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DRUG RESISTANT TUBERCULOSIS

Practical Guide For Clinical Management

Rafael Laniado-Laborín

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DRUG RESISTANT TUBERCULOSIS

Practical Guide for Clinical Management

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FOREWORD

Drug-resistant tuberculosis (DR-TB) has become one of the main obstacles for global control of the disease. This problem, generated by inadequate treatment is particularly worrisome when resistance includes isoniazid (H) and rifampin (R) simultaneously, the most potent and active drugs against *Mycobacterium tuberculosis*. Treatment for this form of TB known as multidrug-resistant tuberculosis (MDR-TB) requires a minimum of 18-24 months of treatment with drugs that are less effective, more toxic and more expensive than those needed for drug-susceptible TB; unfortunately the rate of success of treatment for this form of TB hardly reach 70%.

As it is well known, prognosis of drug-resistant TB worsens even more when drug resistance extends to include fluoroquinolones and second-line injectables, the two most useful groups of the second-line drugs. This form of TB is known as extensive drug resistant TB or XDR-TB has even worst prognosis with a cure rate of only 50%.

Unfortunately, the extensive and inadequate use of rifampin in the past 30 years has generated an ever increasing number of MDR-TB cases that has reached epidemic levels in some regions of the world. It is estimated that by the year 2013 there were more than 480,000 cases of MDR-TB and that more than half of them were new cases never treated before, and thus the result of transmission of drug-resistant strains in the community and confirms its epidemic nature.

This growing scenario of MDR and XDR-TB has many experts considering that we are going to face soon forms of TB that will be virtually incurable. This, however, is not true since all forms of TB, even those with the most extensive degree of resistance have a possibility of being cured. This will depend decisively on the adequacy of the medical treatment available and this in turn will depend on the standards of quality for the programmatic management of TB by national TB programs.

For this reason, sound clinical management of patients with suspected or confirms DR-TB is fundamental for successful management. And here lies the problem, since DR-TB is a relatively recent phenomenon for which, the best clinical approach has not been fully standardized. Standardization of this complex clinical problem is therefore urgently needed. That is why, that books like this one, written in a rational and simple style by Dr. Laniado, are very helpful for clinicians caring for these unfortunate patients.

I was fortunate to meet Dr. Laniado in his native Tijuana, Mexico. And from the beginning I knew that I had the luck to become acquainted with a clinician that not only had exquisite

knowledge of TB and MDR-TB, but also had the passion and dedication to his patients and the will to explore to the maximum their possibilities of being cured. During all these years, many patients have benefited from the quality and warmth that Dr. Laniado offers them every day. He has published extensively from his TB Clinic in Tijuana. And now we are in luck that he has dedicated innumerable hours to this book in which in a very straightforward way presents the fundamental principles of the best clinical management that can be offered to these patients. There will be many clinicians, pulmonologists and nonpulmonologists that will benefit from this nice treatise.

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"We have known how to cure TB for more than 50 years. What we have lacked is the will and the resources to quickly diagnose people with TB and get them the treatment they need."

Nelson Mandela, (1918-2013)

PREFACE

The emergence of highly drug-resistant strains of *Mycobacterium tuberculosis* (MTB) threatens to undermine global advances in tuberculosis (TB) control and challenges the goal of elimination of TB in the 21st century; unfortunately, despite rampant drug resistance in many regions of the world, TB is still extremely unpopular as a field of interest to clinicians, policymakers, and the media.

We have unfortunately witnessed an accelerated progression in resistance in many of the high TB-burden countries: multidrug-resistant TB being followed by extensively drug-resistant which in turn has been followed by what has been called totally drug-resistant TB which represents the most extreme form of amplified drug resistance.

The main objective of this practical guide is to help those physicians who are not experts in drug resistant tuberculosis but have to diagnose and treat such cases in everyday practice. It includes a description of the latest diagnostic tests and treatment regimens for the different types of drug-resistant tuberculosis. In the last chapter, we have included a series of hypothetical cases to illustrate some of the most frequent problems encountered while treating patients "in the real world". I sincerely hope that this work meets its goal.

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CHAPTER 1

Epidemiology of Drug Resistant Tuberculosis

Abstract: In its Global Tuberculosis Report for 2013, the World Health Organization (WHO) estimated a total of 8.6 million tuberculosis (TB) incident cases and 1.3 million deaths from the disease during the previous year. Most of the drug resistant TB (DR-TB) cases were not even detected due to a variety of weaknesses of national TB programs. Only 28% of the 300,000 pulmonary TB patients expected to have MDR-TB in the world were reported; the WHO estimates that globally 3.6% of new TB cases and 20.2% of previously treated cases have MDR-TB, and of those, approximately 9.6% will have XDR-TB. In 2012 only 5% of the strains from new bacteriologically-confirmed TB cases and 9% of those previously treated for TB were cultured and tested for drug susceptibility. Outcome of treatment for patients with extensively drug resistance TB (XDR-TB) in a cohort from 26 countries was dismal with an overall cure rate of 20% and a 44% death rate.

Keywords: Bacteriological, Cohort, Countries, Death, DOT, Drug, Epidemiology, Global Report, MDR-TB, Pulmonary, Rates, Resistance, Self-administered, Tuberculosis, WHO, XDR-TB.

INTRODUCTION

The epidemic of drug resistance tuberculosis has evolved over the past 40 years, with resistance patterns progressively more complex and difficult to treat [1, 2].

In its Global Tuberculosis Report for 2013, the World Health Organization (WHO) [3] estimated a total of 8.6 million tuberculosis (TB) incident cases and 1.3 million deaths from the disease in 2012. Most of the drug resistant TB (DR-TB) cases are not even detected due to a variety of weaknesses of national TB programs (lack of access to medical care, lack of laboratory support, insufficient drugs supply, *etc.*).

Globally, only 28% of the estimated 300,000 MDR-TB cases were reported [3]. The WHO estimates that 3.6% of newly diagnosed TB cases and 20.2% of previously treated cases will have MDR-TB; of those an estimated 9.6% will have

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XDR-TB, and according to that 2013 report, at least one case of XDR-TB has been reported in 92 countries. In 2012 only 5% of the strains from new bacteriologically-confirmed TB cases and 9% of those previously treated for TB were cultured and tested for drug susceptibility (DST) [3]. Reaching the WHO proposed goals of performing DST in at least 20% of new cases and in 100% of previously treated cases will be extremely difficult, since the countries with the highest burden of disease are those with the lowest income, with limited or no available laboratory facilities with the infrastructure needed for DR-TB diagnosis.

Drug susceptible TB has an expected cure rate of ≥95%; outcomes of treatment for patients with drug resistance are much lower. Globally, rates of success for treatment of MDR-TB are barely around 70%. Cure rate for extensively drug resistance TB (XDR-TB) in a 2012 cohort from 26 countries was even worst with an overall cure rate of 20% and a 44% death rate [3].

The heart of the WHO DOTS strategy is the directly observed treatment (DOT) component to guarantee adequate adherence, and although a recent meta-analysis [4] reported no statistical differences in rates of treatment failure, clinical relapse or acquired drug resistance between DOT and self-administered regimens (SAT), there might be concealed bias in the estimates, since patients are reported by TB programs frequently as in DOT when in reality they are under SAT [5].

CONFLICT OF INTEREST

The author confirms that this chapter has no conflict of interest.

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None declared.

