

Zaporizhzhia state medical university
Department of phthiology and pulmonology

R.M. Yasinskiy, Yu.S. Solodovnik

**THE GENERAL PRINCIPLES AND METHODS
OF TREATMENT
OF PULMONARY TUBERCULOSIS**

STUDY GUIDE

**for practical classes for students – foreign citizens of 4th course
on speciality «Phthiology»**

Zaporizhzhia 2015

UDC: 616.24-002.5-07-08(075.8)=111

Considered and approved at the phthisiology and pulmonology department session: protocol № 42 from 30.05.2016. Recommended of Zaporizhzhia state medical university Central Methodological Council as study guide for practical classes on speciality «Phthisiology» for students – foreign citizens of 4th course. The report № 5 from 20.05.2015.

The reviewers:

Skorohodova Natalia Olegivna – the dean of therapeutic faculty of state institution «Zaporizhzhia medical academy of postgraduate education of Ministry of healthy of Ukraine», MD, associate professor of phthisiology and pulmonology department.

Ryabokon Olena Vyacheslavivna – the head of infectious diseases department of Zaporizhzhia state medical university, MD, professor.

R.M. Yasinskiy, Yu.S. Solodovnik

Я 73 The general principles and methods of treatment of pulmonary tuberculosis / R.M. Yasinskiy, Yu.S. Solodovnik. – Zaporizhzhia, 2015. – 80 p.

The study guide is made according to the work program of phthisiology for students – foreign citizens of 4th course for practical classes. The manual described the history of tuberculosis treatment, the general principles and methods of treatment, medicines to treat pulmonary tuberculosis and patients' treatment regimens.

THE LIST OF ABBREVIATIONS

Am – Amikacin
Amx/Clv – Amoxicillin/Clavulanate
Cfz – Clofazimine
Cm – Capreomycin
Cs – Cycloserine
DR-TB – drug resistant tuberculosis
DST – drug susceptibility test
E – Ethambutol
Et – Ethionamide
FQ – Fluoroquinolones
H – Isoniazid
Ipm/Cln – Imipenem/Cilastatin
Km – Kanamycin
Lfx – Levofloxacin
Lzd – Linezolid
MDR-TB – multi-drug resistant tuberculosis
Mfx – Moxifloxacin
MTB – mycobacterium tuberculosis
NTP – National tuberculosis control programme
PAS – *para*-Aminosalicylic acid
Pt – Protionamide
Rif – Rifampicinum
S – Streptomycin
TB – tuberculosis
Thz – Thioacetazone
Trz – Terizidone
XDR – extensively drug resistant tuberculosis
Z – Pyrazinamide
WHA – World Health Assembly

CONTENT

1. The introduction.....	5
2. History of treatment methods and antituberculosis drugs.....	6
3. Principles and methods of treatment of tuberculous patients.....	13
4. Drugs: structure, pharmacokinetics and toxicity.....	18
4.1. First line drugs.....	18
4.2. Other drugs against tuberculosis.....	24
5. Drug interactions.....	31
6. Standard regimens for pulmonary tuberculosis.....	36
7. Drug resistance or intolerance.....	46
8. Common drug side effects.....	52
9. Management of side effects.....	56
10. Treatment of extrapulmonary tuberculosis.....	59
11. Treatment regimens in special situations.....	60
12. Monitoring the patient.....	63
13. Surgical treatment.....	64
14. Pathogenetic treatment of tuberculosis.....	74
15. References.....	78

1. THE INTRODUCTION

Tuberculosis (TB) is a major public health concern worldwide: burden of TB remains enormous: 9 million new cases and 1,5 million deaths per year. TB is by all means a poverty-related disease, mainly affecting the most vulnerable populations in the poorest countries. Study Guide is devoted to the actual problem of modern of phthisiology – tuberculosis treatment. The World Health Organization (WHO) has recently launched a new global TB strategy for the «post-2015 era» aimed at «ending the global TB epidemic» by 2035.

Study guide has a great practical importance because it allows students to evaluate the complexity of tuberculosis treatment`s problem and to contribute finding ways to raise treatment efficiency.

