and to validate data. However, local (national) reference laboratories must not be by-passed, as they also need to develop the capacity to conduct such tests. The notion of mutual assistance and technology transfer is clearly important.

If resources permit, resistant strains should have restriction fragment length polymorphism (RFLP) typing performed on them to begin a catalogue of resistance patterns for future study.

Chapter 4: Checklist for DOTS-Plus Pilot Projects

- Local capabilities of:
  sputum smear microscopy through a laboratory network;
  culture of *Mycobacterim tuberculosis*;
  DST for isoniazid, rifampicin, streptomycin and ethambutol;
  information management; and
  representative drug resistance surveillance.
- DST performed using indirect method and proportion method.
- All tests performed in duplicate.
- Collaboration with a Supra-national Reference Laboratory.

5 TREATMENT STRATEGY

5.1 Provisos

While the ideal treatment of MDR-TB in resource-rich countries relies on individualised regimens based upon DST, the feasibility of using such an approach in resource-poor settings has not been assessed. Thus, treatment of MDR-TB in resource-poor areas should, at this point in time, be considered in the context of a DOTS-Plus pilot project. Various approaches for the treatment of MDR-TB in resource-poor settings exist; examples of some of these approaches are included in Annex 1-4. Two generic protocols for the management of MDR-TB are available.[6] These protocols are based, respectively, on the standardisation and individualisation of regimens using second-line anti-TB drugs. Because MDR-TB treatment in resource-poor settings is still in a trial stage, the Guidelines do not call for specific treatment regimens for patients. During the planning of a DOTS-Plus pilot project, it is important, in order to guide treatment strategy, to obtain representative and valid drug susceptibility data on strains prevalent in the community through drug resistance surveillance following WHO/IUATLD recommendations.[7]

If second-line anti-TB drugs have been used in the area prior to implementation of a DOTS-Plus pilot project, susceptibility to these drugs should be determined, if possible.

Basic principles of TB treatment call for combination chemotherapy. Strong evidence demonstrates short-course chemotherapy regimens are poorly effective in the treatment of patients with MDR-TB. Accordingly, it is recommended that treatment regimens for MDR-TB contain **at least** three effective drugs (i.e., second-line anti-TB drugs not previously used by the patient and to which the organism is likely to be susceptible, and/or first-line anti-TB drugs to which the organism is found to be susceptible). Additionally, an injectable (streptomycin, if the patient is still susceptible to streptomycin) should be used with such a regimen. However, the number of drugs in the regimen may vary, since drug efficacy is related to resistance to specific drugs. Principles of selecting regimens for the treatment of MDR-TB have been reviewed elsewhere.[8 9]

The selection process for recruitment of patients should be explicitly defined and justified before a DOTS-Plus pilot project is initiated.

All treatment with second-line anti-TB drugs must be administered as DOT. Current WHO recommendations call for daily treatment of MDR-TB for a minimum duration of eighteen months. Intermittent treatment with second-line anti-TB drugs might reduce drug toxicity, but efficacy has not been tested.

---

6 *Basis for the Development of an Evidence-based Case-management Strategy for MDR-TB within the WHO's DOTS Strategy.* WHO/TB/99.260.

7 *Guidelines for Surveillance of Drug Resistance in Tuberculosis.* WHO/TB/96.216.

8 *Guidelines for the Management of Drug-resistant Tuberculosis.* WHO/TB/96.210.

9 Iseman MD. Treatment of multidrug-resistant tuberculosis. *N Engl J Med* 1993; 329(11):784-91.

While there are many possible treatment regimens for MDR-TB, these regimens fall into two strategies: individualised treatment regimen (ITR) and standardised treatment regimen (STR). Examples of the application of each strategy and the corresponding regimens are provided in Annex 1-4.

5.2 Individualised Treatment Regimen

ITRs rely upon DST, including first- and second-line anti-TB drugs, performed for each patient enrolled into the project. Often, but not always, patients are placed on an empiric regimen based upon history of previous treatment and DST results, contact history, and the predominant drug susceptibility pattern in the community for the initial period until DST results are available. After DST results are available, patients are switched to an ITR designed according to the DST result. Systematic monitoring of a patient's clinical response is used to determine if treatment needs to be altered or is successful. This approach requires advanced knowledge of drug combination use and may be more difficult to apply on a large scale.

5.3 Standardised Treatment Regimen

STRs use DST information from a representative sample of the population of the patients to be treated in a project, and history of previous use of second-line anti-TB drugs in the project area. Based upon a predominant DST pattern, a STR is designed to treat patients who will not undergo DST, especially DST for second-line anti-TB drugs, on a systematic basis. All patients enrolled into the project are placed upon this regimen for the duration of the treatment.

The comparative effectiveness of the ITR versus the STR under programme conditions has not been determined. In theory, the individualised strategy should produce greater treatment success in comparison to the standardised strategy. In theory, the utility of the STR in projects where "real-time" valid and reliable first-and second-line anti-TB DST results will not be available to guide individual treatment decisions should be advantageous. Presently, there are insufficient data to evaluate either theory.

Examples of standard regimens using second-line anti-TB drugs are available.[10]

5.4 Management of Adverse Reactions

Of equal importance to the treatment strategy used is the proper management of adverse reactions. Special attention should be made for the management of adverse reactions and for the systemic collection of data on adverse reactions.

Adverse reactions should be classified under the following categories:

---

[10] *Guidelines for the Management of Drug-resistant Tuberculosis.* WHO/TB/96.210.

- Minor side effects.
- Toxic reactions.
- Hypersensitivity reactions.
- Idiosyncratic reactions.
- Reactions not classified in any of the above.

Since patients receive combination chemotherapy, it is often difficult to determine which drug is the source of the undesired effect; drug-drug interactions may produce adverse reactions. Some adverse reactions disappear within a short period after treatment begins. Given these considerations, the following sequential steps for the management of adverse reactions are suggested:

1. Direct management of adverse reactions with standardised algorithms.
2. Reduced dosage of suspected drug(s) on an individual drug basis.
3. Removal of drugs from regimen.

Some adverse reactions can be managed with over-the-counter and common prescription drugs. If adverse reactions cannot be managed through such means, and the adverse reactions are not deemed serious, then patients may be encouraged to tolerate the reactions until they subside. If it is determined that a patient cannot comply with the regimen in use, the dosage of the suspected drug may be reduced until the adverse reactions subside. If it is not clear which drug is the cause of the adverse reaction(s), dosages of each drug can be reduced sequentially until the culprit drug is identified. In this case, when the dosage of a second drug is reduced, the first drug of which the dosage was reduced should be returned to normal dosage. If reduction of dosage of individual drugs does not result in the disappearance of the adverse reaction(s), then it may be necessary to reduce the dosage of multiple drugs simultaneously. If this does not alleviate the adverse reaction(s), then it may be necessary to remove a drug from the regimen, or to replace the drug with another drug. This final option should be chosen only as a last resort.

Refer to Annex 5-8 for information on adverse reactions and examples of management strategies from potential DOTS-Plus pilot projects.

5.5 Outcome Parameters

In settings in which MDR-TB poses significant problems, conventional cohort analysis is likely to be inadequate. Some patients' bacilli may be transiently suppressed (smear-negative) with first-line anti-TB drugs only to become smear-positive after such regimens are completed. Where possible, it is best to use both smear microscopy and culture to evaluate efficacy of therapy.

In terms of evaluation of outcome of treatment, new definitions need to be established, e.g., definition of a cure and of failure of treatment with second-line anti-TB drugs. At this point in time there is insufficient information available to establish such definitions. It is critical that every pilot project collects the minimum data set listed in Annex 9 to ensure that results from DOTS-Plus pilot projects can be comparable across pilot projects. Each pilot project should define the maximum treatment duration to know when to stop treatment in case bacteriological conversion is not achieved.

With these caveats, standard case definitions should be applied in DOTS-Plus pilot projects.[11]

Chapter 5: Checklist for DOTS-Plus Pilot Projects

- Results of drug resistance surveillance of first-line anti-TB drugs, and, if possible, second-line anti-TB drugs available.
- Description of recruitment of patients for MDR-TB treatment and estimation of the total number of patients to be treated within the proposed time frame.
- Treatment administered via DOT.
- Justification of approach to designing a treatment regimen.
- Selection of treatment regimen:
  Use of DST to design regimens;
  Use of regimens including *at least three* drugs to which the strain is known or likely to be susceptible;
  Inclusion of an injectable agent in the regimen (if the strain is still susceptible); and
  Treatment duration of at least eighteen months.
- Plan for recording and management of adverse reactions.
- Use of outcome parameters as defined in Annex 9 and justification for additional outcome parameters.

11 *Treatment of Tuberculosis: Guidelines for National Programmes.* WHO/TB/97.220.

6 INFORMATION SYSTEM AND DATA MANAGEMENT

When developing an information system relevant to DOTS-Plus pilot projects, four areas need to be addressed:

- Programme planning.
- Case management.
- Programme management.
- Project monitoring and evaluation.

Most importantly, it should be determined to what extent each of these areas need to be expanded beyond what is conventionally done within TB programmes using the DOTS strategy. The first level should have detailed information (individual patient files and treatment cards) and the second level may be more simple (reports with aggregate data).

A detailed project manual with a comprehansive work plan describing all the roles and responsibilities of all parties involved in the pilot project (as illustrated in Chapters Two and Three) should help to properly address the four issues above.

6.1 Programme Planning

Present Structure

The following questions should be answered with respect to the present programme structure:

- What information is collected and reported in the current TB control programme?
- What forms are in use?
- Who is responsible for collecting, recording, and reporting of data?
- Who is responsible for aggregation, analysis, and interpretation of these data?
- Are there any quality assurance / data validation mechanisms?

These facts provide important information for the planning of and training for the implementation of an information system specific to DOTS-Plus pilot projects.

Early identification and treatment of MDR-TB affect conventional DOTS cohort evaluation. It is imperative that the information recorded and collected in a DOTS-Plus pilot project be an integral component of the general TB information system in the pilot project area so that the overall TB control effort can be evaluated and meaningful evaluation of the DOTS-Plus pilot project can be performed.

Drug resistance surveillance

Reliable and representative surveillance of resistance to first-line anti-TB drugs is a necessary component in assessing the need for, and the efficacy of, a DOTS-Plus pilot project. To establish a baseline, surveillance should have begun prior to implementation of the pilot project. Drug resistance surveillance data should distinguish between drug resistance among "new" patients (i.e. not previously treated or treated for less than one month) and drug resistance among "previously treated" patients (including chronics). If resources permit, a base-line study of the prevalence of resistance to second-line anti-TB drugs should be conducted. This study will be used as a tool to guide the selection of the treatment strategy and treatment regimens for the patient cohort. Subsequent surveys should be used to monitor potential creation and spread of resistance to these second-line anti-TB drugs. Additionally, base-line studies of resistance to second-line anti-TB drugs may be hampered by the changing influx of migrant populations.

Description and evaluation of the current treatment delivery process

Before initiating a DOTS-Plus pilot project, the causal factors that led to the emergence and spread of drug-resistant TB should be identified and measures should be taken to prevent replication in the future. This requires, at a minimum, the following information for each pilot project:

- How was the diagnosis of TB established?
- Who was providing treatment?
- What treatment regimens were used?
- Was treatment directly observed? If not, what was the mechanism of drug delivery to the patients?
- How was treatment monitored?
- How were defaulters and treatment interruptions managed?
- What was the role of the private sector, including pharmacies?
- What was the system of drug procurement, supply and distribution?
- What was the outcome of treatment (using indicators recommended by WHO such as cure, defaulter, failure and death rates) for all patients enrolled in the programme?

6.2 Case Management

Recording in DOTS-Plus pilot projects differs from recording in conventional TB programmes. Differences include different time frame (longer duration of treatment); monitoring of bacteriological conversion using both smear and culture; and using results of DSTs to guide treatment. The importance of collecting more information for operational research is a priority. In addition, the definitions used both

in classification of patients and evaluation of outcome of treatment (failure, cure, etc.) are more complex and not enough evidence is available to determine some of these definitions. Documentation of adverse reactions and resulting complexity of (changing) treatment regimens may need to be addressed. Thus, classical DOTS recording and reporting forms need to be adapted accordingly.

As a minimum, the following is recommended:

- Smear and culture at months 0, 2, 3, 4, 5, 6 and then every three months until treatment is completed.
- DST at initiation of treatment and then at three month intervals until the patient converts to culture-negative status.
- All tests should be performed in duplicate (on different specimens collected at different times).

Examples of all proposed forms used in the pilot project should be included in the project manual.

6.3 Programme Management

Drug supply

Reliable drug supply is one of the most critical components of the DOTS strategy. The ordering, stock-up, and delivery of drugs is more complex when treatment is individualised. Interruption of stock and misuse of drugs (through theft, mismanagement, erroneous prescribing practices, black marketing, etc.) have serious consequences for any TB control programme. DOTS-Plus pilot projects require an adapted drug management system that guarantees an uninterrupted supply of high-quality first-line and second-line anti-TB drugs. This system should allow for monitoring stock in relation to authorised use of these drugs, allowing, in turn, for adequate ordering and prompt identification of irregularities. A stock register should be developed, taking into account treatment strategies, case-finding and drug logistics (such as the time between drug ordering and delivery). It should be clear who is responsible for collecting and recording the data, for the actual delivery of drugs, and for supply management. A regulatory mechanism should be established (if one does not exist) to guarantee proper use and distribution of first-line and second-line anti-TB drugs. Centralised procurement through a procurement agency can help address many of these issues. However, all projects should have an accurate and reliable drug-tracing system that accounts for each dose of drug from the point of delivery of the drugs to the directly observed administration to the patient (i.e. a unit-dose system of accounting or a similar system).

Laboratory supply and laboratory quality control

Culture of *Mycobacterium tuberculosis* and DST form a critical part of DOTS-Plus pilot projects. The laboratory components of the DOTS-Plus pilot projects need to be adapted accordingly and to guarantee timely ordering of materials. Additionally, it is important to establish internal and external quality control of the laboratory.

6.4 Programme Monitoring and Evaluation

Regular monitoring by a review committee (independent of the Green Light Committee), and supervision of case management and service delivery should be planned in all DOTS-Plus pilot projects. Formal training courses *per se* are important. In addition to establishing good practices and preventing an adverse outcome of the intervention, continuous monitoring and training in the form of on-site supervision is critical.

Performance of DOTS-Plus pilot projects should be evaluated using classical indicators such as case finding (using a well defined denominator); bacteriological confirmation of cases; proportion of diagnosed patients who are registered for treatment; smear conversion; and treatment outcome (cohort analysis). Pilot projects may need additional indicators, e.g.:

- Treatment recurrence frequency, which can be determined with active follow-up of patients for at least twenty-four months beyond treatment completion.
- Proportion of cultures that are smear-positive/culture-negative out of all cultures performed.
- Time to smear and culture conversion or proportion of patients (out of all patients) converting sputum to smear-negative and culture-negative status by the end of three and six months of therapy (smear and culture conversion ratio).
- The proportion of patients with sputum that is smear-negative and culture-negative after six months of treatment and maintaining that status throughout the completion of the rest of treatment (smear and culture cure ratio).
- Degree of adherence to treatment.
- Timing and duration of interruption during the course of treatment.
- Proportion of smear-positive/culture-positive defaulters out of all defaulters.
- Proportion of patients (out of all patients) with drug toxicity and adverse reactions to second-line anti-TB drugs resulting in modification in and/or adverse outcome of treatment.
- Trends in the proportion of previously treated cases among all TB cases.
- Trends in the prevalence of drug resistance (regularly for first-line and, ideally, second-line anti-TB drugs) in the pilot project area.
- Proportion of contaminated culture tubes or disks out of the total number of tubes or disks used.
- Evidence of acquisition of further drug resistance (amplification) during treatment.
- Duration of time between the date sputum sample is taken and the date DST results are reported.

Cohort analysis (that must account for all patients enrolled in the pilot project) can only be performed when all patients have had a chance to complete a full course of treatment. Treatment of MDR-TB is extremely long. Final outcome evaluation of MDR-TB treatment ideally includes evaluation, by smear microscopy, of relapse rate (treatment recurrence frequency) through active follow-up for at least twenty-four months, after a patient is declared cured.

6.5 Data Management

With reference to data management, all points and sources of data collection should be identified at the local, district, and national levels including the central TB authority (if one exists). While it can be beneficial and strongly recommended for DOTS-Plus pilot projects to collect as much data as possible, it is recommended that a pilot project collect, at a *minimum*, the information in Annex 9. Additionally, pilot projects should ensure that staff are well-trained in practices of data collection and understand the importance of collecting data. Staff should also be trained in the use of the data for programme management.

Chapter 6: Checklist for DOTS-Plus Pilot Projects

- Description of the present programme structure.
- Description and evaluation of the past and present treatment delivery process.
- Description of the procedures used in surveillance of drug resistance in the area where the pilot project is to be conducted.
- Results of surveillance of drug resistance in the area where the pilot project is to be conducted.
- Description of the drug management system.
- Description of the laboratory reporting system.
- Description of regular monitoring of the pilot project and training of personnel in the form of on-site supervision.
- Details of case management data to be collected and data collection forms to be used.
- Integration of the information system for the pilot project into the general TB information system.
- Definitions of the indicators to be used for evaluation of the pilot project.

Annex 1

TREATMENT REGIMENS PROPOSED BY HARVARD MEDICAL SCHOOL/PARTNERS IN HEALTH IN THREE DISTRICTS OF LIMA, PERU

Treatment Strategy

1. The Individualised Treatment Regimen (ITR) will consist of:

   - a minimum of four (and, in some cases, as many as eight) anti-TB drugs to which the patient's isolate has demonstrated susceptibility;
   - high-end recommended doses; and
   - an eighteen to twenty-four month regimen.

   An initial, empiric ITR will be followed by a definitive ITR after final drug susceptibility results become available.

2. Direct observation of every dose throughout the course of treatment is an essential component of this strategy.

3. The treatment strategy will be implemented by local health providers and community members, under the aegis of the NTP with consultation from MDR-TB experts as appropriate. Training, continuing education, and other forms of community capacity-building will be central to this DOTS-Plus pilot project.

4. Complete DST of all MDR-TB isolates of those patients referred for evaluation requires transnational collaborative linkages between the NTP and a Supra-national Reference Laboratory.

Treatment Procedures

Duration of treatment

ITRs will be administered for eighteen to twenty-four months. A consulting TB specialist will be provided who will recommend, based on the patient's clinical status and susceptibility results, a treatment regimen. Each regimen will include a parenteral anti-mycobacterial agent, which will be administered until at least six consecutive months of smear- and culture-negativity have been documented. The consulting TB specialist will determine both the overall duration of the ITR and the duration of use of the parenteral medication after a thorough clinical evaluation. Decisions regarding treatment termination will rely on radiographic, clinical, and laboratory data.

Design of the empiric ITR

Guidelines for the design of the empiric ITR include the following:

1. Adequate empiric ITRs must include at least four (although may include as many as eight) anti-TB drugs, including one parenteral anti-TB drug, to which the patient is likely to be susceptible. Isoniazid and rifampicin should

be included in empiric ITRs in addition to the minimum of four other anti-TB drugs when proof of resistance of the infecting strain to isoniazid and rifampicin is lacking.