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CHAPTER 2

Mycobacterium Tuberculosis: Etiological Agent of Tuberculosis

Abstract: The *Mycobacteria* genus, member of the *Mycobacteriacea* family and *Actinomycetales* order, are nonmotile, nonsporulating, acid-fast bacilli, 2-4 μ in length and 0.2-0.5 μ in width. Their waxy cell wall, rich in mycolic acid plays an important role in its resistance to many antibiotics. The *Mycobacterium genus* can be separated into two major groups. One group includes the *Mycobacterium tuberculosis* complex and the other includes non-tuberculous (also known as environmental) mycobacteria. The *Mycobacterium tuberculosis* complex includes *M. tuberculosis (Mtb), M. canettii, M. africanum, M. microti*, *M. bovis*, *M.caprae* and *M. pinnipedii*. Mycobacteria are facultative intracellular bacteria that multiply within phagocytic cells. In addition to the ability to acquire new resistance through the acquisition of chromosomal mutations, *Mtb* has a variety of intrinsic resistance mechanisms that allow active neutralization of antibiotic actions. *Mtb* intrinsic drug resistance can be divided into two categories: passive resistance and specialized resistance mechanisms; besides the cell wall barrier that helps slow down the penetration of antibiotics, *Mtb* operates multiple specialized resistance mechanisms that allow active detoxification of drugs once they reach the cytoplasmic space. *Mtb*, acquired drug resistance is caused by spontaneous random mutations in chromosomal genes, facilitating the selection of resistant strains during sub-optimal drug therapy. Clinically, drug resistance in *Mtb* represents the selection of random genetic mutations, not a change caused by exposure to the medication.

Keywords: Acquired resistance, Actinomicetales, Chromosome, Detoxification, Genus, Intrinsic resistance, *M. africanum*, *M. bovis*, *M. canettii*, *M.caprae* and *M. pinnipedii*, *M. microti*, *M. tuberculosis*, Mutations, Mycobacteria.

INTRODUCTION

The *Mycobacteria genus*, member of the *Mycobacteriacea* family and *Actinomycetales* order, are nonmotile, nonsporulating, acid-fast bacilli, 2-4 μ in length and 0.2-0.5 μ in width. Their waxy cell wall, rich in mycolic acid plays and is responsible for many of its biological characteristics: acid-fastness, variable degrees of hydrophobicity, resistance to drying, extreme changes in pH, and very

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important from a clinical point of view, at least in part, resistance to many antibiotics [1]. Both acid-fastness and low permeability are due to the presence of long chain α-alkyl, β-hydroxy fatty acids in the cell wall [2].

The *Mycobacterium genus* can be separated into two major groups on the basis of their growth rate in solid cultures. One group includes slow-growing species: *Mycobacterium tuberculosis* complex, *Mycobacterium bovis* and *Mycobacterium leprae* (etiological agents of human tuberculosis, bovine tuberculosis and leprosy respectively); the other group includes fast-growing species such as *M. fortuitum* and *M. chelonae/abscessus*. The *Mycobacterium tuberculosis* complex refers to a group of species (*M. tuberculosis (Mtb), M. canettii, M. africanum, M. microti*, *M. bovis*, *M.caprae* and *M. pinnipedii*) that are genetically very similar. Although many mycobacterial species are environmental, *Mtb* is strictly parasitic and infects more than one-third of the world's human population. *M. canettii* and *M. africanum*, closely related to *Mtb*, can also cause human tuberculosis. In most cases reported in the literature this species has been isolated from African patients. *M. bovis* can infect humans, domestic or wild bovines and goats. Humans will usually acquire the infection by consumption of unpasteurized milk or unpasteurized milk products (*e.g.* fresh cheese). *M. caprae* has been isolated only from goats. *M. microti* is a rodent pathogen, usually isolated from voles that can also cause disease in immunocompromised human patients. Finally, *M. pinnipedii* infects seals [2].

As mentioned, *Mycobacterium tuberculosis* (*Mtb*) is a member of the *Mycobacterium tuberculosis* complex, characterized by a 24-36-hour division rate and prolonged culture period in solid media (4-8 weeks). As mentioned mycobacteria are facultative intracellular bacteria that multiply within phagocytic cells. If environmental conditions requires it, *Mtb* metabolism mode can change from an aerobic mode that obtains most of its energy from carbohydrates, to one with reduced oxygen requirements, obtaining most of its energy requirements from lipid substrates. When cultured in solid media (either Middlebrook's 7H10 agar medium or Lowenstein-Jensen egg based medium) *Mtb* colonies are small and beige colored [1, 2].

Basic Mechanisms of Drug resistance in *Mycobacterium Tuberculosis*

Although even wild strains of *Mycobacterium tuberculosis* will have some drug resistant bacteria as a result of spontaneous random mutations, the proportion in a given population of bacteria is so low (<1%) that this resistance is not clinically relevant. Significant drug resistance in TB, in the clinical setting is defined as the genetically increased capacity to survive and multiply when exposed to a specific drug (or drugs) in comparison to drug-susceptible bacillβ [3]. Furthermore, in addition to the ability to acquire new resistance through genetic mutations, *Mtb* has a variety of biological resistance mechanisms that allow active neutralization of antibiotic actions.

Mtb intrinsic drug resistance can be divided into two categories: passive resistance and specialized resistance mechanisms [4].

Passive Resistance Mechanisms

Mtb cell wall plays an important role in mycobacterial physical resistance mechanisms against antibiotics, limiting the degree of penetration of some of the antituberculosis drugs. Mycobacterial cell wall is thick, multi-layered and hydrophobic, preventing the transport of hydrophobic molecules, including antibiotics. Nonetheless, due to the prolonged doubling time of *Mtb* (24-36 hrs.), even the slow penetration rate of some antibiotics might in some cases be high enough to allow drugs to accumulate to inhibitory levels before cell division occurs [3 - 5].

Efflux mechanisms (mechanisms that transport compounds out of the cell) have also been recognized as an important factor in physical resistance of drug resistance in mycobacteria. Efflux pumps are physiologic mechanisms of mycobacteria for transportation of nutrients, toxins and waste through the cell wall. These mechanisms have evolved in mycobacteria and can also expel antibiotics using efflux pumps, including fluoroquinolones and aminoglycosides, among others [4].

Mycobacterium tuberculosis in most cases of human infection is inhaled to the lungs. *Mtb* are then phagocyted by alveolar macrophages and contained in

CHAPTER 3

Biological Basis for Drug Resistant Tuberculosis

Abstract: This chapter deals with the classification and mechanisms of drug resistance in tuberculosis, from mono-resistant to extensive drug resistance (XDR) strains. Resistance can be classified as "new cases" for patients never treated before (or treated for less than a month) with antituberculosis drugs and infected by an already drug resistant strain, and "previously treated cases". There are multiple factors associated to drug resistance but they can be grouped in three basic categories: clinical, biological and social factors. Clinical factors include, among others, inadequate treatment regimens (wrong drugs, wrong doses), using drugs of unproven quality, drug shortages, and treatment with weak regimens by private physicians. Biological factors can include factors both the host and from the mycobacteria: being infected with an already resistant strain or host immunosuppression. Social factors include residing in areas with high rates of DR-TB, extreme poverty and lack of social support, illiteracy, poorly structured and supported TB control programs and lack of political compromise.

Keywords: AIDS, Beijing, Extensive drug resistance, HIV, Immunosuppression, MDR, Mono-resistance. poly-resistance, Multidrug resistant, Mycobacteria, Susceptible, Virulent, XDR.