2. HISTORY OF TREATMENT METHODS AND ANTITUBERCULOSIS DRUGS

Tuberculosis has a long history. It was present before the beginning of recorded history and has left its mark on human creativity, music, art, and literature; and has influenced the advance of biomedical sciences and healthcare. Its causative agent, that is called *Mycobacterium tuberculosis*, may have killed more persons than any other microbial pathogen.

The introduction of the sanatorium cure provided the first widely practiced approach to anti-tuberculosis treatment.

Hermann Brehmer (1826-1889) a Silesian botany student suffering from TB, was instructed by his doctor to seek out a healthier climate. He traveled to the Himalayas where he studied the mountain's flora. He returned home cured and began to study medicine. In 1854, he presented his medical dissertation "Tuberculosis is a Curable Disease". Brehmer then opened an in-patient hospital in Gorbardsdorf, where patients received good nutrition and were continuously exposed to fresh air. This became the model for all subsequent sanatoria, including the one depicted in Thomas Mann's "The Magic Mountain".

A young doctor named **Edward Livingston Trudeau** (1848-1915) established the most famous sanatorium in the United States at Saranac Lake, in New York's Adirondak Mountains. He also suffered from TB and, in 1882, became aware of Koch's experiments with TB bacteria and of Brehmer's sanatorium. Trudeau established the Saranac Laboratory for the Study of Tuberculosis. It was the first institution devoted to TB research in the United States.

Sanatoria, increasingly found at that time throughout Europe and the US, provided a dual function. Firstly, they protected the general population by isolating the sick persons, who were the source of infection. Secondly, they offered TB patients bedrest, exercise, fresh-air, and good nutrition, all of which

assisted the healing process. Many of them improved and returned to "life in the flatland"; many did not.

The TB specialist, the phthisiologist, was responsible for the complete physical and mental care of the patient and the separation of TB care from the practicing clinician became commonplace.

Architectural features were essential to early sanatorium design. These included deep verandas, balconies, covered corridors, and garden shelters, furnished with reclining couches for the "Cure", the obligatory two-hour period of rest in the open air that was frequently observed in silence. Furniture for TB patients had to be robust, able to be thoroughly cleaned and disinfected, and shaped with a concern for the patient's anthropometric needs.

Alvar Aalto (1898-1976), **Jan Duiker** (1890-1935) and **Charles-Edouard Jeanneret (Le Corbusier)** (1887-1965) were modernist architects and designers that adapted and interpreted the ideas of functionality and rationality derived from concepts used in the treatment of TB, and their designs for buildings and furniture became icons of modernism. Aalto won the competition of Architecture, Interior Design and Furniture Design for the construction of the *Paimio Tuberculosis Sanatorium* in 1928, and Duiker designed the *Zonnestraal Sanatorium*. The symbolic association of light and air with healing made a profound influence on modernist ideas for design. Flat roofs, balconies, terraces and reclining chairs were subsequently adopted for the design of fashionable buildings in rapidly expanding cities such as Paris and Berlin.

Probably, it will never be known whether sanatorium treatment was a success or a failure, because no study was undertaken comparing the rates of mortality of sanatorium patients with those of TB patients who were similar in age, sex, and economic position, but who remained untreated or were treated by other methods.

Nevertheless, physicians with a long and intimate experience with the disease were unanimous in the opinion that open-air treatment was an improvement for the average consumptive.

During the early '60s, many sanatoria started to close. By the middle of that decade only a few beds remained available for patients suffering from TB. Yet, the real end of the TB sanatorium began even earlier, when the depressing era of helplessness in the face of advanced TB was substituted by active therapy.

The Italian physician **Carlo Forlanini** (1847-1918) discovered that the collapse of the affected lung tended to have a favorable impact on the outcome of the disease.

He proposed to reduce the lung volume by artificial pneumothorax and surgery, methods that were applied worldwide after 1913. These and other initial therapies are now considered dangerous and, at least, controversial:

- *Artificial pneumothorax* – pleural cavities were filled with gas or filtered

air, with the result of splinting and collapsing that lung.

- *Bilateral pneumothorax* – only parts of the lungs were collapsed in such a way that the patient could still live a relatively normal life. The patient suffered from shortness of breath caused by the reduction in the gas exchange surface.