2. Resistance to a given anti-TB drug must be considered likely if:

- the patient has previously received the anti-TB drug,
- the patient has previous documentation of *in vivo* resistance to the anti-TB drug, or
- the patient has had close or long-term exposure to a patient with documented resistance to the anti-TB drug.

3. When relying on previous DST results, consider the following:

- Discrepancies in drug resistance patterns. If there are discrepancies in an individual's drug resistance patterns over time, one should "fear the worst" and avoid reliance on any anti-TB drugs to which even a single isolate has demonstrated resistance. If testing has been performed at more than one laboratory and discrepant results are reported, design of a regimen should be guided by the resistance data from the mycobacteriology laboratory deemed most experienced. There are several Supra-national Reference Laboratories; results from these laboratories should be considered the most reliable.

  It is important to note that discrepant results may be the consequence of any of a number of factors, including different testing methods, laboratory errors, or mislabelling of specimens. When discrepant results are encountered, the bacteriologist(s) responsible for the testing should be contacted in order to exclude laboratory error as the cause of discrepant susceptibility results.

- Treatment since last available results. If a patient has received treatment since the collection of the sample for which DST results are available, the acquisition of further resistance to drugs should be excluded. New specimens should be obtained prior to initiation of therapy, and empiric ITRs (while awaiting these results) should not rely on anti-TB drugs to which the infecting strain may have acquired resistance.

4. A parenteral medication is an important component of the empiric ITR.

5. "Other-line" drugs (e.g., amoxicillin-clavulanic acid, clofazimine) may be used for reinforcement of the empiric ITR.

6. In the most difficult cases, after all other treatment options have been exhausted, surgical intervention and the use of two concomitant parenteral anti-TB drugs may be considered.

Design of the definitive ITR

As mentioned above, patients whose isolates demonstrate pan-susceptible disease should be referred back to the NTP for treatment at the patient's local health centre. There, patients will be placed on a standardised short-course regimen and evaluated by the NTP according to established guidelines.

Patients whose isolates demonstrate MDR-TB will see their empiric ITR changed to a definitive ITR, based on complete susceptibility testing. Anti-TB drugs to which the strain demonstrates *in vitro* resistance will be discontinued; drugs which had not been included in the empiric ITR but to which the strain demonstrates *in vitro* susceptibility will be added to the definitive ITR. Thus, all drugs used in the definitive ITR will be those to which the individual's infecting strain has demonstrated susceptibility.

Changes to the definitive ITR during the course of therapy

The parenteral medication may be discontinued as early as six months after smear- and culture-conversion, based on the recommendations of the consulting TB clinician. Monitoring of response to treatment will be conducted in close collaboration with the NTP and will include:

- monthly smear microscopy and culture;
- monthly weight surveillance;
- chest radiograph every six months; and
- baseline examination of liver function and renal function with frequency of monitoring depending on the anti-TB drugs used and the patient's baseline clinical status, age, and co-morbid conditions.

After six months of ITR, treatment failure is suggested at any point by persistence of symptoms consistent with active TB, positive sputum microscopy or positive culture. Possibility of treatment failure will be thoroughly evaluated, and the possibility of incorrectly administered DOT must be excluded.

Annex 2

GENERAL TREATMENT REGIMENS USED BY THE NATIONAL TUBERCULOSIS PROGRAMME IN PERU

Category I: 2RHZE/4R_2H_2 (intensive phase is given daily for six days a week; continuation phase is given twice weekly). New bacteriological positive and severe forms of TB patients are enrolled in this regimen.

Category II: 1RHZES/2RHZE/5$R_2H_2E_2$ (first two phases are daily for six days a week, third phase is twice a week). This is for bacteriological positive relapses and defaulters of the Category I regimen.

Category Reinforced II (R2): 3RHZES/5$R_2H_2E_2S_2$ (first phase daily for six days a week, second phase is given twice weekly). This is for failures of the Category I regimen. Patients with clinical, bacteriological and radiological unfavorable response are assessed at the third month of treatment for a change to a standardised MDR-TB regimen.

Standardised MDR-TB Regimen: 3KCxEtZE/15KEtZE (daily for six days during entire regimen). This is for failures to Category II and R2. Patients are followed with smear microscopy and cultures monthly, and radiological testing every three months.

Adverse reactions are intensely monitored.

Drug Abbreviation Key

R	=	Rifampicin
H	=	Isoniazid
Z	=	Pyrazinamide
E	=	Ethambutol
S	=	Streptomycin
Cx	=	Ciprofloxacin
Et	=	Ethionamide
K	=	Kanamycin

Annex 3

TREATMENT REGIMENS PROPOSED BY THE PUBLIC HEALTH RESEARCH INSTITUTE/MEDICAL EMERGENCY RELIEF INTERNATIONAL/UNIVERSITY OF ALABAMA-BIRMINGHAM IN TOMSK OBLAST, RUSSIAN FEDERATION

TB Treatment Categories
The following definitions are used and modified to account for culture/DST results obtained for each new or current TB patient.

Category I: same as WHO definition (with addition of possibility for culture results)
New smear- or culture-positive pulmonary TB (PTB), new smear- and culture-negative PTB with extensive parenchymal involvement, and new cases of severe forms of extra-PTB.

Category II (a-d): for intermediate drug resistance patterns (**not MDR**)
For cases with known DST results that show any resistance (other than streptomycin). Subtypes a-d are based on the specific resistant patterns found in Tomsk.

Category III: same as WHO definition (with addition of possibility for culture results)
New smear- and culture-negative PTB (other than Category I) or new less severe forms of extra-pulmonary TB.

Category IV: for chronic cases (those cases failing the WHO retreatment regimen defined by the DOTS strategy) or confirmed MDR-TB cases.

Empiric MDR-TB re-treatment/defaulter regimen (pending DST results):
for any patient with a high risk of drug resistance. Whenever the DST pattern becomes known, the patient will be placed on the appropriate Category I, II, III, or IV regimen.

Use empirically for:

i. New cases in prison with (a) smear-positive disease or (b) smear-negative disease plus the presence of any cavitation and/or bilateral parenchyma destruction on chest radiograph.

ii. New cases in civilian sector with exposure to a known MDR-TB case, history of ever being in prison or jail, or history of exposure to a TB patient ever treated in prison or ever incarcerated. If the patient is exposed to a known MDR-TB patient with a documented DST result from a qualified laboratory, then the appropriate regimen should be given based on the Category IV regimen.

All relapse and treatment failure patients (re-treatment cases) should be started on the empiric MDR-TB regimen pending sputum culture and DST results. Defaulters will also be started on the empiric MDR-TB regimen according to specific criteria unless a recent DST, within three months of defaulting, is known.

Treatment Category Summary (Based on Local DST Epidemiology)

The following treatment (tx) regimens are based on resistance patterns found in the Tomsk prison during 1998.

HERS	N=102	TX CATEGORY
SSSR*	6	I
SRSS	0	I
SSSS	33	I
RSSR	23	IIa
RSSS	2	IIa
RRSR	2	IIb
SSRR	4	IIc
SSRS	0	IIc
SRRS	0	IId
RRRR	16	IV
RSRR	15	IV
RSRS	1	IV

*S = sensitive, R = resistant

Drug Abbreviation Key
H = Isoniazid
E = Ethambutol
R = Rifampicin
S = Streptomycin
Z = Pyrazinamide
O = Ofloxacin
Cm = Capreomycin*
Et = Ethionamide
PAS = PAS (Para-aminosalicylic Acid)
Cs = Cycloserine

* Note that in any regimen which utilises capreomycin, when the second-line DST results show the isolate to be susceptible to amikacin or kanamycin, then these drugs should be used in place of the capreomycin (as tolerated).

CATEGORY I **2(*3)HREZ/4HR** *If smear-positive at month two, the intensive phase should be continued one additional month. If smear-positive at month five, then start the empiric MDR-TB regimen pending DST result.

CATEGORY II

IIa **2REZ/7RE** (currently treated patients who already completed the intensive phase under Category I)

6REZ (new patients) [plus 3RE for slow converters i.e. smear-positive at month three and/or poor clinical response with severe x-ray findings]

IIb **2ROZ+Cm/7RO[Z]*** *if tolerated then dose Z at 20 mg/kg

IIc **3HOEZ+Cm*/15HE** *if slow converter, cavit on x-ray, or severe disease seen, consider longer use of Cm

IId **3HOZ+Cm/12HO**

CATEGORY III* **2HREZ/2HR** *if smear-positive at month two, perform culture/DST and start MDR regimen pending results

+For certain forms of extra-pulmonary disease (miliary, meningeal, cerebro-spinal fluid, bone/joint), Category III treatment should be continued for nine to twelve months total duration.

CATEGORY IV **6 EOZ+Cm +[Et or PAS or Cs]/ 12 EO+[Et or PAS or Cs]**

Cm should be continued for minimum of six months. If culture conversion occurs beyond the end of month three, then continue Cm for six months beyond the culture conversion date.

EMPIRIC MDR-TB REGIMEN **HREZ + Cm + O +/- [PAS]***
(empiric MDR-TB regimen pending DST)
*Depending upon availability, severity of disease, and history of prior fluoroquinolone use.

Explanation of Drug Regimens

CATEGORY I **2(3)HREZ/4HR or 2(3)$H_3R_3E_3Z_3$/4H_3R_3**

This is the standard therapy for all new cases of sputum smear-positive or culture -positive PTB unless DST results indicate that another Category of therapy should be used (Category II or IV).

The intensive phase of therapy is begun with four drugs (HREZ) for two months. These drugs may be given either once daily for six days a week (Monday-Saturday) or on a three times a week schedule (with appropriate dose adjustments). If the sputum is smear-negative at the end of month two, the continuation phase of therapy is given with two drugs (HR) given for four more months. If the sputum is smear positive at the end of month two, then continue the intensive phase with all four drugs for another month, then switch to the two-drug continuation phase (HR) regimen for four months. The drugs in the continuation phase can also be given either as daily doses or on a three times a week schedule (with appropriate dose adjustments). The total treatment duration is six to seven months.

If the sputum is either smear- or culture-positive at the end of, or after, month five of therapy, then send for culture and DST and change to MDR treatment until DST results are known.

Note: If a patient is known to have ethambutol resistance, then this drug should not be administered to the patient.

CATEGORY II

These therapies are for TB cases who demonstrate variable resistance patterns and for which the DST results are already known. Sub-categories a-d are based on the specific resistance patterns found in Tomsk. Note that exclusions from this category are isolated resistance to either streptomycin or ethambutol (which are treated as Category I), as well as chronic cases/MDR-TB (which are treated as Category IV).

Category IIa

This therapy is used if the isolate demonstrates isolated resistance to isoniazid or combined resistance to isoniazid and streptomycin.

2(H)REZ/7RE or 2(H)$R_3E_3Z_3$/7R_3E_3
For currently treated patients (i.e., those who are found to have isoniazid resistance after the pyrazinamide is stopped after two months of use), the intensive phase is with three drugs (REZ) for two months followed by two drugs (RE) for seven months (continuation phase). During the intensive (REZ) phase and the continuation (RE) phase, drugs can be given either daily (six days a week, Monday-Saturday) or three times a week, with appropriate dose adjustments. Total treatment duration is nine months.

6REZ or 6$R_3E_3Z_3$
For new patients (i.e., those who are known to have isoniazid resistance at the beginning of treatment or before pyrazinamide is stopped), therapy is with three drugs (REZ) for the entire six months. These may be given either daily (six days a week, Monday-Saturday) or three times weekly (with appropriate dose adjustments). For patients who are slow converters (i.e., smear positive at the end of month three and/or poor clinical response with severe x-ray findings) then three additional months of rifampicin and ethambutol should be given (daily [3RE] or three times weekly [3R_3E_3]). Total treatment duration is six to nine months.

Category IIb 2ROZ+Cm/7ROZ or 2$R_3O_3Z_3$+Cm_3/7$R_3O_3Z_3$

This therapy is used if the TB isolate shows resistance to three drugs (HES), but sensitivity to rifampicin remains. This patient group is at very high risk for developing MDR-TB.

The intensive phase is with four drugs (ROZ+Cm) for two months followed by seven months of continuation phase therapy with three drugs (ROZ). Drugs in the intensive and the continuation phases can be given either daily (six times a week) or three times a week, with appropriate dose adjustments. If the patient cannot tolerate pyrazinamide at a dose of 20 mg/kg (when given daily), it can be dropped from the continuation phase. Total treatment duration is nine months.

Category IIc **3HOEZ+Cm/15HE or $3H_3O_3E_3Z_3+Cm_3/15H_3E_3$**

This therapy is used if the isolate demonstrates isolated resistance to rifampicin or combined resistance to rifampicin and streptomycin.

The intensive phase is with five drugs (HOEZ+Cm) for three months followed by fifteen months of the continuation phase with two drugs (HE). Drugs in the intensive and continuation phases can be given either daily (six times a week, Monday-Saturday) or three times a week, with appropriate dose adjustments. If the patient is a slow converter (smear-positive at the end of month three) or there is unresolved cavitary disease on x-ray, consider extending the use of capreomycin further than the initial three months, after consultation and discussion. Total treatment duration is eighteen months.

Category IId **3HOZ+Cm/12HO or $3H_3O_3Z_3+Cm_3/12H_3O_3$**

This therapy is used if the isolate demonstrates combined resistance to both rifampicin and ethambutol.

The intensive phase of therapy is with four drugs (HOZ+Cm) for three months followed by the continuation phase using two drugs (HO) for twelve months. During the intensive and continuation phases, these drugs may be given either daily (six days a week, Monday-Saturday) or three times weekly, with appropriate dose adjustments. Total treatment duration is fifteen months. If the patient is a slow converter (smear positive at the end of month three) or there is unresolved cavitary disease on x-ray, consider extending the use of capreomycin further than the initial three months after consultation and discussion.

CATEGORY III **2HREZ/2HR or $2H_3R_3E_3Z_3/2H_3R_3$**

This therapy should be given for new cases of sputum smear- and culture-negative PTB (other than Category I) as well as new less severe forms of extra-PTB.

The first two months of therapy (intensive phase) are with four drugs (HREZ). A sputum is checked at the end of month two, and if remains smear-negative, begin the continuation phase of therapy with two drugs (HR). The intensive and continuation phases may be given either daily (six days a week, Monday-Saturday) or three times a week (with appropriate dose adjustments). Total treatment duration is four months. Note that if the extrapulmonary presentation was meningeal/cerebrospinal fluid, miliary or bone and joint TB, treatment should be continued for a total of nine to twelve months after consultation and discussion.

If at month two sputum is smear-positive, then send a culture and DST and begin MDR-TB empiric regimen pending DST results.

CATEGORY IV **6 EOZ+Cm +[Eth or PAS or Cs]/**
12 EO+[Et or PAS or Cs]

This therapy is for known MDR cases, defined by an isolate demonstrating combined resistance to at least isoniazid and rifampicin, and may also demonstrate resistance to streptomycin, ethambutol, or other anti-TB drugs.

Core Drugs	Alternate Drugs
Ethambutol (E)	**Ethionamide (Et)**
Ofloxacin (O)	**PAS**
Pyrazinamide (Z)	**Cycloserine (Cs)**
Capreomycin (Cm)	

The intensive phase of therapy must utilise five drugs to which the patient's TB isolate is susceptible, preferentially with four core drugs (OEZCm) plus one alternate drug (Et, PAS, or Cs,) given for six months. If E or Z resistance is documented, additional alternate drugs should be used in their place. If second line drug susceptibilities are unknown, then patients should start six months of EOZ+Cm + two alternate drugs (if E susceptible) or OZ+Cm + three alternate drugs (if E resistant). If a patient's TB isolate is known to be susceptible to fewer than five drugs, then the treatment must be decided upon after case review, discussion, and consultation. If culture conversion occurs beyond the end of month three, then continue Cm for six months beyond culture conversion date.

The continuation phase of therapy must utilise three drugs the patient's TB isolate is susceptible to for an additional twelve months, including two core drugs (O+E) plus one of the alternate drugs. If isolate is resistant to E, then two alternate drugs should be used. If second-line anti-TB drug susceptibilities are unknown, then a total of four drugs should be used, including O and E (if E susceptible) plus two or three of the alternate drugs.

For the intensive and continuation phases of therapy drugs are given daily and Cs, PAS, and Et must be given twice daily (six days per week, Monday-Saturday).

1. Alternate drugs should be utilised in the following decreasing order of preference: Et, PAS, and Cs.

2. Other factors involved in selecting alternate drugs include susceptibility to those drugs, drug availability, and the patient's tolerance of a given drug.

3. As noted above, the injectable is used for six months minimum or possibly longer after consultation and discussion.

Note: Pyrazinamide will not be used if resistance is demonstrated by the laboratory.

Empiric MDR-TB Regimen HREZ + Cm + O +/- [PAS]

This is the empiric MDR-TB regimen/re-treatment regimen pending DST results (for patients with high rates of drug resistance).

This therapy is with six (HREZCmO) or seven (plus PAS) drugs, which are continued until the DST results become available, at which time the regimen will be changed to the appropriate Category of treatment. PAS should be added as the seventh drug if (1) it is available, and (2) there is any history of recent fluoroquinolone use (within six months of TB diagnosis).

This regimen is given daily for six days a week (Monday-Saturday); PAS must be given twice daily whenever used.

Annex 4

TREATMENT REGIMENS PROPOSED BY THE CENTERS FOR DISEASE CONTROL AND PREVENTION IN IVANOVO OBLAST, RUSSIAN FEDERATION

Initial Standardised Second-line Regimen for MDR-TB Patients

Preliminary data indicate little or no resistance to fluoroquinolones, capreomycin, and cycloserine; therefore, these drugs will form the consistent core of the initial regimen. Ofloxacin may be more active than ciprofloxacin and would be preferred. All or nearly all isolates were resistant to isoniazid, rifampicin and streptomycin; these drugs will not be used in the initial regimen. Two isolates were susceptible to rifampicin among patients thought to have MDR-TB, indicating some degree of laboratory variability. Of the remaining drugs available in Russia, 35 to 53% of isolates were resistant. Combinations of two or more of these drugs may be effective against more than 90% of strains. Kanamycin and amikacin would be redundant with capreomycin. Rifabutin must be reserved pending DST results. Therefore, ethambutol, pyrazinamide, and ethionamide complete the initial regimen.

In summary, the initial standard regimen will be:
Capreomycin / Ofloxacin / Cycloserine / Ethambutol / Pyrazinamide / Ethionamide

Modifications to Initial Regimen Based on Cost and DST Results.

1. *Aminoglycosides*: If duplicate DST results indicate susceptibility to multiple aminoglycosides, they can be substituted for capreomycin in order of preference: streptomycin > kanamycin > capreomycin > amikacin. This order is based on cost.

2. *Ethionamide*: Ethionamide should be discontinued if duplicate DST results both show resistance to ethionamide.

3. *Fluoroquinolones*: Ofloxacin should be discontinued if duplicate DST results both show resistance to any of the fluoroquinolones.

4. *Isoniazid*: If the duplicate DST results both show susceptibility to isoniazid, isoniazid may be added to the regimen. Since previous DST results showed MDR-TB, either one set of results is wrong or two phenotypes of *Mycobacterium tuberculosis* are present. Of these two possible explanations, laboratory error is much more likely. Therefore, isoniazid can be added but other drugs should not be discontinued on the basis of these DST results.