INTRODUCTION

Definition and Classification of Drug Resistance to Antituberculosis Drugs

Drug resistance to antituberculosis drugs is defined as [1]:

a. Mono-resistance: resistance to one antituberculosis drug
b. Poly-resistance: resistance to two or more antituberculosis drugs that are not isoniazid and rifampin simultaneously
c. Multidrug resistance (MDR-TB): simultaneous resistance to at least isoniazid and rifampin simultaneously
d. XDR TB: extensively resistant strains that are resistant to at least isoniazid and rifampin from the first line drugs, plus resistant to any fluoroquinolone and at least to one of the second line injectables (kanamycin, amikacin, capreomycin)

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e. Resistance greater than XDR: also known as totally resistant TB (TDR-TB); it refers to resistance to all 12 traditional antituberculosis drugs

Resistance can also be classified as "new cases" for patients never treated before (or treated for less than a month) with antituberculosis drugs and infected by an already drug resistant strain, and "previously treated cases".

Treatment strategies for tuberculosis are very different from those used in other bacterial infections. *M. tuberculosis* has a very prolonged generation time (>24 hours); it has also the ability to adopt a latent status with virtual shutdown of all metabolic activity making it a difficult target for most therapeutic agents. *Mtb* thrives in lung cavities and even survives in necrotic areas, sites where penetration of antibiotics is low and where the acidic tissue pH inhibits most antimicrobials including the antituberculosis injectables (pyrazinamide on the other hand is highly active in the acidic intracellular environment). Concentrations of mycobacteria will vary within a host depending on the site: mycobacteria will rapidly multiply on the oxygen-rich lung cavities, while they will adopt a latent status, multiplying only occasionally within necrotic foci [2].

Factors Associated to The Development of Drug Resistance

There are multiple factors associated to drug resistance but they can be group in three basic categories: clinical, biological and social factors.

Clinical factors include, among others, inadequate treatment regimens (wrong drugs, wrong doses), using drugs of unproven quality, drug shortages, treatment with weak regimens by private physicians.

Biological factors can include factors both the host and from the mycobacteria: being infected with an already resistant strain (new case DR-TB), highly resistant strains (Beijing or "W") or host immunosuppression (HIV, malnutrition, diabetes, *etc.*)

Social factors are very important in the genesis of DR-TB and include residing in areas with high rates of DR-TB, extreme poverty and lack of social support, illiteracy, lack of adherence to treatment regimen, poorly structured and supported TB control programs and lack of political compromise [3].

Prescription of inadequate drug regimens is one of the major culprits involved in the development of DR-TB. A poorly structured (and supported) TB control program will create more drug resistant cases than those that it will be able to treat. This is due to lack of directly observed therapy and poor adherence of self administered treatment, use of drugs of poor quality, treatment of relapses, failures and defaulters with first line drugs without the benefit of DST to determine the presence or absence of drug resistance. Under these conditions, a progressively greater proportion of TB cases will be caused by drug resistant strains. When a TB program is unable to diagnose and treat DR cases, it will only cure drug susceptible cases (and with a lower rate of success than expected due to the conditions just mentioned) and drug resistant cases will be gradually selected. The vast majority of drug resistant cases are cases that have been previously inadequately treated (less than 4% of global MDR-TB cases are new cases) [2].

There are several factors that contribute to the selection of mutant resistant strains in patients previously treated for tuberculosis; these include treatment default associated to intolerance of drug regimen due to side effects and/or toxicity, disbelief of the diagnosis or necessity of treatment, alcohol or drug abuse and neuropsychiatric disease [4].

It is well known that not every subject infected with *Mtb* will develop active disease. Approximately 10% of infected individuals without immunosuppressive diseases will eventually develop clinical active disease, most within 18 months of being infected. However, even with this scenario, in communities with high rates of drug-resistant TB, a substantial proportion of that 10% will have a resistant strain as a causative agent. As mentioned in chapter 2, the time-honored idea that drug resistant *Mtb* strains are less virulent than drug susceptible mycobacteria has been proven wrong by the numerous outbreaks of DR-TB reported in the literature [5].

The Human Immunodeficiency Virus (HIV) epidemic has affected mainly those population groups that have also high rates of tuberculosis (particularly due to the fact that both diseases share a common risk factor which is poverty). Since HIV infection affects cellular immunity, the most vital element of the immune response to tuberculosis infection, the AIDS epidemic has created a dramatic global

CHAPTER 4

Clinical Diagnosis of Drug Resistant Tuberculosis

Abstract: This chapter deals with the clinical diagnosis of drug resistant tuberculosis. Clinical detection of drug resistant tuberculosis requires a high index of suspicion by the clinician based in the information obtained from clinical records and the patient's medical history. Underlying drug resistance must be considered in patients who have been previously treated for TB, especially if there is a history of inadequate treatment regimen, in patients who are not showing significant clinical improvement or lack of bacteriological conversion, in contacts of a known drug resistant case and in chronic cases with a history of multiple treatment regimens. Required information includes a detailed clinical history of past tuberculosis episodes, name, dose and time a particular drug was taken by the patient, adverse reactions while under treatment, previous image studies for comparison purposes and all previous bacteriological studies available from clinical or laboratory records. The initial evaluation must include a thorough physical examination and basic laboratory tests (hemogram, blood chemistry, viral panel for hepatitis and HIV), audiometry, new chest x-rays and obtaining appropriate samples for complete bacteriological studies.

Keywords: Audiometry, Bacteriological conversion, Blood chemistry, Chest x-rays, Clinical, Diagnosis, Hemogram, Hepatitis B, Hepatitis C, HIV, Medical history, Physical examination, Previous treatment.

INTRODUCTION

Clinical detection of drug resistant tuberculosis requires a high index of suspicion by the clinician, a suspicion based in the information obtained from clinical records (when available) and the medical history during the patient clinical evaluation. It is of the utmost importance to identify through culture and drug susceptibility testing a drug resistant case as early as possible to start an effective drug regimen, to avoid the development of further resistance and to stop the transmission of a resistant strain in the community.

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Clinical Classification of Drug Resistant Cases [1 - 4]

New Case:

Patient has never been treated with antituberculosis drugs (or has received them for less than a month)

Relapse:

Is defined as a patient who has become (and remained) culture negative while receiving therapy but after completion of therapy becomes culture positive again or has clinical or radiographic deterioration that is consistent with active tuberculosis.

Default:

Patients that interrupted treatment for one or more months

Failure:

Patient that while under treatment persist with positive culture by the end of the fourth month of treatment

Initial Case Evaluation

When evaluating a case with suspicion of drug resistance the following information must be obtained and documented:

- Demographic data (name, address/phone number when available, date of birth, country of birth, *etc.*)
- Detailed clinical history of past tuberculosis episodes: how many times the patient has been treated, where the patient was treated, name, dose and time (months or years) a particular drug was taken by the patient. This information is vital when deciding a new treatment regimen. Also it is important to obtain information about complications while under treatment (adverse reaction to antituberculosis treatment), surgical procedures, *etc.* If possible all this information should be confirmed from available medical records
- Chest radiograph: beside obtaining a new chest radiograph, every effort should be made to obtain previous studies for comparison purposes
- Other relevant information: co-morbidities and associated treatment drugs (diabetes,

hepatitis B or C, *etc.*), allergies, HIV status, illicit drug use, imprisonment, *etc.*
- Contact investigation (household, work, social)
- Thorough physical examination, including vital signs, weight and height
- Audiometry if injectable second drugs will be included in the regimen
- Basal blood exams: hemogram (CBC: red and white cell count, platelets), renal function (serum creatinine, creatinine depuration, BUN), liver function (ALT, AST, LDH, albumin), serum electrolytes, thyroid function tests (if prothionamide or PAS are included in the regimen)
- HIV testing
- Hepatitis B and C serology for subjects with history of intravenous drug use
- Pregnancy test for women in reproductive age

Underlying drug resistance must be considered if:

- patients who have been previously treated for TB, especially if there is a history of inadequate treatment regimen (defaulted, irregular drug intake, unsupervised treatment, *etc.*)
- patients who are not showing significant clinical improvement
- lack of bacteriological conversion (positive cultures after 4 months of treatment)
- immigrants from regions with high rates of drug resistant tuberculosis
- contacts of a known drug resistant case
- chronic cases with a history of multiple treatment regimens

Every effort should be made to obtain any existing clinical record of previous diagnosis and treatment. It is vital to determine if previous episodes where confirmed by mycobacterial culture and if drug susceptibility testing results are available.