- *Thoracoplasty* – ribs from one side of the thorax were removed in order to collapse the infected portion of the lung permanently.

- *Gold Therapy* – **Holger Mollgaard** (1885-1973) from Copenhagen introduced the compound *sanocrysin* in 1925, which is a double thiosulphate of gold and sodium. He tested the compound on animals and considered it safe for human use. However, it was too toxic even in low doses. A controlled trial, completed in the US in 1934, proved the toxic effects of gold therapy. Within a year, most European countries had ceased to use it.

Then, in the middle of World War II, came the final breakthrough, the greatest challenge to the bacterium that had threatened humanity for thousands of years – *chemotherapy*. In 1943, streptomycin, a compound with antibiotic activity, was purified from *Streptomyces griseus* by **Selman A. Waksman** (1888-1973) and his graduate student **Albert Shatz** (1920-2005). The drug was

active against the tubercle bacillus in vitro and following infection of guinea pigs. It was administered to a human patient at the end of 1944.

Two pioneering clinical studies were conducted on the treatment of TB patients with streptomycin, one in Europe and the other in the US (Medical Research Council 1948, Pfuetze 1955). A considerable improvement in the disease was observed in patients on streptomycin therapy, but after the first months, some patients began to deteriorate and these pioneering studies properly interpreted such treatment failure as a consequence of development of resistance to the drug.

In 1943, **Jörgen Lehmann** (1898-1989) wrote a letter to the managers of a pharmaceutical company, Ferrosan, suggesting the manufacture of the para-amino salt of aspirin because it would have anti-tuberculous properties. The Swedish chemist based his theory on published information, stressing the avidity of tubercle bacilli to metabolize salicylic acid. He realized that by changing the structure of aspirin very slightly, the new molecule would be taken up by the bacteria in just the same way, but would not work like aspirin and would rather block bacterial respiration. Para-aminosalicylic acid (PAS) was produced and first tested as an oral therapy at the end of 1944. The first patient treated with PAS made a dramatic recovery. The drug proved better than streptomycin, which had nerve toxicity and to which *M. tuberculosis* could easily develop resistance.

In the late '40s, it was demonstrated that combined treatment with streptomycin and PAS was superior to either drug alone. Yet, even with the combination of the two drugs, TB was not defeated. Overall, about 80 % of sufferers from pulmonary TB showed elimination of their germs; but 20 % were not cured, especially those with extensive disease and cavitation.

Two further findings were very important for TB treatment. Firstly, between 1944 and 1948, the action of nicotinamide on the TB bacillus was discovered by two different groups, but this discovery was not widely appreciated at the time. Secondly, in 1949, reports stated that the Germans had

treated some 7,000 tuberculosis patients with a new synthetic drug of the thiosemicarbazone series (Conteben), developed by **Gerhard Domagk** (1895-1964), the discoverer of the first sulphonamide. There is a remarkable similarity between the atomic structures of nicotinamide, Conteben, and PAS. Conteben and PAS both contain a chemical ring of six carbon atoms, the benzene ring, while nicotinamide contains the pyridine ring in which an atom of nitrogen replaces one of the carbon atoms. Thus, by substituting the benzene ring in thiosemicarbazone by this pyridine ring, a new drug, isoniazid, was developed. By mere coincidence, this was accomplished simultaneously in three pharmaceutical companies – one in Germany (Bayer) and two in the US (Squibb and Hoffman La Roche). Isoniazid was soon submitted for clinical testing and because of the favorable impact of its administration on disease evolution, the lay press headlines already told the story of the “wonder drug” before any scientific paper was published. However, none of the three pharmaceutical companies could patent the new drug, because it had already been synthesized back in 1912 by two Prague chemists, **Hans Meyer** and **Joseph Mally**, as a requirement for their doctorates in chemistry. Nevertheless, while clinical studies were still underway, six studies showed that *M. tuberculosis* readily became resistant to isoniazid.