5. *Rifampicin*: If the duplicate DST results show susceptibility to rifampicin, this drug may be added to the regimen. Since previous DST results showed MDR-TB, either one set of results is wrong or two phenotypes of *Mycobacterium tuberculosis* are present. Of these two possibilities, laboratory error is much more likely. Therefore, rifampicin can be added but other drugs should not be discontinued on the basis of these DST results.

6. *Rifabutin*: If the duplicate DST results both show susceptibility to rifabutin but not rifampicin, rifabutin may be added to the regimen. The clinical effectiveness of rifabutin has not been demonstrated in this situation. Rifabutin can be added but no other drugs should be discontinued on the basis of this result as this time.

Annex 5

COMMON ADVERSE REACTIONS OBSERVED AND PROTOCOLS FOR MANAGEMENT STRATEGIES PREPOSED IN A PILOT PROJECT IN THREE DISTRICTS OF LIMA, PERU (HARVARD MEDICAL SCHOOL/PARTNERS IN HEALTH)

Key:		
Cs	=	Cycloserine
H	=	Isoniazid
S	=	Streptomycin
E	=	Ethambutol
Km	=	Kanamycin
Amk	=	Amikacin
Cm	=	Capreomycin
Clr	=	Clarithromycin
Tha	=	Thiacetazone
Cfz	=	Clofazimine
R	=	Rifampicin
Et	=	Ethionamide
PAS	=	Para-aminosalicylic Acid
0	=	Ofloxacin
L	=	Levofloxacin
Cx	=	Ciprofloxacin
z	=	Pyrazinamide

Key for Other Abbreviations	
>	greater than
<	less than
ALT	alanine aminotransferase
AST	alanine serum deaminase
BID	two times a day
BMI	body mass index
CT	CAT (computed axial tomography) scan
D5W	dextrose 5% in water
EEG	electroencephalogram
EKG	electrocardiogram
GI	gastrointestinal
IM	intramuscolar
IV	intravenous
MRI	magnetic resonance imaging
NSAID	nonsteroidal anti-inflammatory
PO	by mouth
QD	one time a day
QHS	before bed time
QID	four times a day
SC	subcutaneously
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
V/Q	ventilation/perfusion

ADVERSE REACTION	SUSPECTED AGENT (S)	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Seizures	Cs, H, O, L, Cx	1) Initiate anti-convulsant therapy (e.g. phenytoin, valproic acid) 2) Increase pyridoxine to 300mg daily 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) Anti-convulsant is generally continued until MDR-TB treatment completed or suspected agent discontinued 2) History of prior seizure disorder is not a contraindication to the use of agents listed here if patient's seizures are well-controlled and/or patient is receiving anti-convulsanttherapy 3) Patients with history of prior seizures may be at increased risk for development of seizures during MDR-TB therapy 4) Seizures not a permanent sequelae of MDR-TB treatment

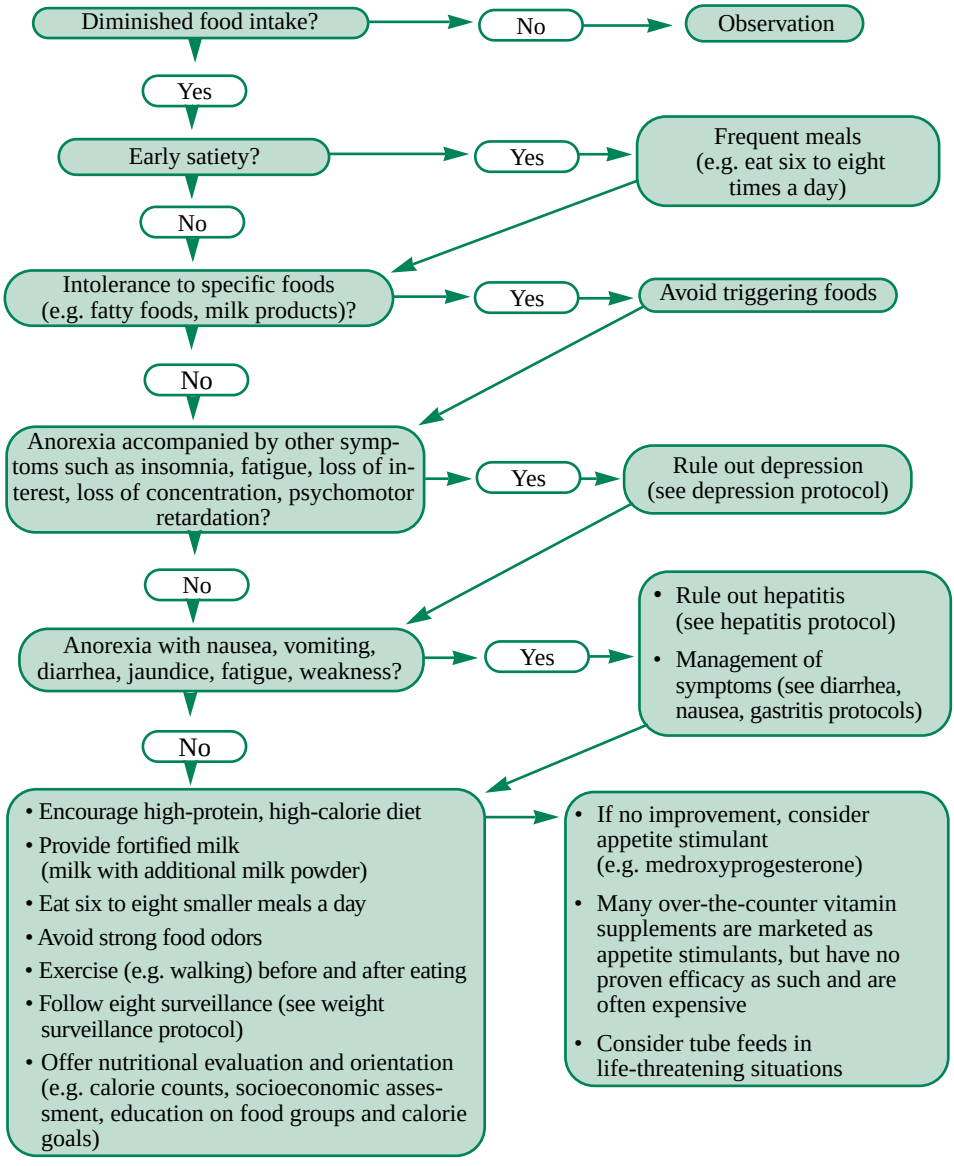
ADVERSE REACTION	SUSPECTED AGENT (S)	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Peripheral neuropathy	Sm, Km, Amk, Cm, M Tha, Cs, E, O, L, Cx	1) Increase pyridoxine to 300mg daily 2) Change parenteral to Cm if patient has documented susceptibility to Cm 3) Begin exercise regimen, focusing on affected regions 4) Initiate therapy with tricyclic anti-depressant drugs 5) Lower dose of suspected agent, if this can be done without compromising regimen 6) Discontinue suspected agent if this can be done without compromising regimen 7) Initiate therapy with neurontin	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 is generally not reversible, although only a minority (approximately 10%) of patients require continued intervention to keep symptoms controlled once MDR-TB treatment completed
Hearing loss	Sm, Km, Amk, Cm, Clr	1) Change parenteral to Cm if patient has documented susceptibility to Cm 2) Lower dose of suspected agent, if this can be done without compromising regimen 3) Discontinue suspected agent if this can be done without compromising regimen	1) If patients have received prior treatment with aminoglycosides, they may start therapy with hearing loss 2) Hearing loss is generally not reversible
Psychotic symptoms	Cs, O, L, Cx, H, Tha	1) Initiate anti-psychotic drugs 2) Hold suspected agent for short period of time (one to four weeks) while psychotic symptoms brought under control 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 generally reversible upon MDR-TB treatment completion or discontinuation of offending agent

ADVERSE REACTION	SUSPECTED AGENT (S)	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Depression	Socioeconomic circumstances, Cs, O, L, Cx, H, Tha	1) Improve socioeco-nomic conditions 2) Group or individual supportive counselling 3) Initiate anti-depressant drugs 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) Importance of socioeconomic conditions should not be underestimated as contributing factor to depression 2) Depression and depressive symptoms may fluctuate during therapy 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
Hypothyroidism	PAS, Tha, especially when given in combination	1) Initiate thyroxine therapy 2) Substitute equally efficacious agent for Tha or PAS	Completely reversible upon discontinuation of PAS or Tha
Nausea and vomiting	PAS, Tha, H, E, Cfz, PZ	1) Rehydration 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	1) Nausea and vomiting ubiquitous in early weeks of therapy and usually abate with supportive therapy 2) Electrolytes should be monitored and repleted if vomiting severe 3) Reversible upon discontinuation of suspected agent
Gastritis	PAS, Tha, H, E, Cfz, PZ	1) Antacids (e.g. calcium carbonate, H_2-blockers, proton-pump isoniazidibitors) 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 manifest by hematemesis, melena or hematechezia not observed in this cohort 2) Dosing of antacids should be carefully timed so as to not interfere with the absorption of anti-TB drugs 3) Reversible upon discontinuation of suspected agent(s)

ADVERSE REACTION	SUSPECTED AGENT (S)	SUGGESTED MANAGEMENT STRATEGIES	COMMENTS
Hepatitis	PZ, H, R, Tha, O, L, Cx, E, PAS	1) Stop therapy 2) Rule out other potential causes of hepatitis 3) Re-introduce drugs grouped serially while monitoring liver function, with most likely agent introduced last	1) History of prior hepatitis should be carefully analysed to determine most likely causative agent(s); these should be avoided in future regimens 2) Generally reversible upon discontinuation of suspected agent
Renal failure	Sm, Km, Amk, Cm	1) Discontinue suspected agent 2) Consider using Cm if an aminoglycoside had been prior parenteral in regimen	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
Optic neuritis	E	Stop E	1) Not observed in this cohort of patients
Arthralgias	PZ, O, L, Cx	1) Initiate therapy with non-steroidal 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 some patients but are of little therapeutic relevance and anti-gout therapy (e.g. allopurinol, colchicine) is of no proven benefit in these patients

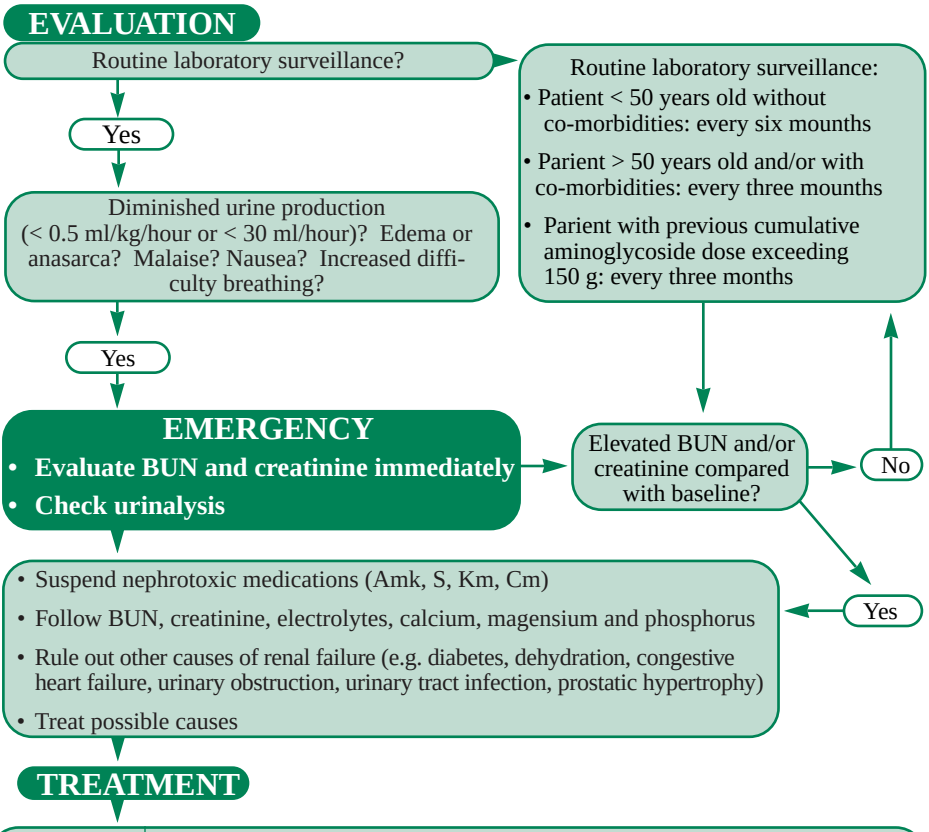
Nutritional Surveillance Protocol

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 tempo of weight loss, and any symptoms which may suggest an etiology (e.g. nausea, vomiting, diarrhea, jaundice). Monthly weights provide one of the most sensitive indicators of clinical response to antituberculous therapy. Although many patients lose weight during the first few weeks of therapy with second-line anti-TB drugs, failure to regain weight or continued weight loss during therapy must be considered an urgent management issue. Both BMI and chronological weight curves provide useful data. The following approach should be adopted in treating patients with a low BMI or poor growth curve.



Management of Nephrotoxicity

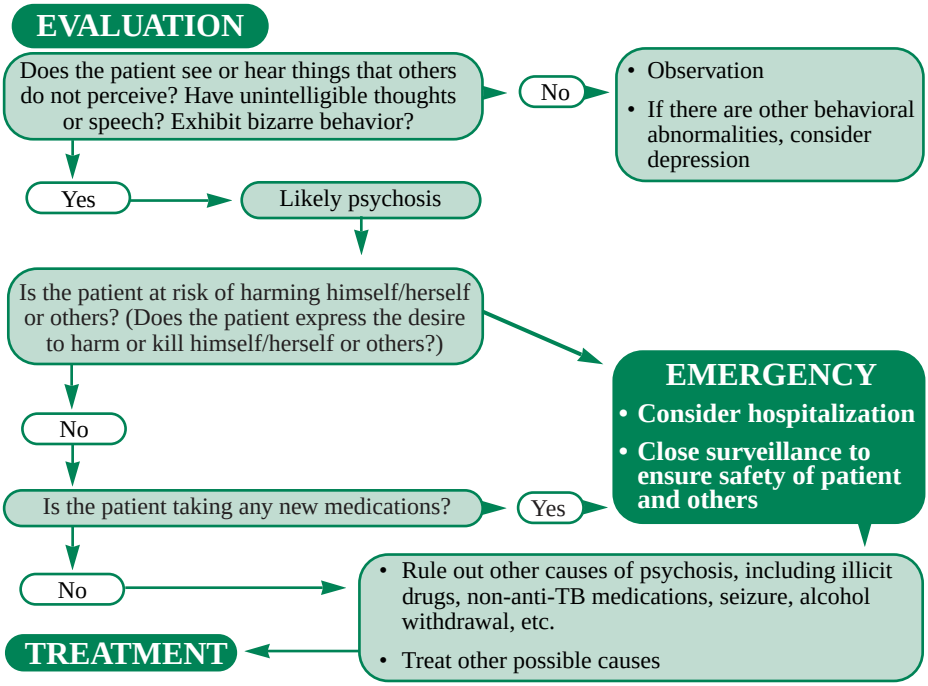
While many recommend a six-month maximum of parenteral administration and maximum cumulative aminoglycoside doses of ≤ 150 grams, anecdotal evidence suggests good tolerance to far larger cumulative doses of injectable agents. Blood urea nitrogen (BUN) and creatinine should be documented at the beginning of therapy, and renal function should be followed regularly throughout treatment. In general, however, routine testing of creatinine clearance of non-hospitalized patients is not recommended due to the difficulties of ambulatory twenty-four hour urine collection.



PHASE 1	• Follow BUN and creatinine • Consider inpatient management in patients with severe symptoms • Follow for clinical improvement and normalization of BUN and creatinine prior to reinitiating parenteral medication
PHASE 2	• If receiving an aminoglycoside, change to Cm if susceptible to Cm • If unable to change to Cm, reduce dose of parenteral to 750 mg or replace with equally efficacious PO anti-TB drug if possible • If severe renal failure, discontinue all nephrotoxic medications and replace with equally efficacious PO anti-TB drugs if possible
PHASE 3	Throughout treatment • Follow creatinine and BUN every one to two months thereafter • Maintain close surveillance for treatment failure and/or resistance amplification if period of irregular therapy during acute management

Management of Psychosis

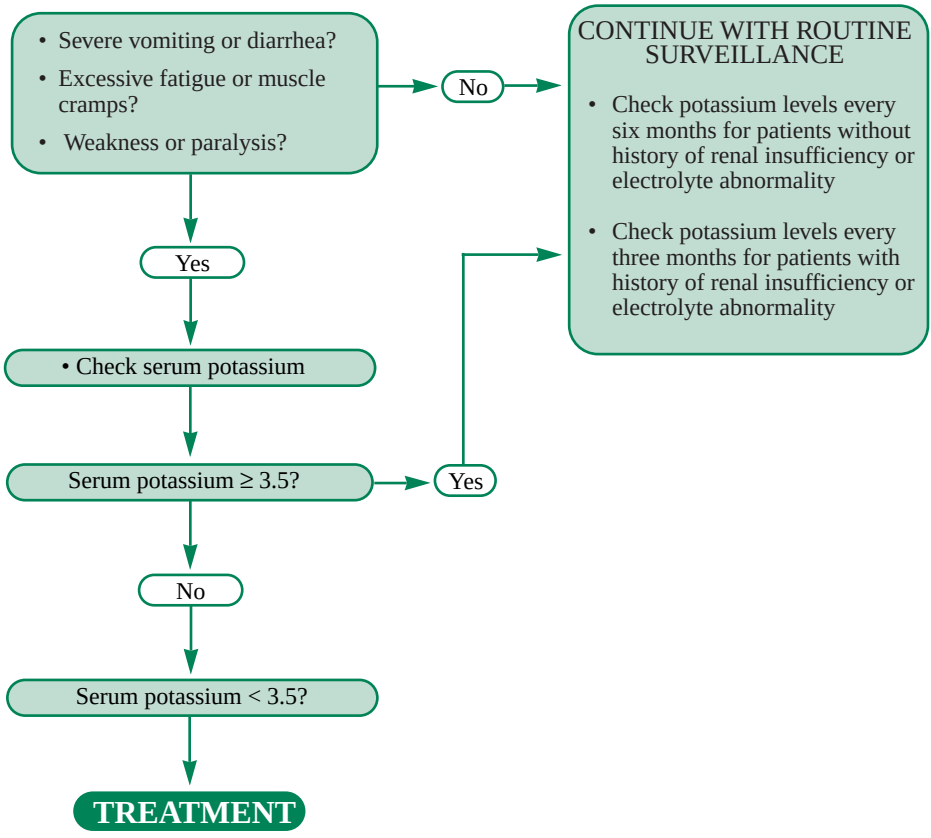
Psychotic symptoms refer to a constellation of symptoms that indicate a disintegration of personality or a loss of contact with reality. Patients tend to present with hallucinations or delusions. The causes of psychotic symptoms in patients with MDR-TB may be related to socioeconomic circumstances, underlying psychiatric disease, and medications (especially cycloserine).