Regarding previous treatment regimens we need to Know:

- When the patient was treated (when did treatment started and when it ended)?
- Where the patient was treated (it might be possible to obtain medical records)?
- What drugs where used (patient might not remember the names but might recall color and size of the pills, if they where injectables, *etc.*)?
- While under treatment did sputum became negative?
- How long did the patient received treatment?
- Was treatment strictly supervised?
- Was drug intake irregular with intermittencies?

CHAPTER 5

Drug Resistant Tuberculosis: Laboratory Diagnosis

Abstract: This chapter covers the available techniques for the diagnosis of tuberculosis (TB) and drug resistant tuberculosis. Definite diagnosis of tuberculosis requires the isolation on culture or the identification by molecular biology methods of *M. tuberculosis* (*Mtb*). Resistance to antituberculosis drugs, once *Mtb* has been identified can be carried through conventional culture methods (phenotypic methods) or molecular biology (genotypic methods). Ideally, susceptibility to at least isoniazid and rifampin should be carried in every case, especially in regions with high burden of drug resistant TB. The World Health Organization (WHO) recommends that at least 20% of all new cases and 100% of previously treated patients should be tested for drug resistance. Although the isolation of *Mtb* in cultures is still considered as the gold standard, advances in the field of molecular biology allows for a much rapid identification of *Mtb*, with excellent sensitivity and specificity. Drug susceptibility testing by phenotypic methods can be carried out in both solid and liquid media, but this process is slow, especially with the time-honored proportions method; we now have available molecular biology methods with excellent reliability for isoniazid and rifampin with results in a matter of hours.

Keywords: Antibiotics, Assay, Automated, BACTEC, Culture, DST, Drug-resistance, Isolation, Isoniazid, PCR, MGIT, MODS, Molecular, *M. tuberculosis*, Rifampin.

INTRODUCTION

Definite diagnosis of tuberculosis requires the isolation on culture or the identification by molecular biology methods of *M. tuberculosis (Mtb)*. Identification of *Mycobacterium tuberculosis* complex is vital as the first step in laboratory diagnosis. Nontuberculous mycobacteria (NTM) are genetically resistant to most antituberculosis drugs and since they are also acid-fast in microscopy a case could be mistakenly diagnosed as tuberculosis. There are several techniques for the identification of *Mtb*. Traditional biochemical testing

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(niacin, catalase inhibition, and nitrate reduction) has a turnaround time of several weeks and has been displaced by several rapid tests: commercial genetic probes (Gen-Probe Amplified MTD, Gene-Probe®, San Diego, California), automated real time PCR (GeneXpert®, Cepheid, Sunnyvale, CA), a lateral chromatography rapid test for the MGIT system (MGIT TBc ID™ identification test, Becton Dickinson) among others.

Ideally, susceptibility to at least isoniazid and rifampin should be carried in every case, especially in regions with high burden of drug resistant TB. The World Health Organization (WHO) recommends that at least 20% of all new cases and 100% of previously treated patients should be tested for drug resistance. If resistance to rifampin (R) is proven the case is classified as pre-MDR (approximately 80% of R resistant cases are also resistant to isoniazid), and susceptibility tests for fluoroquinolones and second lines injectables should be requested to rule out as soon as possible the presence of an XDR-TB strain, and allow treatment with an efficient regimen avoiding the development of further resistance [1].

The traditional method of culture isolation of *Mtb* is still considered as the gold standard for diagnosis. The proportions method described by Canetti [2] allows for drug susceptibility testing (DST) for most of the first (FLD) and second line drugs (SLD), but it requires from 8 to 12 weeks, a major disadvantage for the treating clinician.

The BACTEC MGIT 960® system (Mycobacterial Growth Indicator Tube 960®, Becton Dickinson), is an automated method that has become a standard method for detection of drug resistance to FLD, (excluding pyrazinamide). It uses liquid media (Middlebrook 7 H9) with a fluorescent sensor to detect bacterial growth. Depending on the bacterial load in the sample cultivated, it takes an average of 3 weeks from time of inoculation to reporting of drug susceptibility [3]. Mycobacteria are first isolated in pure culture from clinical specimens (at this time identification with the MGIT TBc ID™ will take only 15 minutes), followed by inoculation of drug-containing broth (indirect method). It is possible to inoculate drug containing media directly with processed samples of AFB positive sputa (direct method); results of FLD DST will available in less than two weeks

[4]. However, the direct method for DST has a much higher rate of contaminated cultures resulting in failure rates up to 15% and therefore is rarely used. One important limitation of BACTEC MGIT 960® system is the high cost of the reagents. Because of its higher rate of contamination, cultures on liquid media should always have the backup of simultaneous cultures on solid media (*e.g.* Lowenstein-Jensen media and Stonebrink media in regions with high prevalence of disease by *Mycobacterium bovis*) [5].

Rapid Phenotypic DST Methods

There are some low cost phenotypic methods for DST that the WHO recently validated. These methods for rapid detection of resistance include the MODS assay and the nitrate reductase assay (NRA; Griess method).

The NRA (Griess method) is carried out in solid media supplemented with sodium or potassium nitrate as indicator of growth. Mtb possesses an **enzyme** (nitro-reductase) that reduces nitrate to nitrite; this reaction will produce a change in the color of the media (green in Lowenstein Jensen media) to red-purple when the Griess reagent is added to the media (Fig. **5.1**). The change in color in the media with an antibiotic means that the strain is resistant to this particular drug. Susceptibility to FLD can be determined in 8-10 days after obtaining a positive culture [6].

The Microscopic-Observation Drug-Susceptibility (MODS) assay uses liquid media (7H9 supplemented with OACD) in 24-well tissue-culture plates containing a combination of antibiotics (PANTA: polymixin, amphotericin B, nalidixic acid, trimethoprim and azlocillin) to prevent contamination with bacteria and fungi; antituberculosis drugs are added to media that then inoculated with the sputum sample; 12 wells are used: 4 control wells with no drugs, and two different concentrations of 4 antituberculosis drugs being tested in the remaining 8 wells. The cultures are examined under an inverted light microscope. Positive cultures are identified by cord formation, characteristic of *M. tuberculosis* growth in liquid media. The average time to culture positivity (and DST results) is about a week. Unlike other rapid methods the results of MODS are not affected by smear status [7].

CHAPTER 6

Antituberculosis Drugs

Abstract: This chapter includes a comprehensive review of all drugs to treat tuberculosis. The WHO has classified these drugs in five groups, with drugs in Group 1 being the most effective, and less toxic and drugs in Group 5 being drugs with unproven efficacy or frequent side effects and/or toxicity. Each drug is discussed in detail, including its mechanisms of action, suggested doses and side and adverse effects, as well as the required clinical and laboratory monitoring for each drug. Recently added drugs bedaquiine and delamanid are also included in this review.

Keywords: Adverse effects, Antituberculosis drugs, Bedaquiline, Cycloserine, Delamanid, Dose, Effectiveness, Ethambutol, Ethionamide, Fluroquinolones, Injectables, Isoniazid, Laboratory, Linezolid, Monitoring, PAS, Pyrazinamide, Rifampin, Toxicity, WHO .