In the view of many doctors in those early stages of chemotherapy, the role for drug therapy was to bring the disease under sufficient control to allow surgeons to operate the diseased organs. **John Crofton** (1912-2009), working at the University of Edinburgh, developed a protocol that resulted in a breakthrough in TB treatment and control. With his “Edinburgh method” based on meticulous bacteriology and application of the available chemotherapy, a 100 percent cure rate for TB was a reasonable objective. With the success rate obtained by using three drugs together, (streptomycin, PAS, and isoniazid) TB was completely curable, making surgical treatment redundant.

Dr. Crofton believed that the conquest of the disease would also imply other measures, such as pasteurization of milk, tuberculin testing in cattle, BCG

vaccination, mass radiography screening for early diagnosis of disease, isolation of infectious cases, and general population measures, including reduction of overcrowding and general improvement of the standard of living.

The “*Madras Experiment*” was carried out in India in 1956 to test a totally different concept of therapy, by comparing the results of treatment in a sanatorium with treatment at home with daily PAS and isoniazid for a year. After a 5-year period of follow up, the proportion of persons clear of disease in the two groups was similar and approached 90 %.

The spirit of optimism that followed was encouraged by the discovery of a series of new anti-tuberculosis drugs. The drug company Lepetit discovered that the mold *Streptomyces mediterranei* produced a new antibiotic, Rifamycin B. Chemical manipulation of this compound by CIBA resulted in the production of rifampicin, which has a remarkable potency against *M. tuberculosis*. Other compounds with anti-tuberculosis activity were discovered: pyrazinamide, ethambutol, cycloserine, and ethionamide.

At the end of the '70s, the primary care of TB patients moved from specialized institutions to general hospitals and ambulatory care services. At that time, many hospitals were reluctant to assume such responsibility for fear of spreading the disease to other patients and to hospital personnel. To overcome their apprehension, rational safety measures were introduced for the provision of primary care to TB patients in those settings. Earlier studies on TB transmission performed by Wells and Riley provided an insight into the characteristics of TB transmission and set the basis for its containment. By applying the experimental design of his mentor **William Firth Wells**, **Richard Riley** pioneered the study that first documented the role of the droplet nuclei in the transmission of TB. The experiments were carried out using guinea pigs lodged in chambers above wards where TB patients were hospitalized. Only particles small enough to be carried by the air reached the animals, which, as a result of the inhalation of these particles, became infected with the same strains as those infecting the patients. This could be confirmed by comparison of drug susceptibility patterns.

Indeed, the conclusions of those investigations still stand strong. During coughing, sneezing, talking or singing, sputum smear-positive TB patients can eliminate large or small droplets of moisture containing viable bacilli. Large droplets tend to settle quickly onto the floor and, if inhaled, are trapped in the upper airways and destroyed by local muco-cilliary defenses. Smaller droplets (1-10 μm) remain suspended in the air for prolonged periods of time. Evaporation of moisture leaves a residue – the droplet nucleus. This frequently contains only one or a few bacteria, which are the infectious units of TB. It was thus established that the risk of TB transmission is proportional to the concentration of droplet nuclei in the environment.

Infectivity was also found to be associated with environmental conditions and the characteristics of the disease in each individual case, such as the bacillary content of sputum, the presence of cavitation, the frequency of cough, and the presence of laryngeal TB. Therapy with anti-tuberculosis drugs was identified as the most effective measure for controlling patient's production of infectious particles and thus readily reversing infectivity. Therefore, patients should only require isolation while they were sputum positive and before initiation of specific therapy. Hospitalization was either abolished or reduced to a few weeks for most patients. Once a patient's diagnosis and treatment program had been defined, physicians who had no particular expertise in chest medicine could maintain a quality treatment program in most instances. That was the end of the phthisiologist's era.

3. PRINCIPLES AND METHODS OF TREATMENT OF TUBERCULOUS PATIENTS

The aim of treating tuberculosis in adults is to eliminate the clinical features of tuberculosis and promote a stable healing of the tubercular lesions; with restoration of the working capacity and social status of the patient. Whereas the goal in treating tuberculosis in children to cure without any residual changes or with minimal changes.

Among some patients, it is impossible to achieve these goals because there are objective limitations of treatment. In these cases it is necessary at least to achieve prolongation of the patient's life, improvement of his condition, if possible to terminate or reduce MBT expectoration and to preserve partial work capacity.