PHASE 1	• Consider psychiatric consult • Evaluate Cs as one of the potential etiologies • Administer haloperidol 1-5 mg PO or IM, repeat every hour or as needed (IV less effective) • Administer benzodiazepines if concomitant anxiety (use benzodiazepines with caution if tenuous respiratory status and at risk of retaining CO_2). Also, paradoxical effect of increased psychosis may be observed with benzodiazepine use, especially in elderly patients. • Increase pyridoxine to 300 mg
PHASE 2	• Continue to adjust antipsychotic therapy in consultation with psychiatry if psychosis continues • Administer with diphenhydramine 25 mg PRN to alleviate extrapyramidal symptoms
PHASE 3	• If no improvement:administer clonazepam; start 25 mg PO BID, increase to 300 mg daily (perform complete blood count every two weeks to monitor for leucocytosis)
PHASE 4	• If no improvement, lower Cs to 750 mg QD
PHASE 5	Additional therapy • Evaluate sources of stress in the patient's life • Provide psychological therapy • Use benzodiazepines if significant anxiety • Use anti-depressives if depression

Management of Hypokalemia

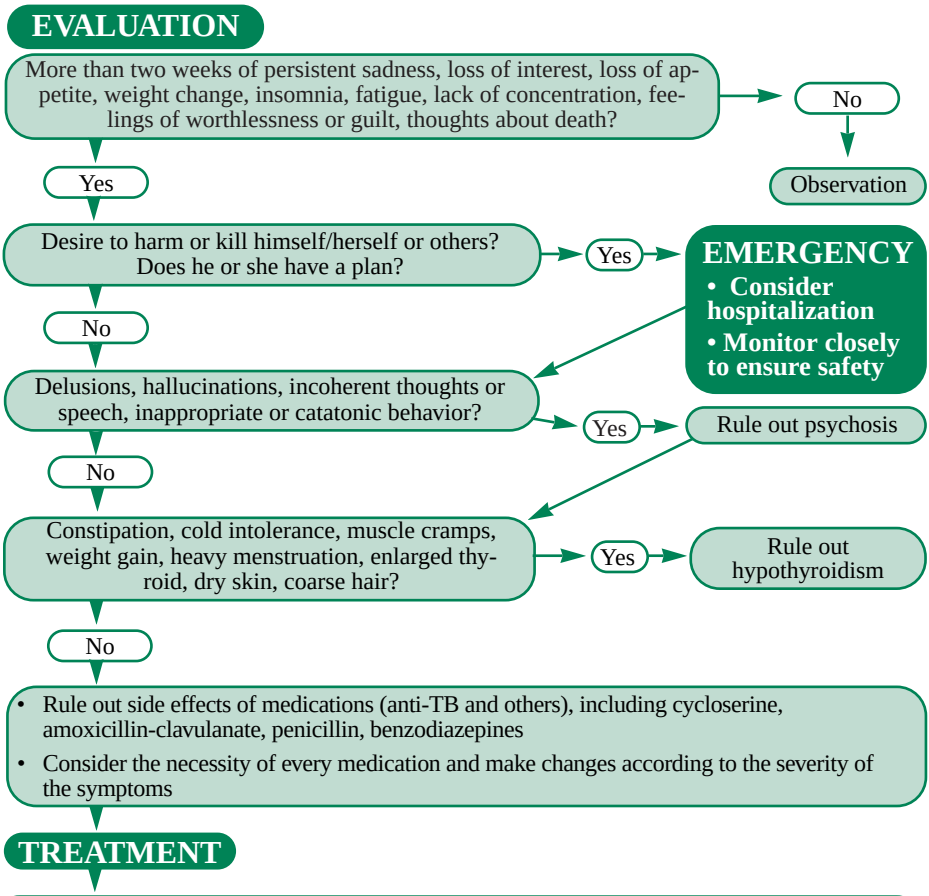
Hypokalemia signifies a low level of potassium in the blood (< 3.5). It can also be associated with other electrolyte abnormalities, such as hypomagnesemia. Persistent vomiting and diarrhea are the most likely causes of hypokalemia. Some of the anti-TB medications— in particular the aminoglycosides— cause wasting of potassium and magnesium in the renal tubules. In most patients with MDR-TB and hypokalemia, the cause of the electrolyte abnormality is likely multifactorial. Because hypokalemia can occur without clinical signs or symptoms and because it can be life-threatening, it is recommended to check potassium levels every three to six months and if the patient has severe vomiting or diarrhea.



PHASE 1	• Replete potassium orally or IV • Treat associated conditions such as vomiting or diarrhea • Monitor potassium every-other-day to determine when repletion can be stopped
PHASE 2	• Check magnesium if potassium does not improve with Phase 1 measures • Replete with 2 gm $MgSO_4$ IV or IM qd if magnesium < 2 mg per dl • Continue potassium repletion with every-other-day monitoring of potassium and magnesium to determine when repletion can be stopped

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 thoughts. Depression can be considered a normal reaction for a patient with a chronic illness such as TB; however, additional factors (including side effects from anti-TB drugs) may exacerbate this condition. 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.

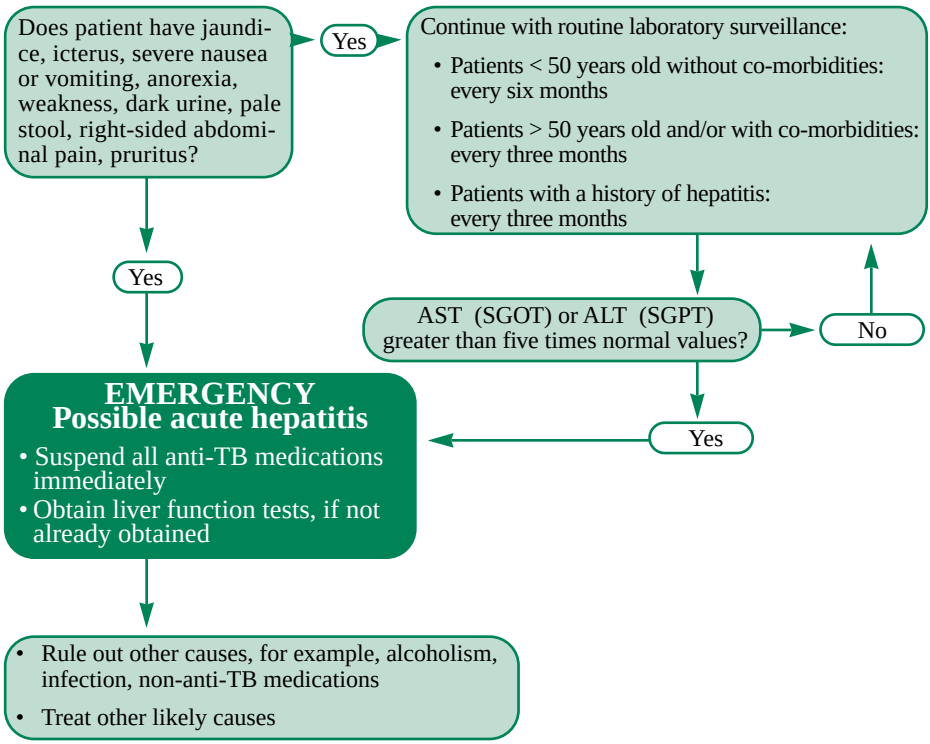


PHASE 1:	• Intensive psychological therapy with counseling to patient and family • Emotional support from the family and health promoter aimed at resolution of causes of stress • Group therapy or informal support groups
PHASE 2:	If no improvement in symptoms: • Increase pyridoxine to 300 mg per day in patients receiving cycloserine • Initiate antidepressant therapy (amytriptyline, nortiptyline, fluoxetine, sertraline, etc.) • Use antidepressants with caution in patients with a history of convulsions • Consider anti-psychotics and/or benzodiazepines according to the patient's condition • Consider psychiatric consult.

Evaluation and Management of Hepatitis

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

EVALUATION

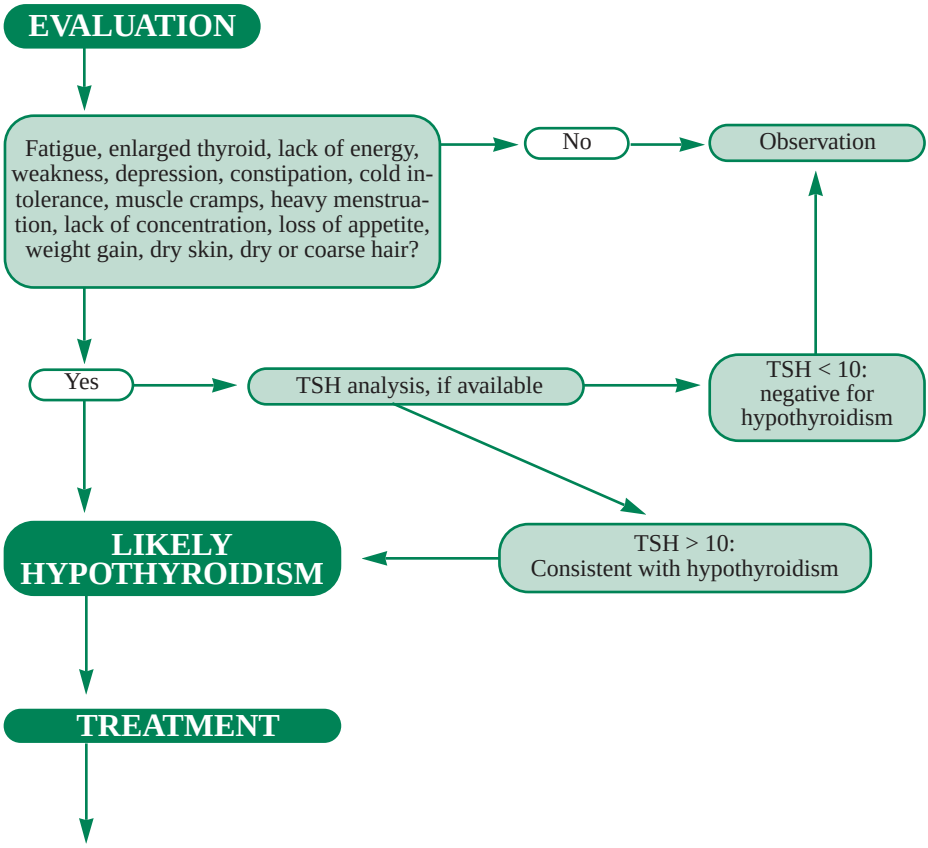


TREATMENT

PHASE 1	• Monitor for symptomatic improvement • Follow liver functions tests and clinical exam for signs of improvement • Treat symptoms as needed
PHASE 2	Once symptomatic improvement:: • Reinitiate anti-TB medications, one by one, with serial monitoring of liver function tests; introduce most likely culprits last • If possible, replace the hepatotoxic medications with equally efficacious anti-TB medications
PHASE 3	Throughout treatment: • Follow liver function tests every one to two months thereafter • Maintain close surveillance for treatment failure and/or resistance amplification given period of irregular therapy

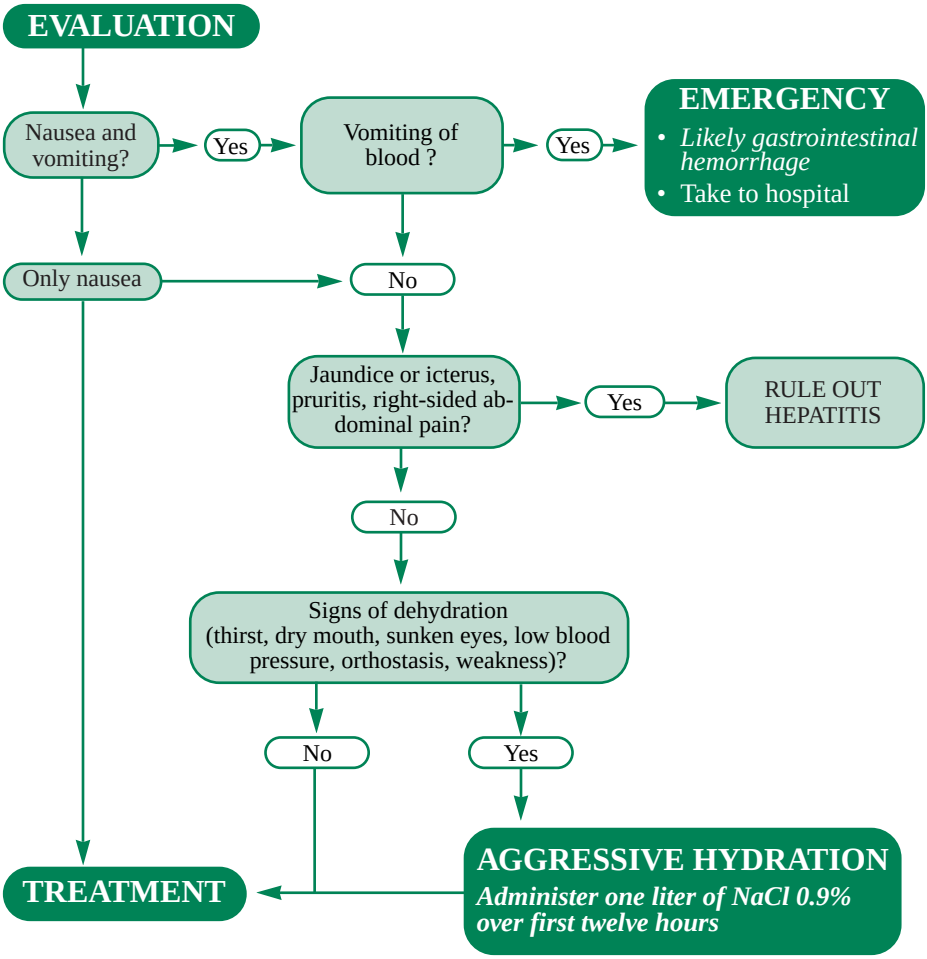
Management of Hypothyroidism

Hypothyroidism refers to suppression of the thyroid gland with elevation of the thyroid stimulating hormone (TSH) above ten. Chief among causes of hypothyroidism in patients with MDR-TB are medications, particularly ethionamide and PAS when used in combination. Hypothyroidism rarely leads to the discontinuation of anti-TB medications as the disease can be managed with levothyroxine replacement and abates once the patient has completed treatment.



PHASE 1	• Administer levothyroxine • Begin with 25 µg daily, increase every two to three weeks if necessary • Therapeutic dosage often between 25-150 µg daily • If available, repeat TSH every month until the correct dose is found
PHASE 2	If no improvement in symptoms: • Decrease Et dose to 750 mg • Discontinue Et or PAS; replace with another anti-TB drugs of similar potency if possible
PHASE 3	Upon completion of treatment: • Continue to follow TSH • Expect normalization of TSH after two to three months; discontinue levothyroxine according to TSH results • If TSH testing not available, discontinue levothyroxine after two to three months and follow symptoms

Management of Nausea and Vomiting

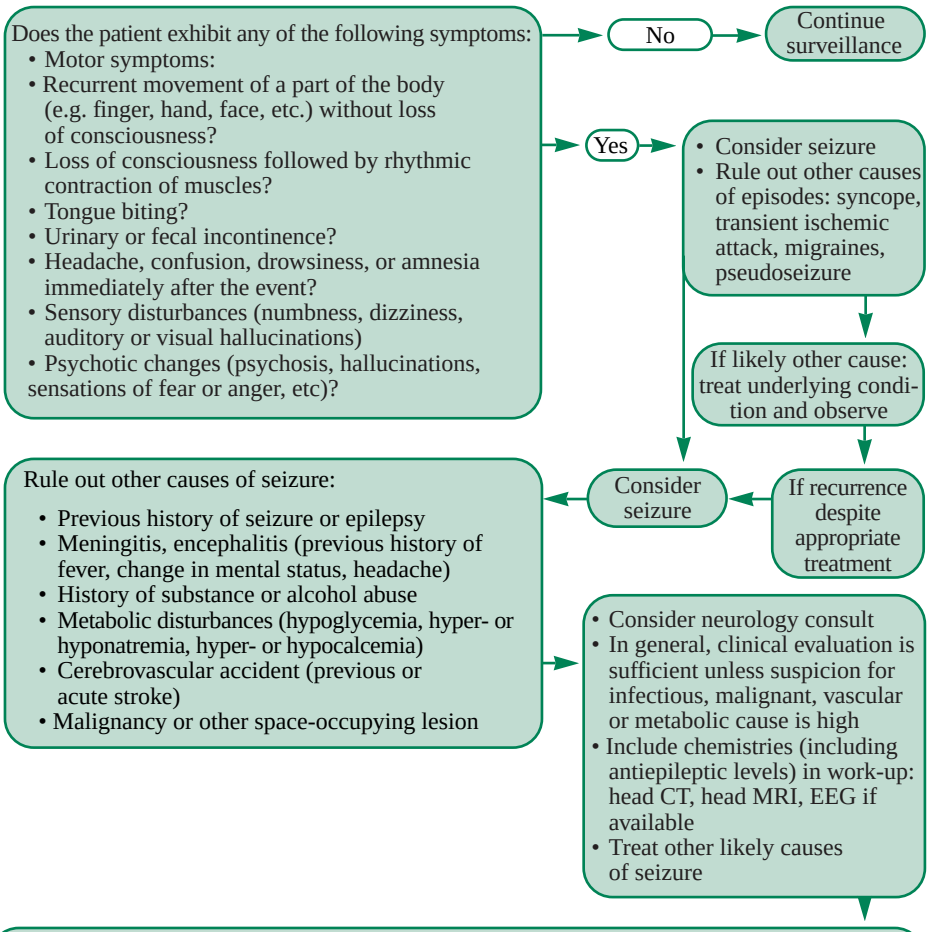


PHASE 1	• Check electrolytes • Adjust administration of medications • Administer Et or Cfz in three separate doses; • Administer medication associated with nausea at night with short-acting benzodiazepine; or • Administer PAS one hour after taking other anti-TB medications
PHASE 2	• Administer anti-emetics PO PRN or as standing dose, thirty minutes prior to taking anti-TB medications (anti-emetics include: prochlorperazine, diphenydramine, lorazepam, dimenhydranate, metoclopramide, phenergan, etc.) • Avoid metoclopramide and prochlorperazine if neurological problems • Use benzodiazepines if anxiety (avoid benzodiazepines in patients with tenuous respiratory status at risk of CO_2 retention)
PHASE 3	• Administer anti-emetics IV or IM as needed
PHASE 4	• If taking Et, reduce to 750 mg QD • If taking Cfz, reduce to 200 mg QD

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 anti-TB drugs have been associated with seizures, as has TB of the central nervous system.