INTRODUCTION

The WHO has classified the antituberculosis drugs in five groups [1 - 3], with drugs in Group 1 being the most effective, and less toxic and drugs in Group 5 being drugs with unproven efficacy or frequent side effects and/or toxicity [4].

GROUP 1 DRUGS: FIRST LINE ORAL ANTITUBERCULOSIS DRUGS

Isoniazid (H)

Isoniazid is a potent bactericidal drug against *M. tuberculosis*, especially during the first few days of treatment exercising its maximal effect on mycobacteria with high metabolic rates. It blocks the synthesis of mycolic acid, a vital component of the mycobacterial wall leading to cell death. It is extremely effective against the large population of extracellular and intracavitary mycobacteria, rapidly reducing infectiousness.

It is recommended at a dose of 5 mg/kg/day orally (PO) up to a maximum of 300

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mg/day. In children H is recommended at a dose of 10-15 mg/kg up to 300 mg daily (or 20-30 mg/kg two or three times a week). High dose H (16-18 mg/kg) has been used in patients with low-level resistance to H in the DST.

H is inactivated in the liver through acetylation and it can exacerbate liver damage if already present and cause hepatitis in patients without pre-existing liver disease. Liver enzymes (alanine transaminase [ALT] and aspartate transaminase [AST]) will increase in 10-20% of patients without clinical significance (<3 times the upper limit of normal) and does not require stopping the treatment.

H does not need dose adjustment in patients with renal failure.

H has a pharmacological interaction with phenytoin and carbamazepine increasing serum levels of both drugs.

Vitamin B6 (50-100 mg PO daily) should be added to the drug regimen in patients with risk of polyneuritis (diabetes, malnutrition, alcoholism, pregnancy) and in patients receiving high doses of H.

Absorption is better with an empty stomach; food with high fat content decreases its absorption in up to 50%.

H is safe during pregnancy and breastfeeding.

Some strains of *M. tuberculosis* display low grade resistance to H (0.2 I1/4g/mL) but are susceptible at higher concentrations (1.0 I1/4g/mL). H can be used in these circumstances at high doses (900 mg three times a week). It should not be used in patients with strains displaying high degree of resistance who have failed in the past with an H containing regimen [5].

Adverse Effects:

1. Hepatitis (directly related to patient's age with increased frequency in older patients). It usually subsides after stopping the drug, but in some cases can lead to acute liver failure
2. Peripheral polyneuritis (prevented with vitamin B6)
3. Optic neuritis (infrequent)
4. Arthralgia (infrequent)

5. Drug induced lupus-like syndrome (infrequent)
6. Psychosis (infrequent)

Monitoring:

In patients receiving other hepatotoxic drugs (or in those with preexisting liver damage, *e.g.* chronic viral hepatitis) liver function tests should be obtained at the start of treatment and then periodically (monthly) thereafter. Serum levels of H are recommended only in patients with suspected malabsorption or those with delayed bacteriological conversion.

Ethambutol (E)

Ethambutol is a bacteriostatic drug (inhibits cell wall synthesis) for oral use. Its importance resides in the fact that when used in a multiple drug regimen it will delay the development of resistance. The recommended dose is 15-25 mg/kg/day. In patients with multidrug resistant TB it should be started with the higher dose. Its absorption is not affected by food. Since it is eliminated through the kidneys, a dose of 30 mg/kg three times a week and serum levels are recommended in patients with renal failure to reduce the probability of serious adverse effects. No dose adjustment is required in patients with liver failure.

Adverse Effects:

1. Optic neuritis (dose-dependent). It is its more frequent adverse effect characterized by a decrease is visual acuity and the ability to discriminate red and green colors. Drug must be stopped immediately because damage is usually irreversible
2. Hypersensitivity
3. Peripheral paresthesia
4. Nausea, vomiting, anorexia, abdominal pain
5. Headache, dizziness

Monitoring:

Visual acuity and color discrimination (Snellen and Ishihara tests; Fig. **6.1**) at start of treatment and monthly thereafter.

CHAPTER 7

Treatment of Drug Resistant Tuberculosis

Abstract: This chapter covers the strategies recommended to build an effective regimen for drug resistant tuberculosis. Treatment outcomes for multidrug resistant tuberculosis (MDR-TB) and beyond show a progressively lower cure rate as the resistance pattern became more complex. Basically all treatment recommendations for drug-resistant tuberculosis are based on expert opinion, with just a few available clinical trials. Rifampin is the most important drug in the first line regimen; if the strain is resistant is considered as pre-MDR TB and the patient must be treated for at least 18 months. There are two types of MDR-TB patients: patients who have never been treated for tuberculosis in the past and that were infected with an already resistant strain and patients previously treated for tuberculosis. The latter are much more frequent and more difficult to treat. To design a regimen for MDR-TB the following order is recommended: include ethambutol and/or pyrazinamide (WHO recommends the use of pyrazinamide regardless of the results of the drug susceptibility testing); however this drugs should not be counted as effective drugs. As a second step, a second line injectable (amikacin, kanamycin or capreomycin) will be included. Then add a fluoroquinolone (levofloxacin or moxifloxacin). Finally to complete the regimen add as many drugs from Group 4 (ethionamide, cycloserine and PAS) as needed. If necessary, include drugs from group 5. The first choice will be linezolid.

Keywords: Amikacin, Bedaquiline, Capreomycin, Clofazimine, Cycloserine, Delamanid, Drug-resistant, Ethambutol, Ethionamide, Fluoroquinolones, Kanamycin, Linezolid, Meropenem, New cases, PAS, Previously treated, Pyrazinamide, Treatment, Tuberculosis.

INTRODUCTION

A recent meta-analysis of treatment outcomes for MDR-TB and beyond, that included over 7,000 patients from 26 treatment centers showed a progressively lower cure rate as the resistance pattern became more complex. The treatment success rate progressively decreased from 64% for patients with MDR-TB without additional resistance, to 56% for MDR-TB+resistance to an SL injectable *only*, to 48% for MDR+resistance to a fluoroquinolone *only* and to 40% for XDR-

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TB [1].

When to suspect drug resistance in a patient with tuberculosis [2 - 4]:

1. Patients who are failing while under treatment (viable microorganisms in culture after four months of directly observed therapy (DOT)
2. Presence of positive cultures after the patient had converted his/her sputum cultures
3. Patients with bacteriologically proven relapse (especially if the patient was treated without supervision (with irregular drug intake being a strong possibility)
4. Patients who have migrated from regions with high prevalence of drug resistant tuberculosis
5. Chronic patients who have received multiple courses of antituberculosis drugs

A high degree of suspicion in these scenarios will allow an earlier detection and start an effective treatment in a drug resistant case which will translate into a better prognosis for the case and a faster curtailment of transmission of a drug resistant case in the community.

Progressive clinical and/or radiographic findings or persistence of positive sputum smears and cultures must raise the suspicion of drug resistance, even in a new case. If not already done, cultures and drug susceptibility (DST) tests must be ordered as soon as possible.