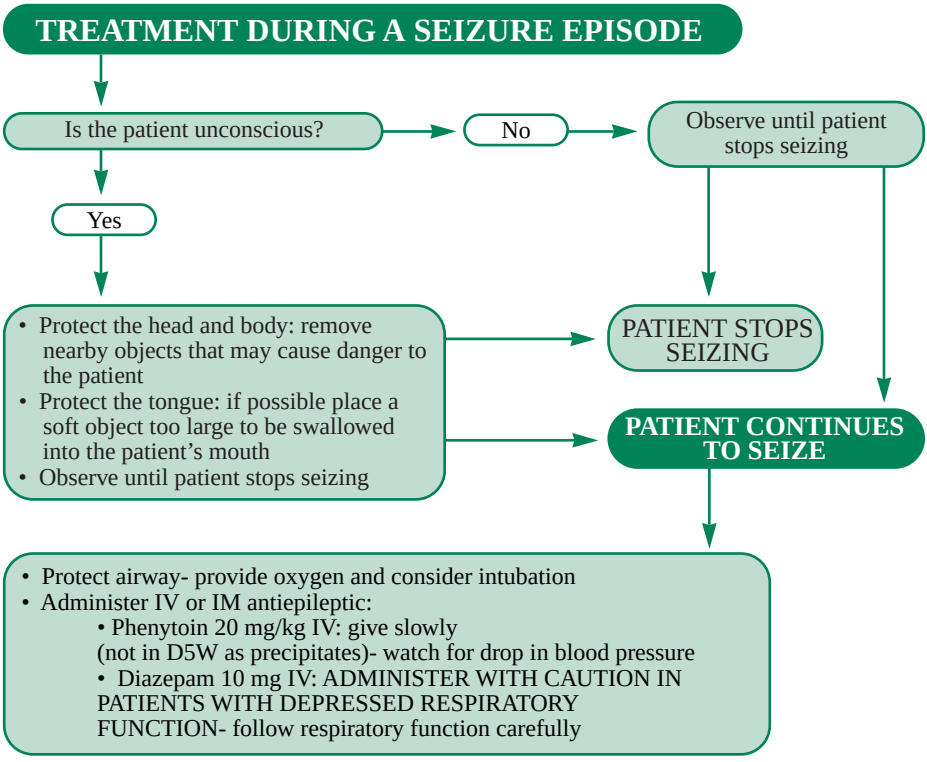
EVALUATION



Even if there is an underlying condition (e.g. history of previous stroke, epilepsy, substance abuse), aggravating triggers should be considered. For instance, subtherapeutic levels of anti-seizure drugs (which can be caused by drug-drug interactions between anti-seizure drugs and anti-TB drugs, especially H and R), sleep deprivation, recent alcohol ingestion, as well as anti-TB drugs may lower seizure threshold. Additionally, patients without pre-disposing conditions may present with first-time seizures due to anti-TB drugs alone. Therefore, aggressive treatment of seizures in patients receiving anti-TB drugs known to cause seizures is recommended.

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.

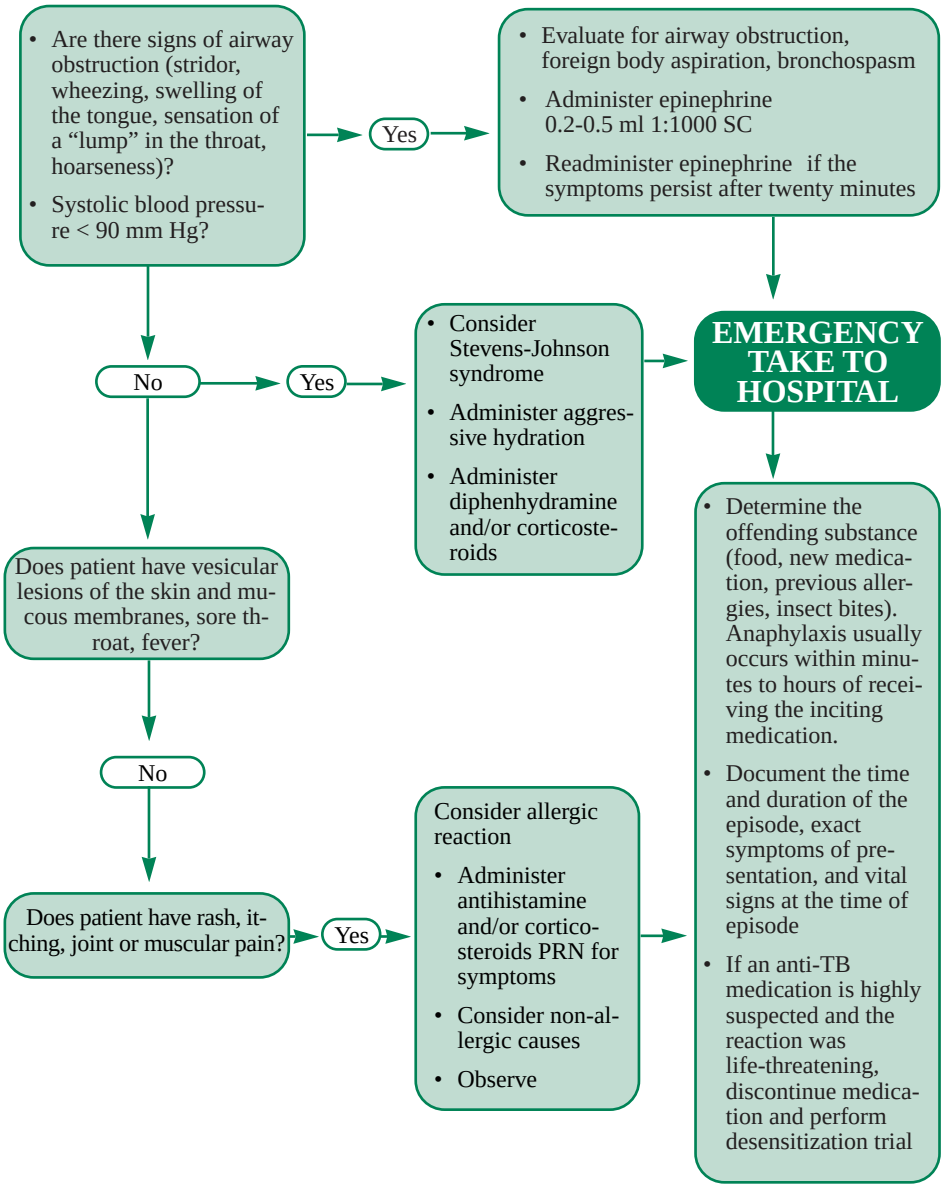


TREATMENT FOR PREVENTION OF FURTHER SEIZURES

PHASE 1:	Initiate antiepileptic treatment for the remainder of MDR-TB therapy: • Phenytoin (3-5 mg/kg/day) Potential adverse effects: ataxia, incoordination, confusion, skin rash, cerebellar dysfunction, hepatotoxicity, gingival hyperplasia, lymphadenopathy, hirsutism. Increased level by H. • Carbamazepine (600-1200 mg/day) Potential adverse effects: ataxia, dizzines, diplopia, vertigo, GI upset, hepatotoxicity; skin rash • Phenobarbitol (60-120 mg/day) Potential adverse effects: sedation, ataxia, confusion, dizziness, decreased libido, depression, skin rash. Enhances metabolism of other drugs, including H. • Valproic acid (750-1250 mg/day) Potential adverse effects: ataxia, sedation, tremor, hepatotoxicity, bone marrow suppression, GI upset, weight gain
PHASE 2:	• Decrease Cs to 750 mg or 500 mg/day • If available, check Cs level and adjust if supratherapeutic • Decrease fluoroquinolone dose

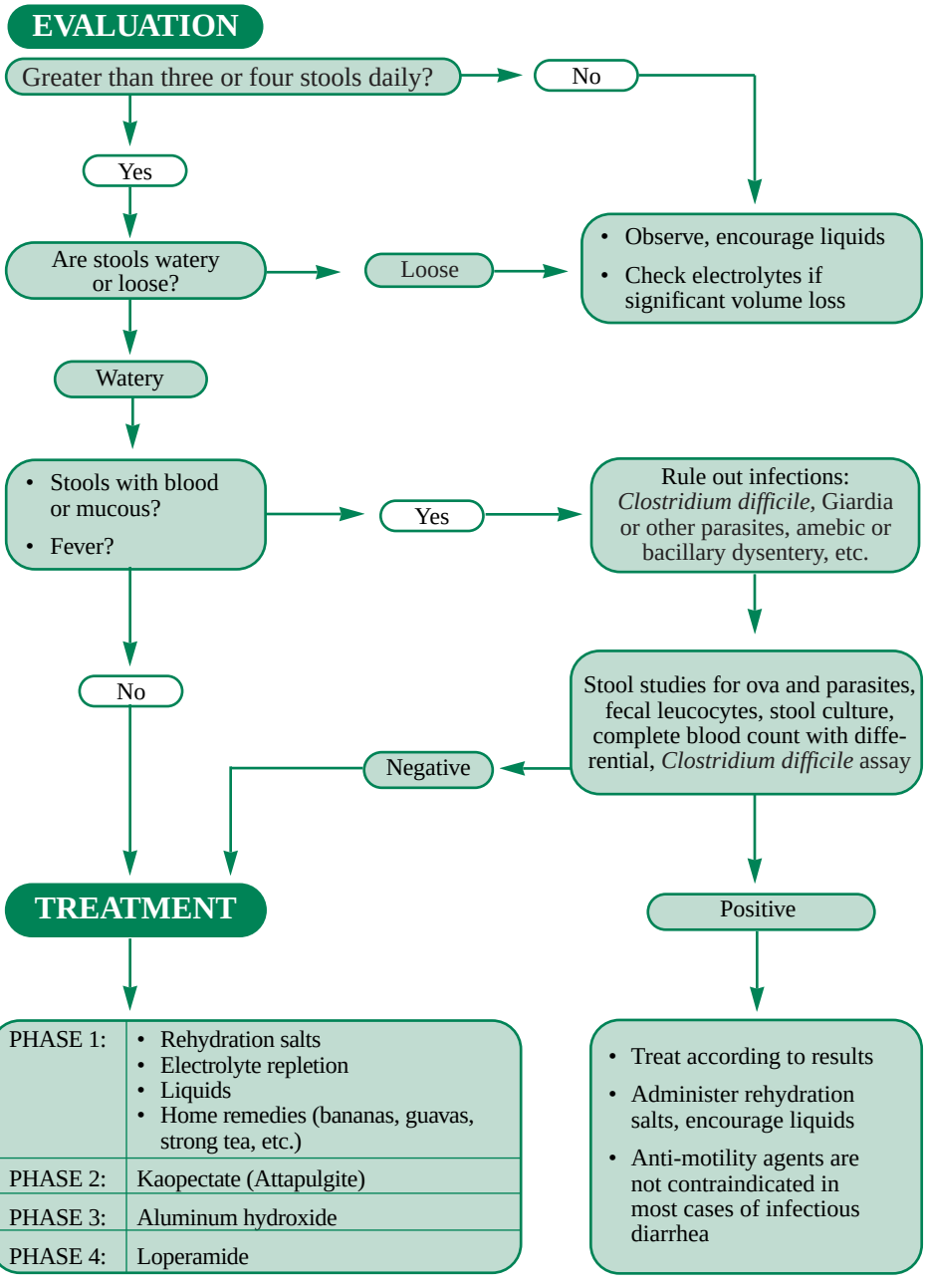
Management of Anaphylaxis

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 (muscular pain).



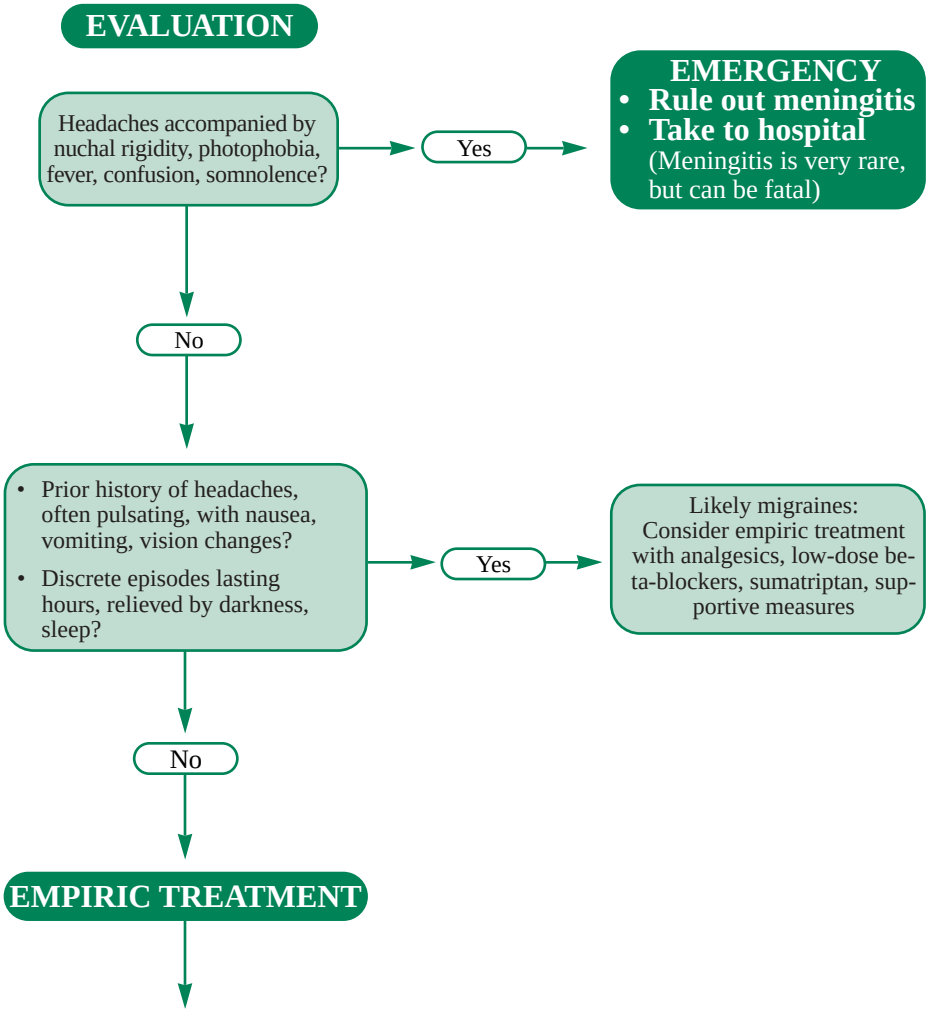
Management of Diarrhea

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 antituberculous medications.



Management of Headache

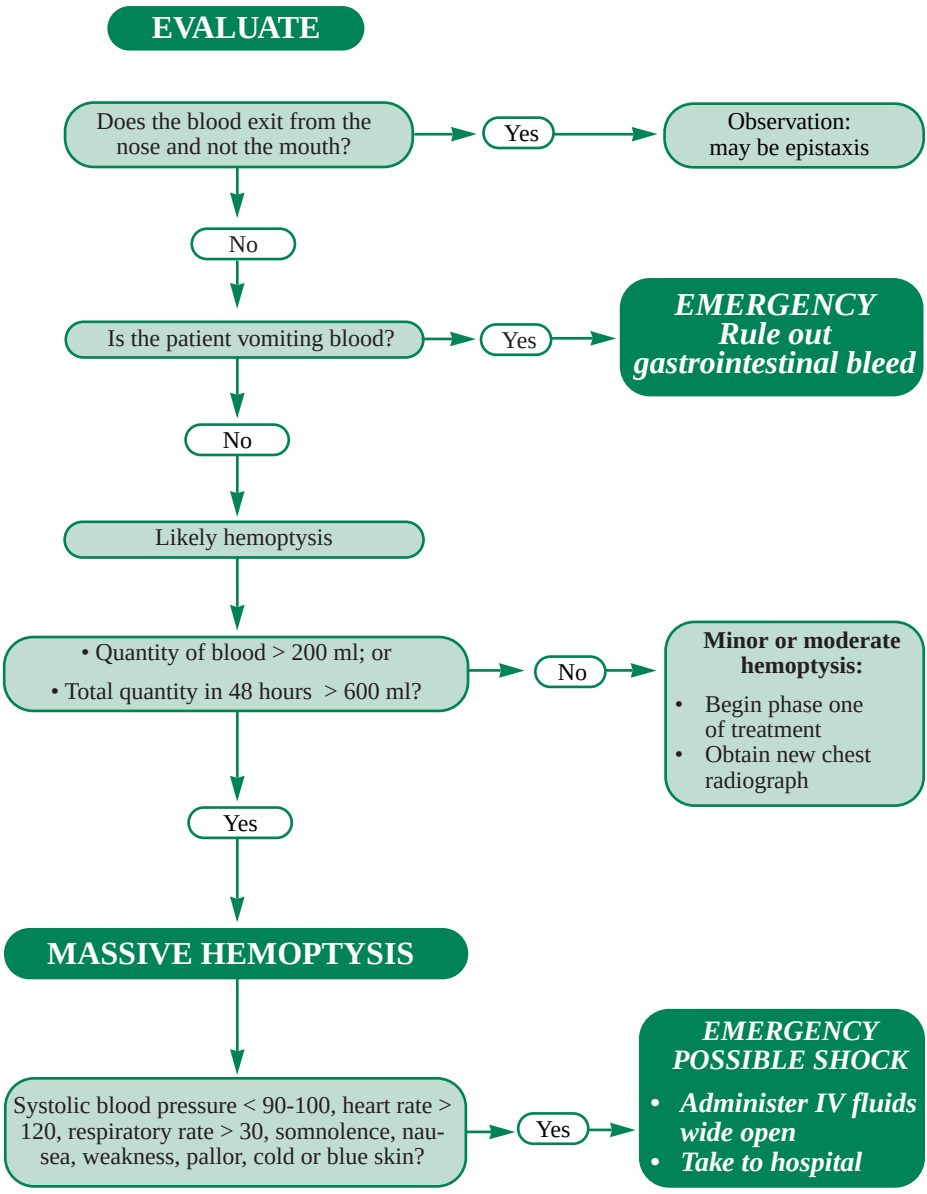
Although headaches are often a side effect of anti-TB treatment, it is important to rule out other causes of headaches, including meningitis, migraines, and cluster headaches.



PHASE 1:	• Administer analgesics PRN (e.g. acetaminophen, ibuprofen, aspirin, etc) • Avoid non-steroidal anti-inflammatory agents in patients with hemoptysis or severe gastritis • If no response to one agent drug, try a different one (e.g. if no response to acetaminophen, use ibuprofen) • Increase pyridoxine to 300 mg in patients receiving cycloserine
PHASE 2:	• Psychosocial support to relieve emotional components that may be contributing to headaches not relieved by the measures listed above • Anti-inflammatory drugs with analgesics (e.g. acetaminophen with codeine)
PHASE 3:	• Amytriptyline 100-150 mg at night

Management of Hemoptysis, Part I

Hemoptysis is the expectoration of blood originating from the larynx, trachea, bronchia or lungs. Because hemoptysis may present as anything from a 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 treatment, as blood transfusion may be required.



Management of Hemoptysis, Part II

ANALYSES:

- ❑ Chest radiograph
- ❑ Hematocrit
- ❑ Type and crossmatch
- ❑ If fever and productive sputum: sputum smear microscopy and culture, Gram stain and culture

TREATMENT

PHASE 1:	• Prescribe bed rest • Monitor patient closely • Avoid NSAIDs and aspirin • If evidence of respiratory superinfection, initiate antibiotic treatment
PHASE 2:	For massive hemoptysis: • Initiate large bore IV with 1-2 L of normal saline within the first hour • Thereafter, maintain fluid (normal saline 0.9%) • Lie patient with likely source of hemorrhage in dependent position • Provide oxygen, if needed • Check vital signs frequently
PHASE 3:	If hematocrit < 30%: • Transfuse with matched blood • Follow-up hematocrit closely
PHASE 4:	If recurrent episodes without improvement: • Consider surgical evaluation: bronchiectasis, cavities, or coin-shaped lesions may be hemorrhagic sources (e.g. tuberculous destruction, erosion of blood vessels, aspergilloma)

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 anti-TB drugs (e.g. alcoholism, diabetes, other medications, etc.).