When the case is a relapse (patient treated in the past and discharged as cured) the possibility of drug resistance must be considered; cultures and DST must be ordered ***in every case***. A history of previous treatment (especially if it was self-administered) is one of the most important risk factors for the development of drug resistance. Patients that were treated under direct supervision (DOT) have a lower risk of harboring a drug resistant strain (but cultures must be processed ***in every case***). Factors involved in early relapses (which actually are disguised failures) include lack of adherence to treatment, inappropriate drug regimen (inadequate doses, insufficient number of drugs), malabsorption and exogenous infection with a different *M. tuberculosis* drug resistant strain. When a new case received a strong regimen under DOT, is highly likely that the relapse is due to drug susceptible mycobacteria (reactivation of latent bacteria that were not killed during treatment). In these cases, treatment with the same regimen can be started

while waiting for the DST. Conversely, if treatment was not supervised and/or irregular and the patient is gravely ill, is immunosuppressed, or has central nervous system involvement, a standardized second line drug regimen should be started while waiting for the DST [2].

TREATMENT OF DRUG RESISTANT TUBERCULOSIS (TABLE 7.1)

Basically all treatment recommendations for drug-resistant tuberculosis are based on expert opinion, with just a few available clinical trials. For this reason, patients with MDR and XDR should be preferably treated by a clinician with experience in drug resistant tuberculosis [2 - 4].

Table 7.1. Drugs used in the treatment of drug resistant tuberculosis.

GROUP	DRUGS
Group 1. First line, oral drugs	Isoniazid (H), rifampin (R), Ethambutol (E), pyrazinamide (Z)
Group 2. Second line injectables	Amikacin (Am), Capreomycin (Cm), Kanamycin (Km)
Group 3. Fluoroquinolones	Ofloxacin (Ofx), Levofloxacin (Lfx), Moxifloxacin (Mfx), Gatifloxacin (Gfx)
Grupo 4. Second line oral drugs	Ethionamide (Et), Prothionamide (Pt), Cycloserine (Cs) Para-aminosalicylate (PAS)
Grupo 5: Drugs with modest to no evidence of efficacy (except for Linezolid)	Clofazimine (Cfz), Amoxicillin/Clavulanate (Amx/Clv), Clarithromycin (Clr), Linezolid (Lzd), Imipenem/Cilastatin (Imp/Cln)

TREATMENT FOR MONO-RESISTANCE [3]

Isolated Resistance to Isoniazid (H)

Patients can be treated with E-R-Z daily for 9 months; in cases with extensive disease a fluoroquinolone (Mfx/Lfx/Gfx) could be added to the regimen to substitute H (R-E- Z-FQ) in a daily regimen for at least 6 months.

Isolated Resistance to Rifampin (R)

Rifampin is the most important drug in the first line regimen; if the strain is resistant to R the case will be considered as pre-XDR TB. Patient can be treated

CHAPTER 8

Adverse Effects and Toxicity of Antituberculosis Drugs

Abstract: This chapter covers side and adverse effects associated to antituberculosis treatment. Gastrointestinal side effects are usually the first to appear after the start of treatment, with nausea and vomiting being the most common. Drug regimens for multidrug resistant tuberculosis include drugs that very frequently produce side effects and/or toxicity that sometimes require the definitive suspension of the drug. Almost all patients undergoing drug treatment for MDR-TB experience some type of side effects and/or toxicity that involve a modification of the drug regimen in up to 50% of the cases. A problem associated to second-line drugs is that several of these drugs share side effects and toxicities, which makes it difficult sometimes to determine which drug is the culprit. It is extremely important to avoid as much as possible interruptions in treatment due to side effects because this decreases the effectiveness of the regimen and increases the risk of amplifying drug resistance. Peripheral neuropathy is more common in patients that are already prone to it such as diabetics, alcoholics, pregnant and malnourished patients. All antituberculosis injectable drugs are toxic to the eight cranial nerve and can cause both vestibular (equilibrium) and cochlear (auditory) damage. Hepatic toxicity is the most common adverse effect of antituberculosis treatment and its severity can range from asymptomatic elevation of liver enzymes to fulminant liver insufficiency with encephalopathy and high mortality. Although any patient under treatment with antituberculosis drugs can develop hepatic toxicity, patients with previous liver damage are at higher risk of this complication.

Keywords: Adverse, Ataxia, Creatinine, Effects, Enzymes, Hepatotoxicity, Hypersensitivity, Liver, MDR-TB, Neuropathy, Renal failure, Stevens-Johnson, Toxicity, Optic neuritis, Urticaria, Vestibular, Vertigo.

INTRODUCTION

Patients undergoing treatment for pan-sensitive tuberculosis usually tolerate the drug regimen without any significant side effect or toxicity, and when they do, these are usually moderate and transient. Quite the opposite, drug regimens for multidrug resistant tuberculosis include drugs that very frequently produce side

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effects and/or toxicity that sometimes require the definitive suspension of the drug.

The true frequency of these side effects is unknown because they are usually not notified by the treating physician and thus are not reported. Clinical experience shows that almost all patients undergoing drug treatment for MDR-TB experience some type of side effects and/or toxicity that involve a modification of the drug regimen in up to 50% of the cases.

A problem associated to second-line drugs is that several of these drugs share side effects and toxicities, which makes it difficult sometimes to determine which drug is the culprit. Although the frequency of very severe side effects is low, in some cases they can be life-threatening, including anaphylactic reactions, Stevens-Johnson syndrome and erosive gastritis with gastrointestinal bleeding, fulminant hepatitis and renal failure.

When a patient has an adverse effect during treatment, the first step will be to verify if the drug doses are correct for the patient´s age, weight and special characteristics (diabetic, renal disease, *etc.*); it is vital to rule out that the symptoms are not due to other causes; for example in a patient developing hepatitis, this could be due to a viral infection and not necessarily associated to drug regimen.

It must be discussed with the patient what are the benefits and risks of treating MDR-TB and the need to include several drugs to integrate an effective regimen. It is very important to explain at the onset of treatment, what side effects and toxicity can be associated to the drugs included in the regimen, and also, our limited margin for modifying the drug scheme, with the purpose of achieving their cooperation and tolerance to avoid modification of the regimen when minor side effects are present. The patient must be fully aware that this might be the last opportunity to be cured, and if they default treatment, the next regimen (if there is still an option for an effective scheme) will be more toxic and less effective. They must be assured that every effort will be made to minimize the side effects associated to treatment by adding ancillary drugs for nausea, polyneuritis, heartburn, *etc.*

It is extremely important to avoid as much as possible interruptions in treatment due to side effects because this decreases the effectiveness of the regimen and increases the risk of amplifying drug resistance. We must pay attention to side effects, actively evaluating them at each visit. Most patients are willing to tolerate minor side effects if we reassure them that a certain side effect is not serious and will not produce sequelae.

To minimize the impact of side and adverse effects on treatment adherence it is vital that health personnel is adequately trained and experienced to be able to diagnose and treat complications as soon as they appear. Standardized protocols and ancillary drugs to treat side effects must be in place and available in all tuberculosis programs.

ADVERSE EFFECTS AND TOXICITY [1 - 4]

Hypersensitivity And Cutaneous Reactions

Hypersensitivity. Virtually all antituberculosis drugs can in theory produce a hypersensitivity reaction. If severe, this type of reaction requires in general stopping all drugs until the reaction subsides. Isoniazid, ethambutol, rifampin pyrazinamide, ethionamide and the fluoroquinolones are the more frequently involved. If the reaction is mild and there is no evidence of anaphylaxis, angioedema or respiratory distress, we can try to identify the responsible drug by reintroducing the drug one at a time; it is recommended to start with the most important drug of the regimen, unless that for some reasons that is the suspect drug. Re-challenge with progressively higher doses can be tried as long as the drug is tolerated; for example, the drug can be re-started at $1/10^{th}$ of its original dose, and then if tolerated, increase the drug progressively to its full dose within a week. If the reaction was severe, the challenge must be conducted with the patient hospitalized to be able to immediately treat an anaphylactic reaction. If the drugs are reintroduced without an adverse reaction, the regimen must be then administered 7 days a week including Sundays, since hypersensitivity reactions are seen more frequently during intermittent treatment. If the patient has an anaphylactic reaction or the reaction included systemic manifestations (fever, urticaria, Stevens-Johnson syndrome) re-challenge is contraindicated and a

CHAPTER 9

Follow Up of Drug Resistant Cases During Treatment

Abstract: This chapter describes the recommended routine for follow-up of drug resistant cases during treatment. Directly observed treatment is absolutely indispensable in patients with drug resistant tuberculosis to avoid the development of further resistance due to inadequate adherence. Monthly evaluation should include active search of side effects and adverse reactions through clinical and laboratory studies. Bacteriological follow-up will consist of monthly sputum smears and cultures, and after culture conversion, monthly sputum smears and bimonthly cultures.