EVALUATION

- Burning sensation, "pins and needles?"
- Numbness of both feet, worse at night or when walking?
- Leg weakness when walking?
- Leg cramps or pain?

→ No → Observation

↓ Yes

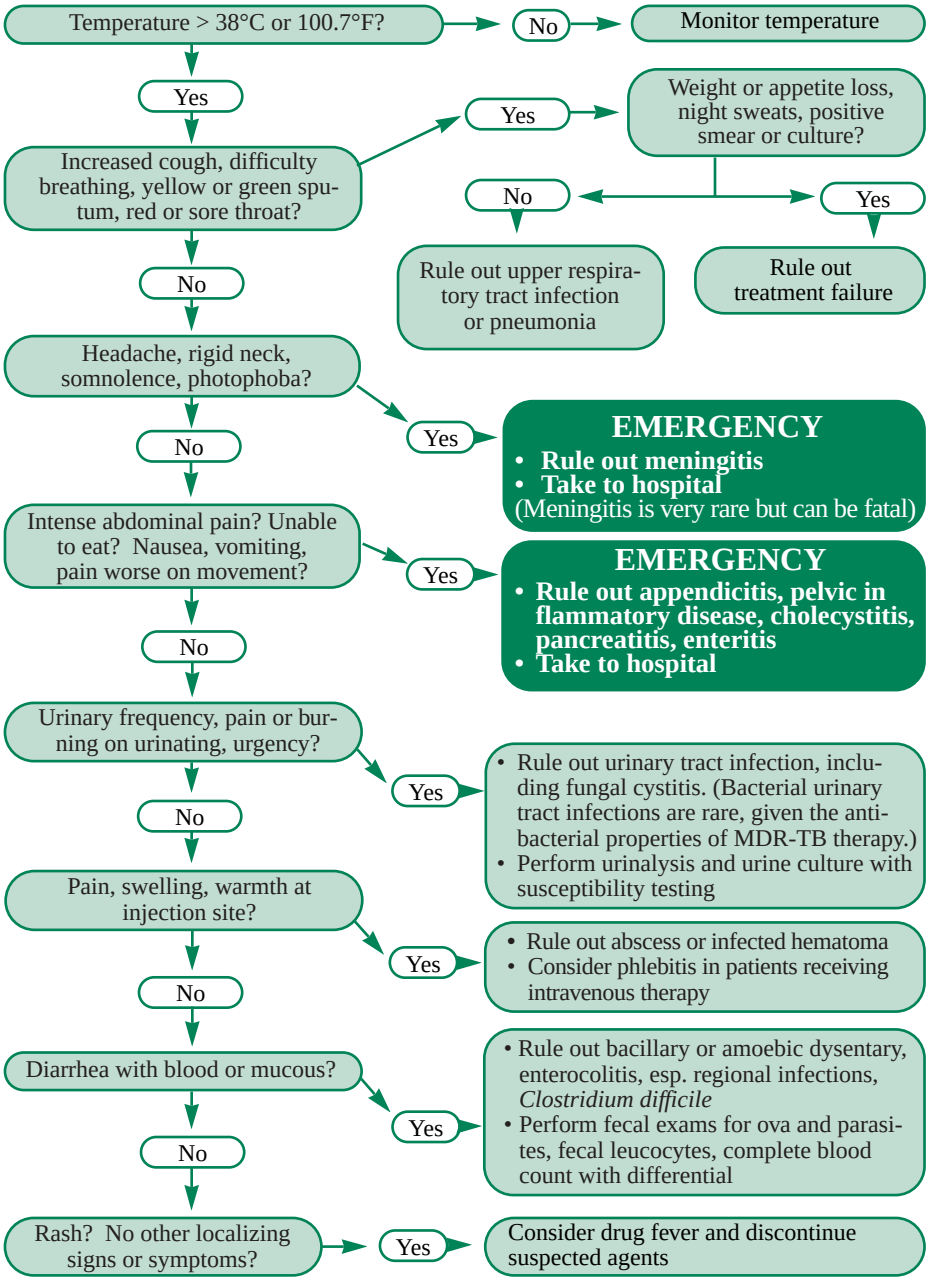
- Rule out other causes, including diabetes, alcoholism, vitamin deficiencies, HIV, hypothyroidism, uremia, other drugs, etc.
- Treat other likely causes

TREATMENT

PHASE 1:	Increase pyridoxine to 300 mg, consider multivitamins
PHASE 2:	Replace drugs most likely responsible if equally efficacious anti-TB drugs available; (H, Km, Amk, Tha, Cs have been associated with neuropathies)
PHASE 3:	For severe pain: • Initiate low-dose tricyclic anti-depressant (e.g. nortriptyline, amytriptyline, desiprimine) • Start at 25 mg at bedtime; increase 10-25 mg every three to seven days until 150 mg/day (although the majority respond to 75 mg/d)
PHASE 4:	If continued pain: • Consider neurology consult • If no improvement, decrease dose of responsible medication (e.g. Eth to 750 mg, Cs to 750 mg, Km, Amk, to 750 mg, etc), then resume normal dose once pain controlled
PHASE 5:	If no improvement: • Start gabapentin at 300 mg QHS; increase by 600 mg every three to seven days until response.; maximum dose 1200 TID • If no improvement, consider carbamezepine (start at 200 mg BID; increase to 600 mg BID) • Consider the use of phenytoin

Management of Fever, Part I

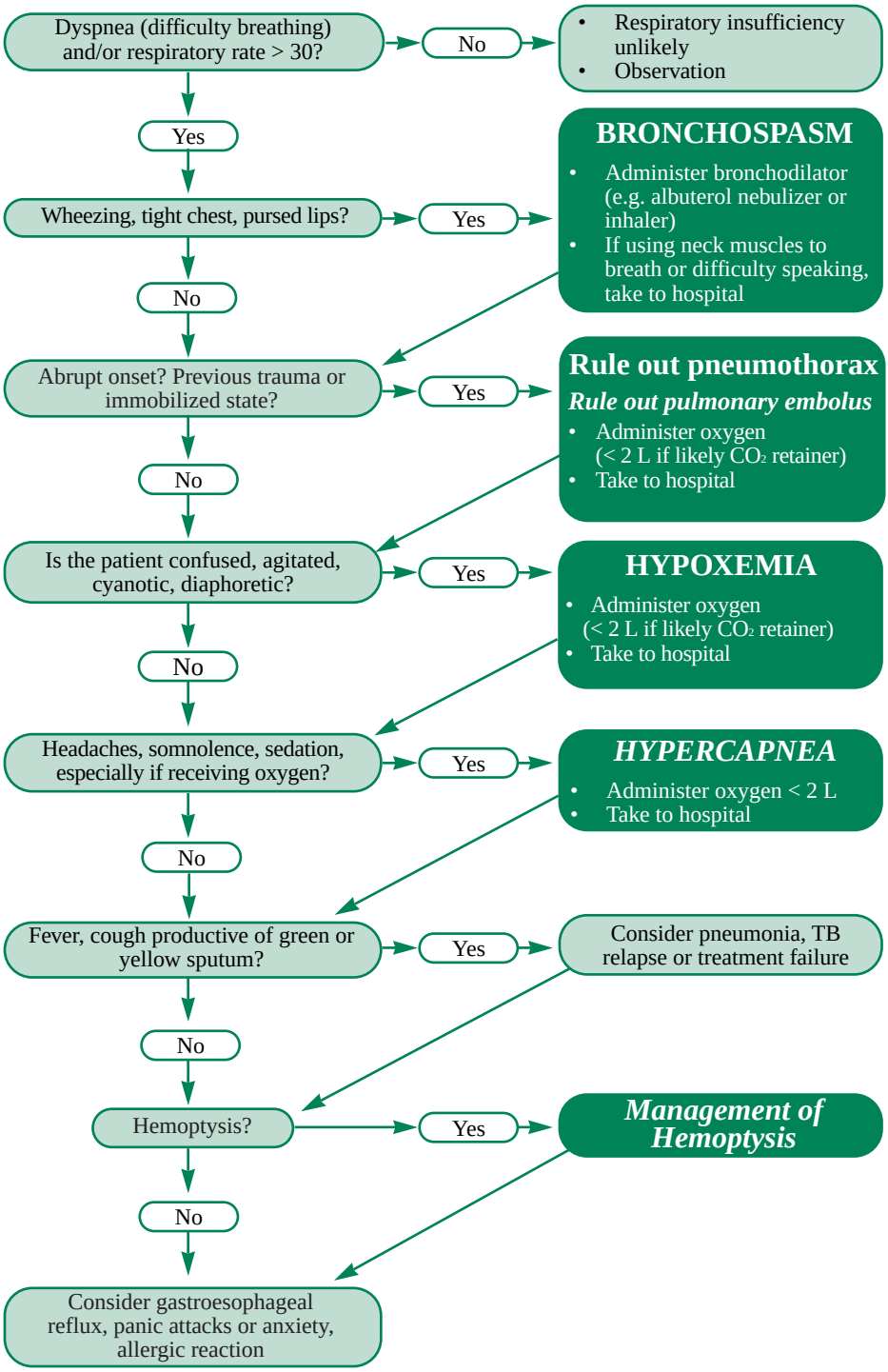
Fever is defined as an elevation in body temperature in excess of normal range, although temperatures within one or two degrees of normal (31° C or 98.6°F) are not generally considered significant. When a patient receiving MDR-TB treatment has a fever, various sources must be ruled out.



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 • Positive Gram stain • Negative urine culture	• Treat with fluconazole 150 mg daily for five days
Abscess, Hematoma		
	Injection site: • Pain • Warmth • Swelling • Fluctuance	• Aspirate with eighteen gauge needle or incise and drain • If abscess, treat with dicloxacillin 500 mg four times a day (or other anti-staphylococcal therapy)
Gastroenteritis, Enterocolitis		
Viral	• Diarrhea, usually without mucous or blood • Negative fecal studies	• Give rehydration salts
Bacterial/Parasitic	• Diarrhea, can be with mucus or blood • Positive fecal leukocytes • Possible *Clostridium difficile* if positive fecal leucocytes, elevated white blood count, fever. Perform *Clostridium difficile* toxin assay if available	• Give rehydration salts • Treat according for fecal study results • If *Clostridium difficile* suspected or confirmed, treat with metronidazole 500 mg TID for ten to fourteen days

Management of Respiratory Insufficiency, Part I



Management of Respiratory Insufficiency, Part II

ANALYSES:

- ❑ Chest radiograph
- ❑ Complete blood count with differential
- ❑ Sputum smear microscopy 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 1: • Inhaled bronchodilators • Treat for infection, if suspected Phase 2: • Administer oral or intravenous steroids Phase 3: • Consider long-term use of inhaled bronchodilutor and/or inhaled steroids Phase 4: • Nebulized bronchodilators
Pneumothorax	• Sharp pain, sudden onset previous trauma • Positive chest x-ray • May have decreased O_2 sat and PO_2	• Administer O_2 • Take to hospital • Thoracic surgery consult
Pulmonary Embolus	• May have fever, chest pain, tachycardia, positive EKG, positive chest x-ray, and/or diminished O_2 saturation/PO_2 • History of previous immobilization or surgery	• 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 • Gram stain/culture	• Treat with antibiotics according to sputum Gram stain/culture results • Treat concomitant bronchospasm as needed • Administer O_2 as needed
Tuberculosis Relapse/ Treatment Failure	• Productive cough, fever, night sweats, weight loss, diminished appetite • Chest radiograph may reveal new infiltrate • Positive smear and/or culture	• Confirm positive smear and/or culture

Annex 6

Adverse Reactions for a Patients Receiving Second-line Anti-TB Drugs for the Treatment of MDR-TB in Latvia (1997)

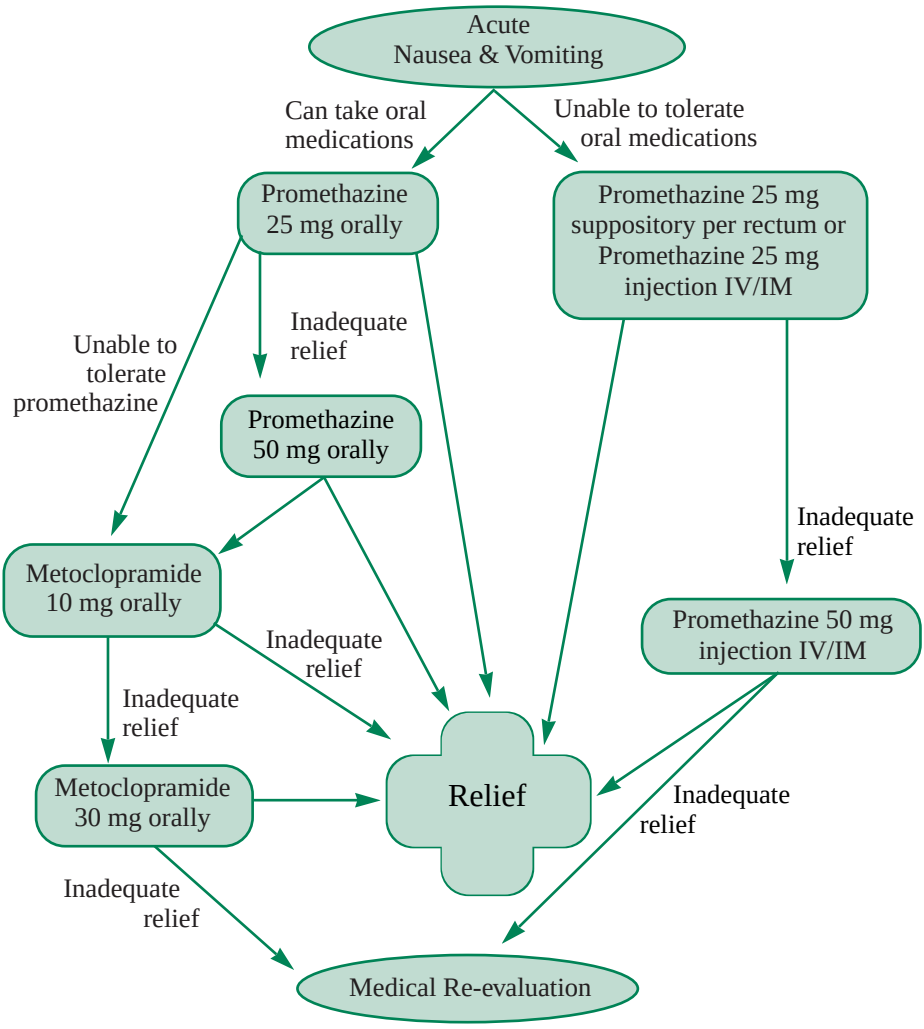
Drug	Number of Patients	Number of Adverse Reactions	Characteristics of Adverse Reactions
Prothionamide	106	6	5: nausea, vomiting 1: allergic skin reactions
Kanamycin	54	5	5: ototoxicity
Amikacin	8	1	1: ototoxicity
Capreomycin	23	4	2: ototoxicity 2: nephrotoxicity
Streptomycin	5	1	1: ototoxicity
Thioacetazone	93	2	1: toxico-allergic skin reaction 1: allergic reaction
Ofloxacin	31	0	-
Ciprofloxacin	76	2	1: allergic skin reaction 1: leukopenia
Para-aminosalicylic Acid	43	2	2: abdominal pain or discomfort, diarrhea
Cycloserine	53	4	1: suicide 2: psychoneurotic reaction 1: allergic skin reaction
Pyrazinamide	75	1	1: hypersensitivity
Ethambutol	76	0	-

Annex 7

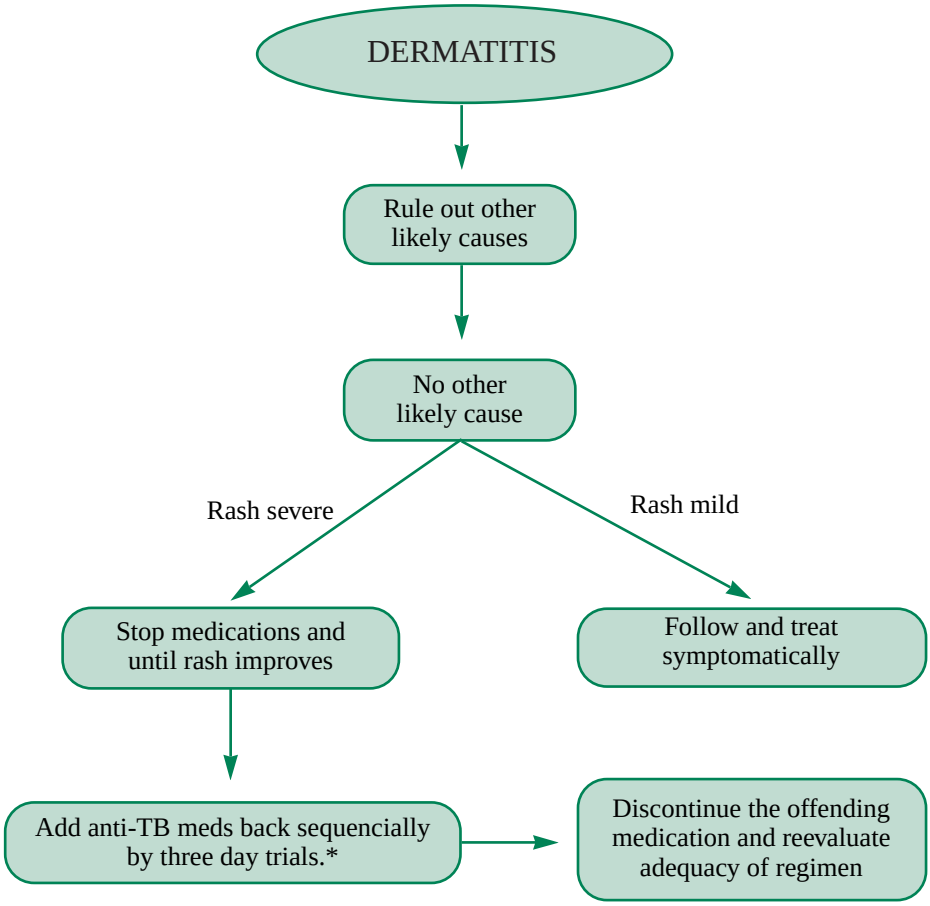
ADVERSE REACTIONS MANAGEMENT STRATEGY PROPOSED BY THE PUBLIC HEALTH RESEARCH INSTITUTE/MEDICAL EMERGENCY RELIEF INTERNATIONAL/UNIVERSITY OF ALABAMA-BIRMINGHAM IN TOMSK OBLAST, RUSSIAN FEDERATION

Key for Other Abbreviations			
>	greater than	ORS	oral rehydration salts
<	less than	PO	by mouth
BID	two times a day	QD	one time a day
GI	gastrointestinal	QID	four times a day
IM	intramuscular	TID	three times a day
IV	intravenous	TSH	thyroid stimulating hormone
LFT	liver function test		