Keywords: Hospitalized, Hemoptysis, Isolation, Monitoring, Out-patient, Promoter, Respiratory distress, Risk.

Strict follow up of any patient being treated for tuberculosis is fundamental for success, but directly observed treatment is absolutely indispensable in patients with drug resistant tuberculosis if one has to avoid the development of further resistance due to inadequate adherence.

FOLLOW-UP OF HOSPITALIZED PATIENTS

Some DR-TB patients will require hospitalization at the start of treatment due to disease complications (respiratory distress, hemoptysis) or to detect and treat early drug side effects. However, unless the hospital has the necessary infrastructure to assure strict respiratory isolation of the patient, health personnel and other patients will be at risk of being infected with a resistant tuberculosis strain. For this reason, the vast majority of drug resistant tuberculosis cases will be treated as outpatients.

OUTPATIENT MONITORING [1, 2]

1. Patients will be supervised daily by the health promoter in charge of directly observed treatment including the administration of the injectable

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2. By the treating physician at least biweekly during the first month, and once a month thereafter
3. The health promoter must be able to contact the treating physician within 24 hours if the patient develops side or adverse effects
4. During the monthly visit the following items should be actively sought and evaluated:

a. symptoms attributable to tuberculosis
b. side effects and toxicity of drug regimen
c. physical exam including vital signs, body weight, eye examination (Snellen and Ishihara charts)
d. routine safety laboratory tests: blood count, serum chemistry (including renal and liver function tests), urinalysis. Creatinine clearance should be monitored in patients at risk of renal damage (*i.e.* diabetics) receiving injectables
e. bimonthly thyroid function test in patients receiving ethionamide and or PAS
f. monthly audiogram while under injectable treatment
g. monthly sputum smear and culture examination until culture conversion; after culture conversion process smears monthly and culture bimonthly
h. When available, drug serum levels if malabsorption could be an issue (gastrointestinal diseases, lack of clinical/bacteriological response), in small or large patients to assure adequate blood levels or to adjust doses in case of significant side effects

WHEN CAN ISOLATION AND THE USE OF FACEMASKS CAN BE DISCONTINUED IN A PATIENT WITH DRUG RESISTANT TUBERCULOSIS?

Unlike contacts of drug susceptible tuberculosis that can receive preventive treatment with isoniazid for latent tuberculosis infection, there is no treatment with proven efficacy for latent infection in contacts of MDR-TB/XDR-TB cases [3]. One must be especially cautious when deciding to stop isolation (including wearing a facemask). In MDR-TB isolation should be maintained at least until culture conversion.

CONFLICT OF INTEREST

The author confirms that this chapter has no conflict of interest.

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None declared.

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[PMID: 17217124]

CHAPTER 10

Drug Resistant Tuberculosis in Special Situations

Abstract: There are three special situations in drug resistant tuberculosis that merit a more detail description: HIV co-infection, pregnancy and drug resistant TB in children. HIV co-infection: The risk of reactivation of latent tuberculosis infection is 50-100 times higher for subject living with HIV and up to 170 times higher for those with AIDS. Every patient diagnosed with TB must be tested for HIV infection and *vice versa*. The WHO recommends that ARV treatment in patients recently diagnosed as co-infected with HIV and tuberculosis should start within 8 weeks from the start on antituberculosis drugs.

Pregnancy: The best way to deal with MDR-TB during pregnancy is to prevent it. All females of child-bearing age being treated for MDR-TB should be encouraged to adopt an effective contraceptive method or even a combination of them. Most of the drugs used to treat MDR-TB are classified as unsafe during pregnancy or their safety is unknown.

Pediatric tuberculosis: Unlike the adults, most MDR-TB pediatric cases are the result of infection with an already resistant strain, frequently from contact with a household adult. Children with signs and symptoms compatible with active tuberculosis and risk factors for MDR-TB should be started on MDR-TB treatment even if the diagnosis has not been confirmed bacteriologically.

Keywords: Child-bearing, Children, Co-infection, HIV, Pediatric, Pregnancy.

HIV CO-INFECTION

The WHO estimates that 9 million new TB cases and 1.5 deaths were attributed to TB in 2013, and that one third (approximately 2 billion people) of the world population is infected with *M. tuberculosis*. The WHO also estimates that globally, thirty five million people are living with HIV infection and 1.5 million HIV-related deaths occurred in 2013 [1].

The risk for reactivation of latent tuberculosis infection (LTBI) progressing to active TB is 50-110 times higher for patients with HIV co-infection and 110-170

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times greater for patients living with AIDS. The rate of reactivation of LTBI in immunocompetent individuals (not treated for LTBI) is of 10% for life. The rate of reactivation of LTBI in subjects with HIV infection is approximately 13% *per year* if CD4 cell count is <200, 6% if CD4 count is between 200-350 cells and of 3% if CD4 is >350 cells. Although the number of people dying from HIV-associated TB has decreased since 2004, it was estimated that there were 360 000 deaths from HIV-associated TB in 2013; this corresponds to approximately 25% of all TB deaths [1].

The WHO recommends that every patient with TB should have an HIV test to rule out co-infection (and that every patient seropositive for HIV should be studied to rule out TB. However, less than half of the patients diagnosed with TB worldwide had a documented HIV test result in 2013 [1].

The proportion of HIV patients receiving antiretroviral (ARV) treatment has increased in recent years, currently being at 70%; nonetheless a lot more effort will be needed to reach the ultimate goal of 100% coverage. The proportion of patients with TB co-infected with HIV that are receiving ARV is much lower (less than a third of the patients.

On the other hand, globally only one fifth of the countries globally reported provision of treatment for latent tuberculosis infection in subjects living with HIV in 2013 [1].

TIMING FOR INITIATION OF TREATMENT WITH ARV DRUGS IN PATIENTS CO-INFECTED WITH TB AND HIV

The WHO recommends that ARV treatment in patients recently diagnosed as co-infected with HIV and tuberculosis should start within 8 weeks from the start on antituberculosis drugs [1]. Early initiation of ARV treatment, especially in patients with low CD4+ T-cell counts (<50 per cubic millimeter) increases survival. Deferring the initiation of ARV to the start of the continuation phase of TB treatment (after the first two months) in those with higher CD4+ T-cell counts reduces the risks of Immune Reconstitution Inflammatory Syndrome (IRIS) related to ARV without increasing the risk of AIDS or death [2].