Algorithm for the Acute Management of Nausea & Vomiting



Algorithm for the Management of Dermatitis

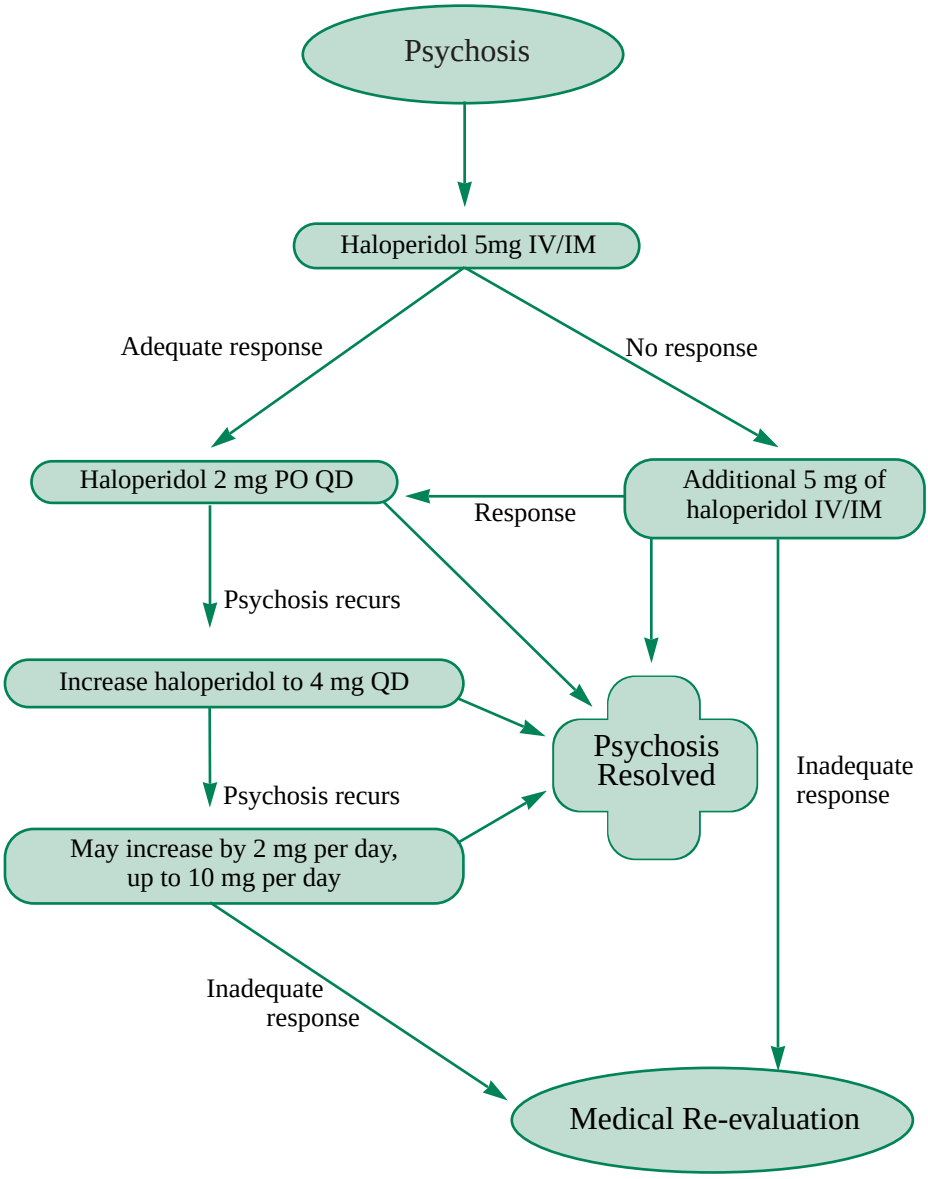


*Add drugs back in the following order (of increasing likelyhood in causing cutaneous reaction):

Isoniazid
Rifampicin
Pyrazinamide
Ethionamide
Cycloserine
Ethambutol
PAS
Streptomycin and other aminoglycosides

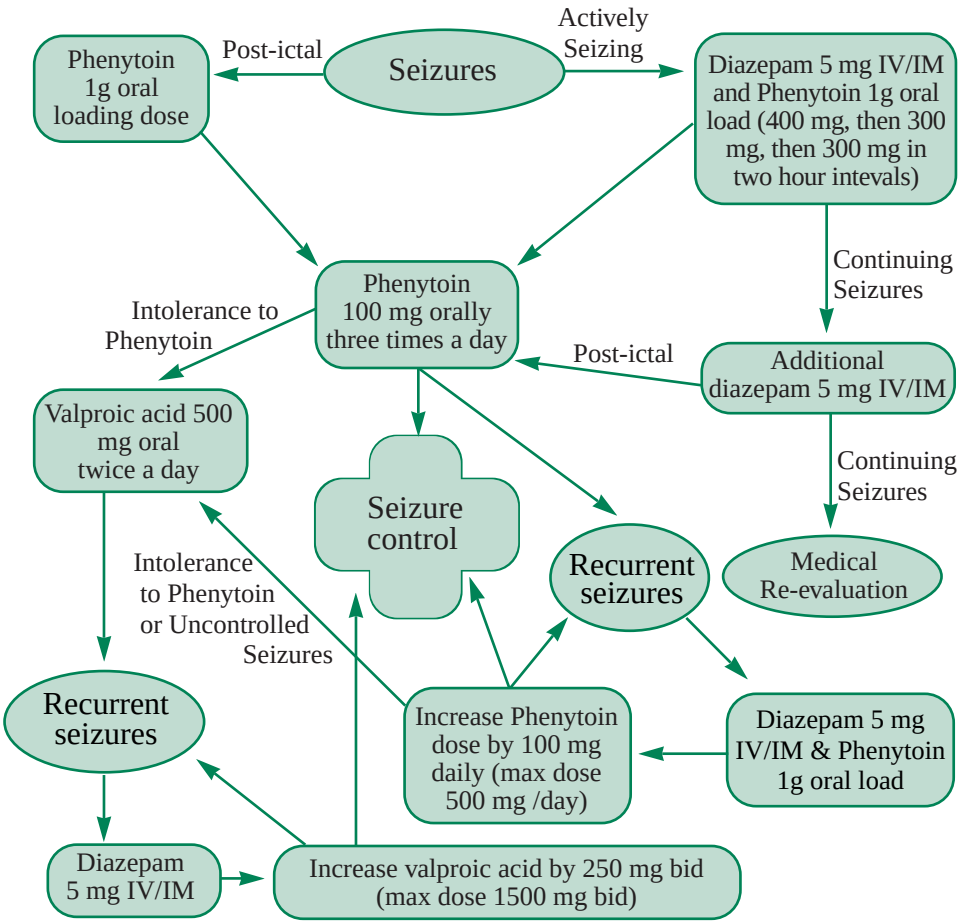
If severe reactions, start medicimes at one-tenth of initial dose.

Algorithm for the Management of Psychosis



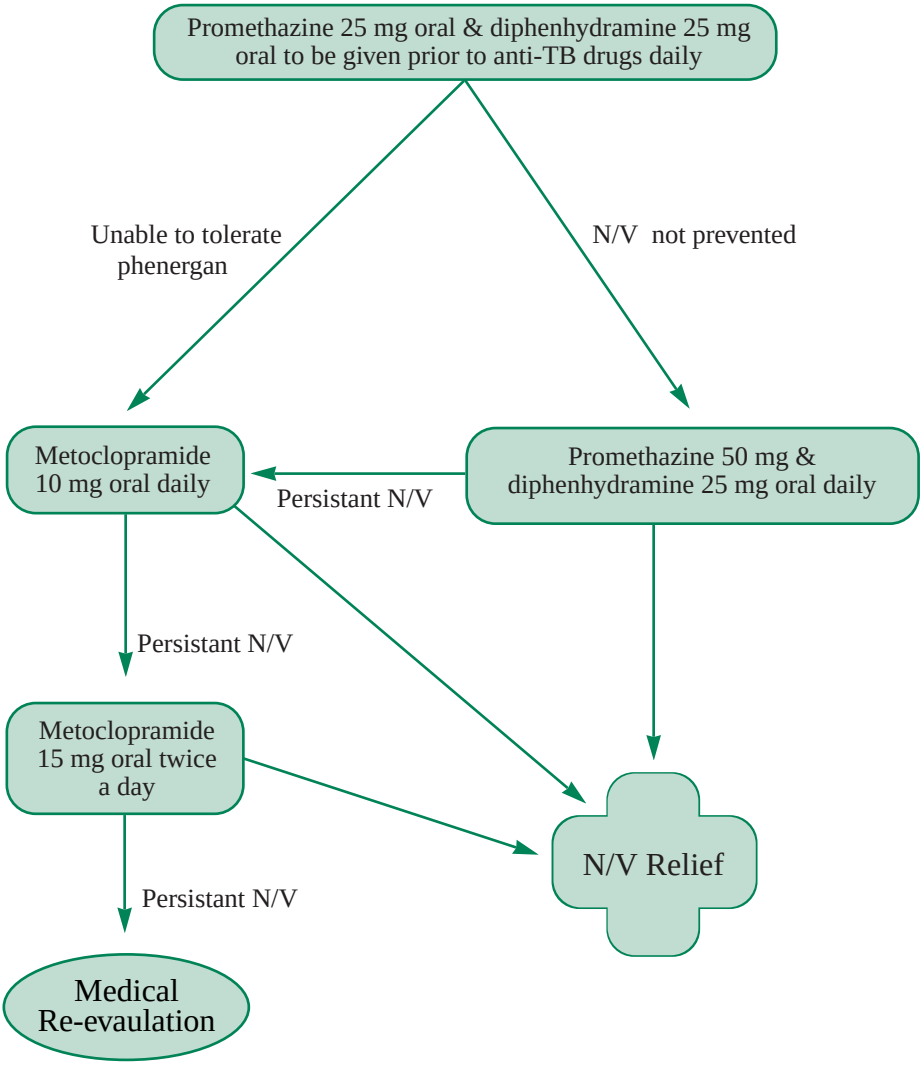
- If patient develops symptoms of neuroleptic syndrome, must discontinue haloperidol immediately.
- If patients develop dystonia, Parkinsonism, or EPS, administer with diphenhydramine 25 mg PO QD.
- Haloperidol has anticholinergic as well as antidopaminergic effects.

Algorithm for the Management of Seizures



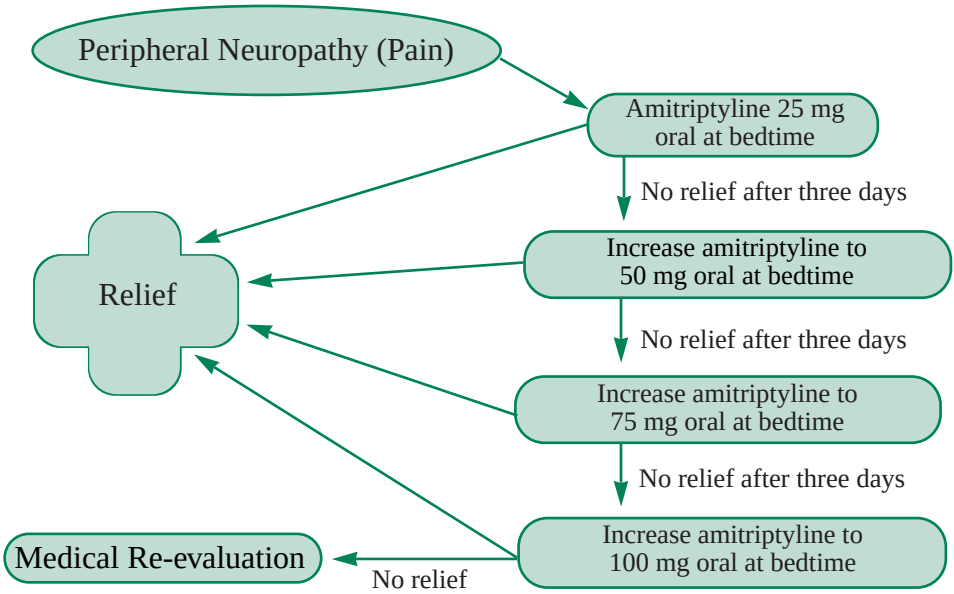
- If patients have recurrent seizures on maximal doses of phenytoin or valproic acid, a second agent, gabapentin, should be added if possible.
- If patients demonstrate intolerance to both phenytoin and valproic acid, medical re-evaluation is required.
- Possible side-effects of phenytoin include: mental status changes, ataxia, slurred speech, gingival hyperplasia, nystagmus, hepatitis, and rash.
- Possible side-effects of valproic acid include: sedation, nystagmus, GI upset, thrombocytopenia, and hepatitis.
- All patients will be on B-complex vitamins and folate, to diminish the risk of seizures.
- If recurrent seizures on cycloserine, daily dose of cycloserine should be reduced by 250 mg.
- If seizures uncontrolled with above measures, phenobarbital may be used.

Algorithm for the Prevention of Nausea and Vomiting (N/V)



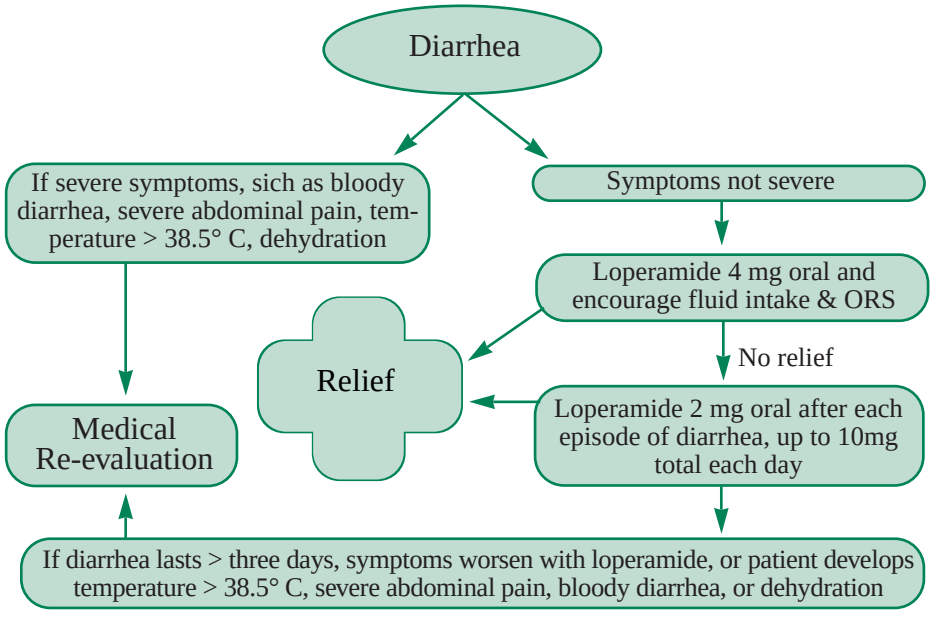
- Antiemetics are to be administered thirty minutes prior to all oral medications throughout the day, whether QD, BID, TID, or QID.
- Metoclopramide is anti-dopaminergic and may cause Parkinsonian symptoms/dyskinesias. If these symptoms develop then diphenhydramine 25 mg is to be administered with each dose of metoclopramide.
- Promethazine has anti-cholinergic effects and may cause dry mouth and urinary retention. In the elderly it may worsen dementia.

Algorithm for the Management of Peripheral Neuropathy

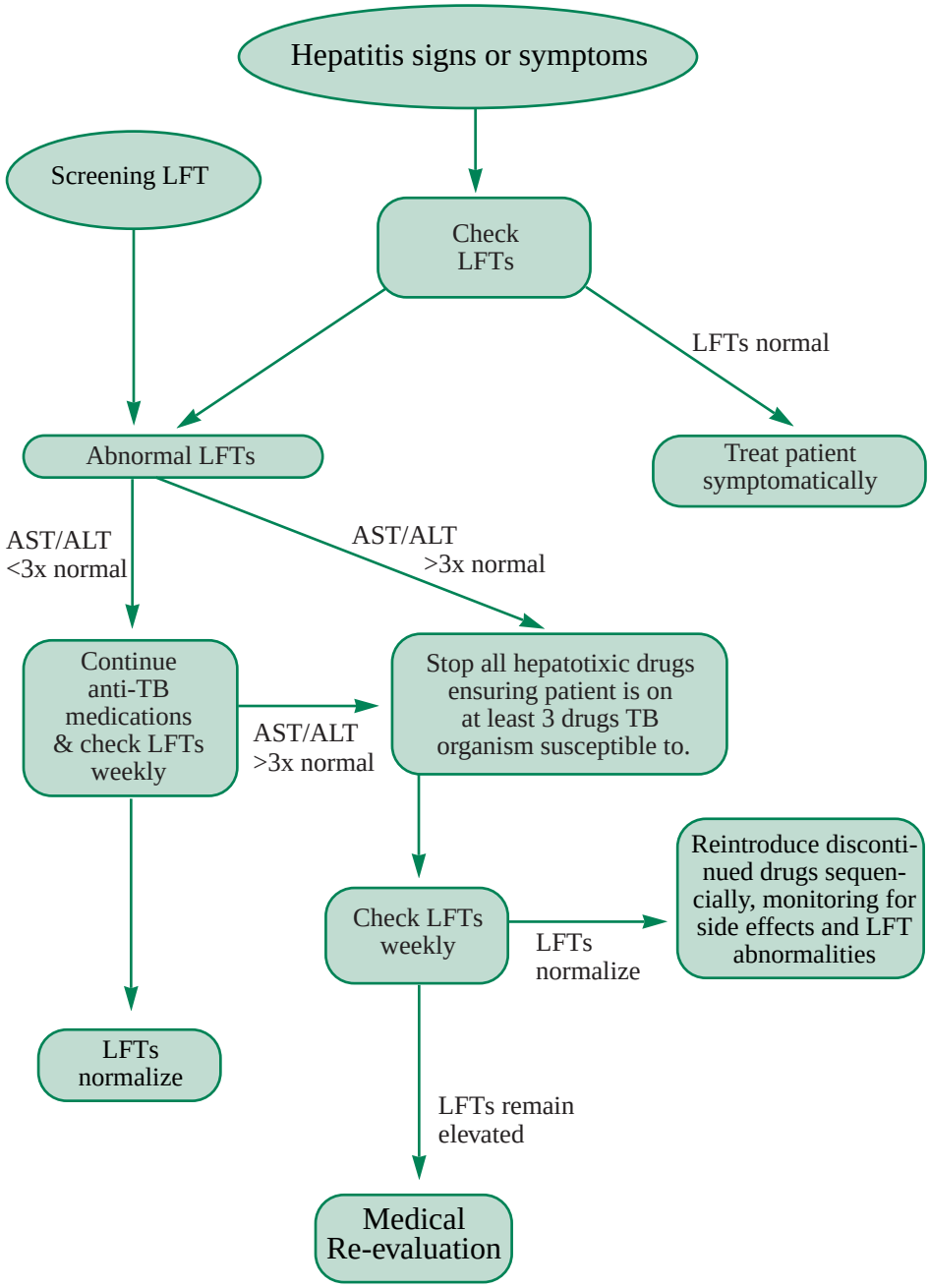


- If patients has weakness, incontinence, loss of reflexes, or gait disturbance more extensive medical evaluation is required.
- All patients will be on B-complex vitamins with additional pyridoxine and folic acid to diminish the risk of neuropathy.