Rifamycins are inducers of cytochrome P-450 and interact with many drugs. Since patients with MDR-TB/XDR-TB are not going to receive rifampin, the interaction of ARV drugs with the TB drug regimen does not represent a problem. Rifampin use will lead to lower level of protease inhibitors and non-nucleoside reverse transcriptase inhibitors [3]. This reduction might be clinically significant in patients over 50 kg (adult patient under 50 kg still get adequate level with standard 600 mg dosing). In adults over 50 kg and on rifampin, expert recommendation is to increase the efavirenz dose to 800 mg total per day. This typically means adding 200 mg of efavirenz to the standard 600 mg. If the efavirenz is in a combo pill (that includes efavirenz, emtricitabine and tenofovir) then just adding 200 mg of efavirenz will be adequate; is important to emphasize that current data is insufficient to support a definitive statement in this regard [4]. While it is true that efavirenz has been extensively used in patients receiving rifampin, in countries with access to many options for ARV treatment drugs without interaction with rifampin could be included in the treatment regimen. Patients that have the co-infection TB-should be treated in collaboration by the TB and HIV programs.

MDR-TB AND PREGNANCY

The best way to deal with MDR-TB during pregnancy is to prevent it. All females of child-bearing age being treated for MDR-TB should be encouraged to adopt an effective contraceptive method or even a combination of them. Most of the drugs used to treat MDR-TB are classified as unsafe during pregnancy or their safety is unknown (Table **10.1**)

Table 10.1. FDA safety classification of medication during pregnancy [5].

A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks

CHAPTER 11

Hypothetical Illustrative Cases

Patients' informed consent was granted to utilize images from their case files to develop these hypothetical cases as long the images are used anonymously.

Abstract: This chapter covers the management of actual MDR/XDR patients with a concise discussion of the importance of previous episodes of TB, the diagnostic algorithm and treatment regimen. Cases with adverse reactions to drugs are also discussed as well as patients with co-morbidities.

Keywords: Adverse reactions, Algorithm, Chest x-rays, Co-morbidities, Culture, DST, Drug-susceptibility tests, GeneXpert®, Management, MDR, Previously treated, Second-line drugs, Toxicity, XDR.

CASE #1

23 year-old male referred to the tuberculosis clinic on June 2010. Negative medical history including smoking, alcohol consumption or illicit drugs.

First diagnosis of tuberculosis in 2005 (based only in positive smears results). Receives treatment with first line drugs (2HZRE/4H_3R_3) for six months. Under DOT only during the intensive phase of treatment. Discharged as cured (negative sputum smears). Relapses in 2006; positive sputum smears, no culture. Treated with auto administered WHO Category II regimen (2HRZES/1HRZE/5$R_3H_3E_3$). Discharged as cured with negative sputum microscopy. Second relapse in 2009 with positive sputum smears. This time was treated by a private physician with an unsupervised regimen of RIZ for 13 months despite persistent positive sputum. The patient develops right pyopneumothorax and the patient is referred to a public hospital. A chest tube is placed and after 2 weeks without lung re-expansion the tube is replaced by an open pleurotomy (Eloesser) for adequate drainage (Fig. **11.1**). Serology for HIV infection was non-reactive. Patient was emaciated weighing only 45 kilograms (BMI 13.1).

Sputum and pleural fluid cultures from admission were positive for *M.*

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tuberculosis complex and resistant to H (at 0.1 µg/mL and 0.4 µg/mL concentrations), R, Z and S; susceptible to E (first line drugs tested with MGIT960®); second line drug DST (BACTEC 460®) reported susceptibility to capreomycin, ethionamide and levofloxacin.

His admission audiometry revealed auditory damage with abnormal levels at high frequencies (hearing threshold at 40 db for 4,000 Hz).

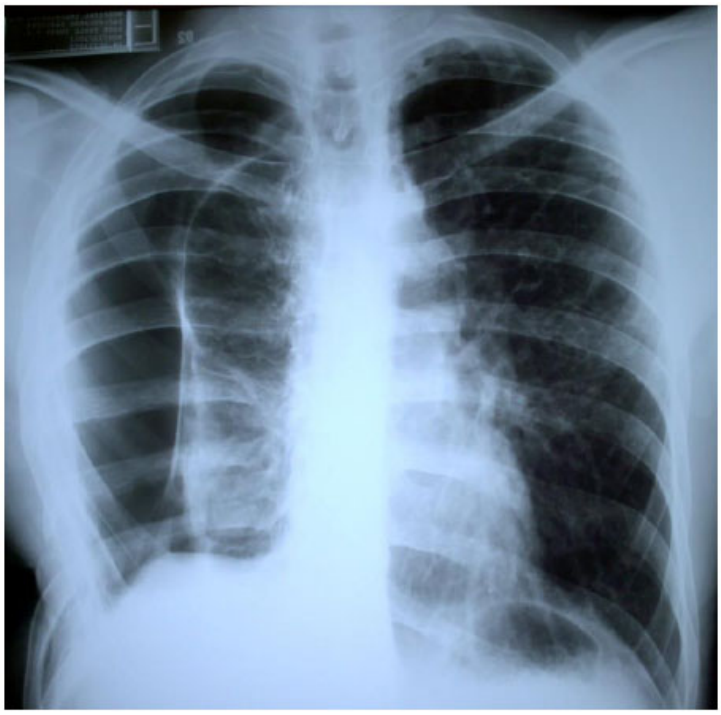

Fig. (11.1). Postoperative chest x-ray with adequate drainage of pus and persistent right pneumothorax and visceral pachypleuritis.

Treatment regimen (started June 2010) included Ethionamide 500 mg QID, Cycloserine 500 mg QID, Levofloxacin (10 mg/kg) 500 mg QID, Ethambutol (25 mg/kg) 1,200 mg QID and Capreomycin (15 mg/kg) 700 mg IM monday through friday. Treatment was directly observed by a health promoter at patient´s home.

The patient converted his sputum cultures after only one month of treatment; the injectable was spaced to three times a week after four months and suspended at

six months. Lung collapse required a thoracotomy (at month 16 of treatment) for pleural decortications, which allowed the lung to fully re-expand.

The patient was discharged as cured after 20 months of treatment after culture conversion (April 2012). He is asymptomatic and culture negative after 2 years of follow-up.

Commentary:

1. Although in most developing countries patients are diagnosed just based on sputum microscopy due lack of local access to culture. However patients that fail relapse or are recovered after default MUST have a sputum culture and drug susceptibility testing (DST) to rule out the presence of drug resistant strains. This patient received treatment 3 times without the benefit of DST. It was later proven that in fact the patient was relapsing due to the presence of a drug resistant strain. Most countries will have regional laboratories or at least a national laboratory that can process cultures and DST. Drug resistance could have been detected years earlier avoiding further morbidity (empyema and need for surgery) and transmission of a resistant strain in the community.
2. Patient was treated with the first line retreatment drug regimen that includes the five first line drugs. This goes against a basic tenet of drug resistant TB treatment: never add a single drug to an empirical regimen when re-treating a TB patient. Since 2003 the WHO has recommended that Category II retreatment should be abandoned [1]. In a retrospective cohort of Category I failures patients were either treated with the empirical Category II regimen (if that regimen failed, a standardized regimen including second-line drugs was used) or with a treatment regimen based on DST [2]. Almost 90% of those with DST´s had MDR-TB. Treatment guided by DST´s was 5 times more effective for attaining cure than the Category II regimen (and even three times for effective than those treated with standardized second-line regimen after failure of Category II treatment).
3. HIV must be ruled out in every patient diagnosed with TB (and TB must be ruled out in every patient diagnosed with HIV).
4. Drug susceptibility testing is reliable for H and R of group one drugs and for fluoroquinolones and second line injectables. In this patient, TB strain was resistant to H at both low and medium concentration. This would suggest cross resistance to ethionamide. Even though the DST showed susceptibility to ethionamide the decision was to start treatment with a 5 drug regimen fearing that there might be resistance to ethionamide *in vivo*.

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