Algorithm for the Management of Diarrhea

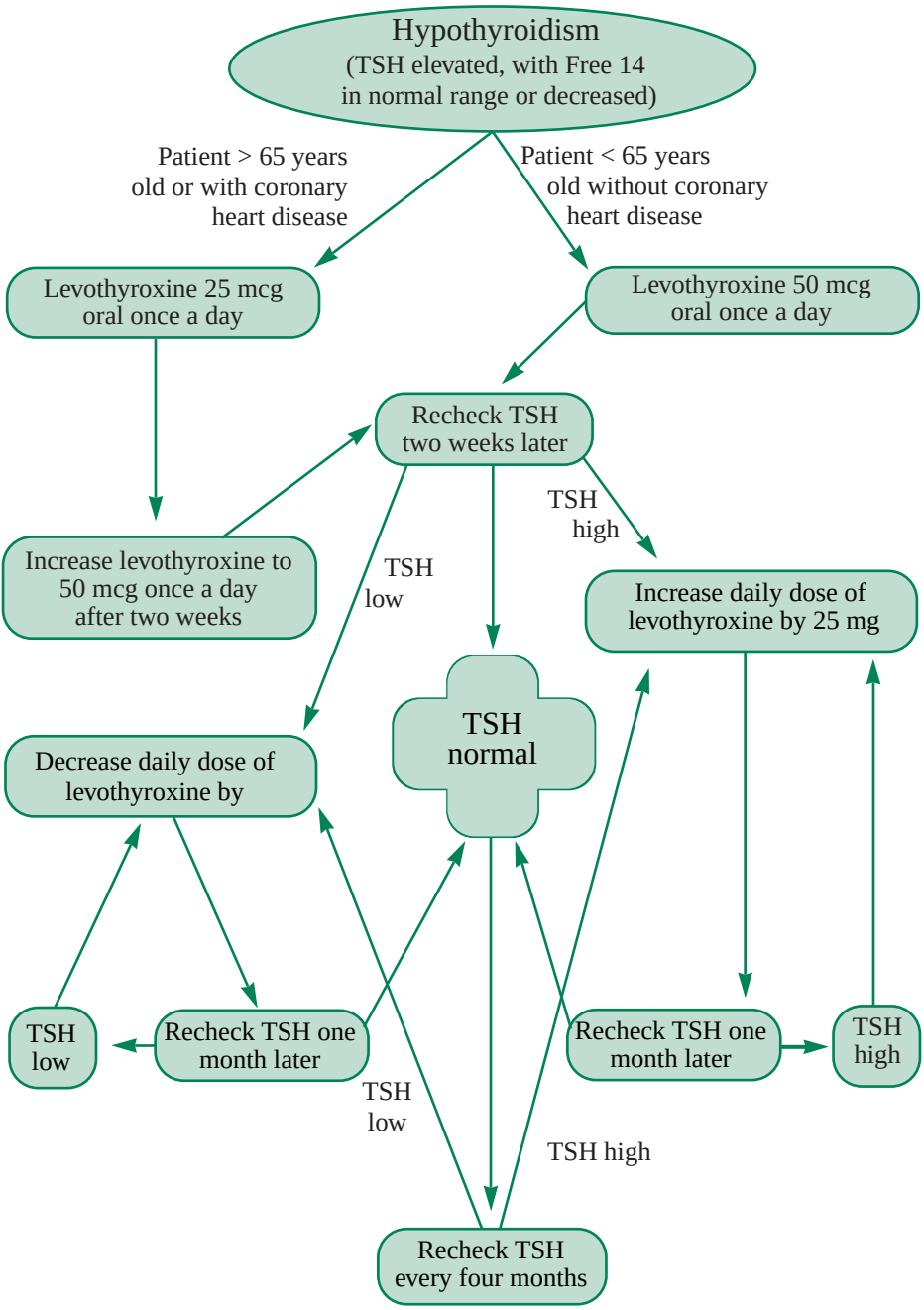


Algorithm for the Management of Hepatitis



- Drugs with potential hepatotoxicity include isoniazid, rifampicin, ethionamide, and pyrazinamide.

Management of Hypothyroidism



Do not give levothyroxine at same time as antacids or phenytoin, as these impair GI absoption.

Annex 8

STRATEGIES TO MINIMISE INTERRUPTION OF TREATMENT AND ABSCONDING PROPOSED BY THE CENTERS FOR DISEASE CONTROL AND PREVENTION IN IVANOVO OBLAST, RUSSIAN FEDERATION

Patient Grievances	Patient Oriented Measures to Address Grievances
Crowded wards	Limit bed capacity; move reliable patients to outpatient treatment as soon as possible; provide off-ward activities.
Bad food, not enough food	Provide additional resources to improve the taste, nutritional quality and quantity of food
Loneliness / homesickness / missing family	Allow weekend passes; allow family to visit (must wear masks); provide structured activities to promote camaraderie among patients
Boredom	Provide structured activities for patients; access to books; video taped sporting events, shows and movies; educational and vocational training opportunities; exercise / sports
Depression	Assess depressive symptoms with standardized depression inventory; treat with anti-depressant drugs; offer group therapy
Hopelessness / pessimism	Offer hope through use of second-line drugs; incentives and rewards for defined milestones in treatment; offer vocational training.
Lack of drugs to ameliorate symptomatic adverse reactions of anti-TB drugs	Provide drugs for symptomatic relief of anti-TB drug adverse reactions: 1) gastrointestinal: H_2 antagonists, antacids, loperamide; reglan; 2) central nervous system/psychiatric: antidepressants, anxiolytics, sedatives; 3) hypothyroidism: thyroid replacement; hyperuricemia: diuretics allopurinol; 4) myalgias / arthralgias: analagesics, NSAIDs
Lack of understanding of TB and TB's contiguousness	Provide appropriate patient educational materials and programs
Witnessing death of other TB patients	Hospice care, allow terminal patients to die at home,
Alcoholism	Collaboration to develop and evaluate interventions; involve narcologist; prevent / treat withdrawal, anxiety, craving with tapering chlordiazepoxide, naltrexone, acamprosate; consider disulfiram; develop local support group; advise patients to limit alcohol ingestion
Narcotics dependence	Involve narcologist; prevent / treat withdrawal; clonidine, naltrexone
Counterproductive incentive system	Offer incentives and rewards for completing treatment; provide appropriate vocational training; consider job opportunities as TB outreach workers; establish homeless shelter

Annex 9

STANDARD DATA COLLECTION SET

This Annex *should not be considered as an example of a standard data collection form* but should be considered the *minimum* set of data to be included in a standard data collection form.

DEMOGRAPHIC AND SOCIAL DATA (REGISTRATION DATA)

It is recommended to record all dates in the following format: mm/dd/yyyy. If dd is not available, then mm/yyyy should be used.

No.	*Variable*	*Comments, explanation, or examples*
1	Where does the patient live? • 1st level political subunit • 2nd level political subunit • city, town, and/or village	Examples Russia: oblast and (city or raion) Baltic Republics: city, raion or district
2	Date of birth	
3	Country of birth	Report the name of the country
4	Sex	M or F
5	How many children live with patient?	• Patient's own children • Record zero if no children living with patient
6	Size of household	Total number of people living in patient's household at time of treatment
7	Homelessness (Y/N)	Homelessness definition: patient sleeps outdoors, in public places, or in a shelter
8	Incarceration	Suggested categories: i. never imprisoned ii. current prisoner iii. history of imprisonment in past iv. if yes to ii or iii, then • number of institutions in which the patient resided • name of institutions (if possible) • duration of stay (in months) of each institution

MEDICAL HISTORY

No.	*Variable*	*Comments, explanation, or examples*
9	Previous TB	<u>Suggested variables</u> i. number of previous treatment regimens ii. date of diagnosis for each treatment iii. microbiologically confirmed or not for each treatment iv. drug susceptibility results (and date) for each treatment v. site(s) of disease for each treatment 1) pulmonary (with description) 2) extrapulmonary (with description) vi. chest roentgenogram for each treatment 1) cavitary vs. non-cavitary 2) extent of parenchymal disease vii. date each treatment started and place treated viii. status of each treatment (completed, interruption defaulted, failed, never treated); if default or interruption the include duration of default/interruption ix. indicate whether or not each treatment is conducted under direct observation (Y/N) x. drug regimen of each treatment 1) drugs used 2) frequency of use (daily or intermittent) 3) duration of use (in months) 4) dose (mg)
10	Addictive substance use (Y/N)	If yes, injection vs. non-injection
11	HIV	Positive, negative, or not available
12	Other major co-morbidity (Y/N)	<u>Examples affecting case management:</u> • hepatitis or cirrhosis • impaired hearing or vision • psychiatric or other central nervous system disease • peptic ulcer disease or chronic pancreatitis • renal insufficiency • thyroid insufficiency • diabetes

CURRENT EPISODE OF TUBERCULOSIS

No.	*Variable*	*Comments, explanation, or examples*
13	Date of onset symptoms	
14	Date of diagnosis	
15	Date treatment started	
16	Microscopy	Suggested variables i. specimen type (sputum or other body fluid or tissue) ii. number examined iii. result for each specimen (oldest to most recent) as 0, 1+, 2+, 3+ iv. date
17	Culture	Suggested variables i. dates of collection ii. dates result reported iii. specimen type iv. number of specimens culture v. result
18	Drug susceptibility test	Suggested variables i. dates of collection ii. dates result reported iii. result iv. laboratory quality control (Y/N)
19a.	Site of disease	Suggested categories i. pulmonary ii. extrapulmonary • if pulmonary is identified, proceed to question 19b, otherwise, skip 19b
19b.	Chest roentgenogram	Suggested variables i. cavitary vs. non-cavitary ii. extent of parenchymal disease
20	New or retreatment	If retreatment indicate if patient qualifies as *interruption, relapse, or treatment failure*
21	Initial regimen	Suggested variables i. drugs used ii. frequency of use (daily or intermittent) iii. duration of use (in months) iv. dose (mg)
22	Weight (kg) and height (cm)	Calculate body mass index with weight and height data

MONITORING

No.	*Variable*	*Comments, explanation, or examples*
23	Sputum smear	Suggested variables i. date ii. result • preferred interval: 2, 3, 4, 5, 6 months and then every three months until treatment is completed **Note: "conversion" does not imply "cure"**
24	Culture	Same as 23.
25	Drug susceptibility test	Every three months until patient converts to culture-negative status
26	Chest roentgenogram	Suggested variables i. cavitary vs. non-cavitary • preferred interval: 3, 6, 12, 18, 24 months (i.e. duration of treatment)
27	Weight	3, 6, 12, 18, 24 months (i.e. duration of treatment)
28	Changes in drug regimens	Suggested variables i. date ii. drug discontinued (if any) iii. new drug added (if any) iv. drug dose changed (if any) v. if yes to iv, record changes in dose
29	DOT performance	Number of doses directly observed / total number of doses
30	Adverse drug reaction	Suggested variables i. suspected drug(s) ii. date of onset of reaction(s) iii. description of reaction(s) • Classify reactions as follows: a) minor side effects b) toxic reactions c) hypersensitivity reactions d) idiosyncratic reactions e) reactions not classified in any category above
31	Treatment interruption (any)	Suggested variables i. source (doctor or patient) ii. date treatment interrupted iii. duration of interruption

OUTCOMES

No.	*Variable*	*Comments, explanation, or examples*
32	Outcome	Suggested categories (standard WHO/IUATLD) i. treatment completed and date ii. cure and date iii. death and date iv. default and date (date of last contact with health services) v. failure and date vi. transfer and date
33	Interim Outcomes	Evaluated at 6, 12, 18, 24 months: i. vital status (dead or alive) ii. status of treatment (default, continuing, or transfer) iii. smear result iv. culture result

Annex 10

SECOND-LINE ANTI-TB DRUGS INCLUDED AS RESERVE ANTI-INFECTIVE AGENTS ON THE WORLD HEALTH ORGANIZATION MODEL LIST OF ESSENTIAL DRUGS (REVISED 1999)

Drug (class)	Formulation
Amikacin (aminoglycoside)	powder for injection: 1000 mg/vial
Capreomycin	powder for injection: 1000 mg/vial
Ciprofloxacin (fluoroquinolone)	tablet: 250 mg or 500 mg
Cycloserine	tablet: 250 mg
Ethionamide (thioamide)	tablet: 125 mg or 250mg
Kanamycin (aminoglycoside)	powder for injection: 1000 mg/vial
Levofloxacin (fluoroquinolone)	tablet: 250 mg or 500 mg
Ofloxacin (fluoroquinolone)	tablet: 250 mg or 400 mg
Para-aminosalicylic Acid - PAS	tablet: 500 mg granules: 4 g sachet
Prothionamide (thioamide)	tablet: 125 mg or 250mg

SUGGESTIONS FOR FURTHER READING

It is *strongly recommended* that the following documents be consulted and used in consort with these Guidelines:

WHO. *Basis for the Development of an Evidence-based Case-management Strategy for MDR-TB within the WHO's DOTS Strategy. Geneva, 1999.* WHO/CDS/CPC/TB/99.260.

WHO. *Guidelines for Drug-susceptibility Testing for Second-line Anti-tuberculosis Drugs for DOTS-Plus.* Geneva, 2001.

WHO. *Guidelines for the Management of Drug-resistant Tuberculosis.* Geneva, 1996. WHO/TB/96.210.

WHO. *Instructions for Applying to the Green Light Committee for Access to Second-line Anti-tuberculosis Drugs.* Geneva, WHO/CDS/TB/2001.286.

WHO. *Treatment of Tuberculosis: Guidelines for National Programmes.* Geneva, 1997. WHO/TB/97.220.

WHO/IUATLD. *Guidelines for Surveillance of Drug-resistant Tuberculosis.* Geneva, 1997. WHO/TB/96.216.

The following documents are suggested for further reading:

Abate G, Miörner H, Ahmed O, et. al. Drug resistance in *Mycobacterium tuberculosis* strains isolated from re-treatment cases of pulmonary tuberculosis in Ethiopia: susceptibility to first-line and alternative drugs. *Int J Tuberc Lung Dis* 1998; 2(7):580-4.

Bastian I, Portaels F. *Multidrug-resistant tuberculosis*. Dordrecht: Kluwer, 2000.

Bastian I, Rigouts L, Van Deun A, et. al. Directly observed treatment, short-course strategy and multidrug-resistant tuberculosis: are any modifications required? *Bull of World Health Organ* 2000; 78(2): 238-251.

Bifani PJ, Plikaytis BB, Kapur V, et. al. Origin and interstate spread of a New York City multidrug-resistant *Mycobacterium tuberculosis* clone family. *JAMA* 1996; 275(6):452-7.

Chaulk CP, Chaisson RE, Lewis JN, et. al. Treating multidrug-resistant tuberculosis: compliance and side effects. *JAMA* 1994; 271(2):103-5.

Codina G, Vidal R, Martin-Casabona N, et. al. Multidrug-resistant tuberculosis caused by 'W'-related strains in three immunocompetent foreign-born patients. *Int J Tuberc Lung Dis* 1999; 3(1):82-4.

SUGGESTIONS FOR FURTHER READING

Coninx R, Mathieu C, Debacker M, et. al. First-line tuberculosis therapy and drug-resistant *Mycobacterium tuberculosis* in prisons. *Lancet* 1999; 353:969-73.

Dye C, Garnett GP, Sleeman K, et. al. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. *Lancet* 1998; 352:1886-1891.

Espinal MA, Dye C, Raviglione MC, et. al. Rational 'DOTS Plus' for the control of MDR-TB. *Int J Tuberc Lung Dis* 1999; 3(7):561-3.

Espinal MA, Kim SJ, Suarez PG, et. al. Standard short-course chemotherapy for drug-resistant tuberculosis. *JAMA* 2000; 283(19):2537-2545.

Farmer PE, Furin JJ, Bayona J et. al. Management of MDR-TB in resource-poor countries. *Int J Tuberc Lung Dis* 1999; 3(8):643-5.

Farmer PE, Furin JJ, Shin SS. Managing multidrug-resistant tuberculosis. *J Respir Dis* 2000; 21(1):53-6.

Farmer PE and Kim JY. Community based approaches to the control of multi-drug-resistant tuberculosis. *BMJ* 1998; 371:671-674.

Frieden TR, Sherman LF, Maw KL, et. al. A multi-institutional outbreak of highly drug-resistant tuberculosis— epidemiology and clinical outcomes. *JAMA* 1996; 276(15):1229-35.

Furin JJ, Mitnick DC, Becerra M, et. al. Absence of serious adverse reactions in a cohort of Peruvian patients receiving community-based treatment for multi-drug resistant tuberculosis (MDR-TB). *Int J Tuberc Lung Dis* 1999; 3(9 S1): S81.

Goble M, Iseman MD, Madsen LA, et. al. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *N Engl J Med* 1993; 328(8):527-32.

Heifets LB, Cangelosi GA. Drug-susceptibility testing of *Mycobacterium tuberculosis*: a neglected problem at the turn of the century. *Int J Tuberc Lung Dis* 1999; 3(7):564-81.

Iseman MD. Treatment of multidrug-resistant tuberculosis. *N Engl J Med* 1993; 329(11):784-91.

Kimerling ME, Kluge H, Vezhnina N, et. al. Inadequacy of the current WHO re-treatment regimen in a central Siberian prison: treatment failure and MDR-TB. *Int J Tuberc Lung Dis* 1999; 3(5):451-3.

Mitchison DA, Nunn AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. *Am Rev Respir Dis* 1986; 133(3):423-30.

SUGGESTIONS FOR FURTHER READING

Park MM, Davis AL, Schluger NW, et. al. Outcome of MDR-TB patients, 1983-1993. Prolonged survival with appropriate therapy. *Am J Respir Crit Care Med* 1996; 153(1):317-24.

Pablos-Mendez A, Raviglione MC, Laszlo A, et. al. Global surveillance for antitiberculosis-drug resistance, 1994-1997. *N Engl J Med* 1998; 338(23):1641-9.

Program in Infectious Disease and Social Change/Open Society Institute. *The Global Impact of Drug Resistant Tuberculosis*. Boston, MA: Harvard Medical School, 1999.

Salomon N, Perlman DC, Friedmann P, et. al. Predictors and outcome of multidrug-resistant tuberculosis. *Clin Infect Dis* 1995; 21(5):1245-52.

Telzak EE, Sepkowitz K, Alpert P, et. al. Multidrug-resistant tuberculosis in patients without HIV infection. *N Engl J Med* 1995; 333(14):907-11.

Turett GS, Telzak EE, Torian LV, et. al. Improved outcomes for patients with multidrug-resistant tuberculosis. *Clin Infect Dis* 1995; 21(5):1238-44.

WHO. *Coordination of DOTS-Plus Pilot Projects for the Management of MDR-TB*. Geneva, 1999. WHO/CDS/CPC/TB/99.262.

WHO. *Global tuberculosis control: WHO Report 2000*. Geneva, 2000. WHO/CDS/TB/2000.275.

WHO. *Procurement of Second-Line Anti-tuberculosis Drugs for DOTS-Plus Pilot Projects.* Geneva, 2000. WHO/CDS/CPC/TB/2000.276.

WHO/IUATLD. *Anti-tuberculosis Drug Resistance in the World. 1st Report.* Geneva, 1997. WHO/TB/97.229.

WHO/IUATLD. *Anti-tuberculosis Drug Resistance in the World. 2nd Report.* Geneva, 2000. WHO/CDS/TB/2000.278.

Printed in Italy
Design and printing: Jotto Associati s.a.s. - Biella - Italy

Stop TB Department
Communicable Diseases Programme
WORLD HEALTH ORGANIZATION

20, avenue Appia
CH-1211 Geneva 27
SWITZERLAND

Telephone 41 22 791 2708
Facsimile 41 22 791 4268