Criteria of effectiveness in the treatment of tuberculosis patients are:

- 1) the disappearance of clinical and laboratory signs of tubercular inflammation;
- 2) the stable termination of MBT expectoration, confirmed by microscopic and cultural examinations;
- 3) the regression of radiographic signs of tuberculosis (focal, infiltrative, destructive);
- 4) the restoration of functional and work capacity.

The peculiarities of tubercular process determine the complexity of treatment. Therefore, this disease requires a rational combination of various medical measures like:

- 1) chemotherapy;
- 2) sanitary-hygienic regime and therapeutic nutrition;
- 3) hormonal drugs;
- 4) tuberculin therapy;
- 5) collapse therapy and surgical interventions;
- 6) treatment of concomitant diseases.

Chemotherapy. Chemotherapy is the method of etiotropic treatment of tuberculosis with the help of the chemical agents. Chemotherapy is directed.

The term regimen means such the daily routine of a patient that provides comfort condition for his health. For that, the patient will require an increased amount of sleeping hours with an additional 2-hour rest in the afternoon; a prolonged exposition in open air; frequent strolls sleep in open air during both summer and winter; oxygen treatment in oxygenated room for more severe cases.

Hospitalization is a difficult period for the patient and for that matter it is useful not to restrict him to realize physical efforts or some kind of labor. Adequate, time-limited physical loads, educational and scientific work, are recommended to patients who are receiving treatment in medical establishments.

In well-organized tubercular establishments, patients may work in hospital workshops, kitchen and participate in gardening activities within the hospital's territory. Such physical activity stimulates normalization of emotional state of the patients. These establishments also offer educational programs for children, teenagers and high school students who had interrupted their studies due to illness.

A rational diets an integral part of modern therapy of tuberculosis. It plays the role of a pharmacodynamics action that normalizes the body's destructed physiological functions. Therefore, the diet should be strictly individualized for each patient. The food should contain fibers, fats and carbohydrates in an optimal amount and proportion according to the patient's needs.

A nutritional diet in case of tuberculosis should contain an increased amount of proteins preferably of animal origin and a moderate amount of carbohydrates. The ratio between these ingredients should be the following: 15–20% of proteins; 25–35% of fats; the remaining — carbohydrates.

Tuberculosis patients with weight deficiency should be provided with a diet exceeding the norm by 15–20%. Multi-vitamins intake is a cardinal part of a

dietary regimen in tuberculosis. Multi-vitamins are prescribed in the form of drinks, fruits and drugs (intra muscular or per os). The quality, variety and taste of food are very important. Various and tasty foods should be served 4–5 times a day.

Sanatorium treatment and treatment in health resorts of the tuberculosis patient is organic form of modern therapeutic methods and is mostly helpful in patients with freshly detected tubercular processes. The purpose of sanatorium treatment is to achieve complete clinical healing. It helps to eliminate exacerbation and to prevent relapses in patients with chronic process.

PRINCIPLES OF TREATMENT

- 1) **Complexity** is combination of specific and non-specific, as well as surgical treatment. Specific therapy includes etiotropic therapy, which is intake of anti-tubercular medication; non-specific therapy includes following hygienic and dietetic regimen, as well as prescription of pathogenic and symptomatic medication.
- 2) **Combination** of treatment is using of no less than 4 medications at the beginning of treatment of all patients with bacterial seeding. Combined therapy prevents MBT drug resistance and increase effectiveness of anti-tubercular medications, besides different medication acts on different structures of microbial cell. Combination of etiotropic medications promotes more complete reparation.
- 3) **Biphasic treatment of tuberculosis.** First intensive phase is aimed at depression of multiplication of MBT population, significant decrease of the latter and partial sterilization of the focus of specific infection. Patients are treated on an in-patient basis.
Second phase (continued treatment) includes daily or intermittent antimicrobial therapy on inpatient basis, outpatient basis or in sanatorium aimed at clinical recovery of patient (stable cease of

bacterial seeding; dissolution of infiltration, healing of destruction cavities) or at preparation for surgical treatment.

- 4) ***Individual treatment of patient with tuberculosis*** is based on results of evaluation of patient and close control over effectiveness of treatment. Thus sensitivity of cultured MBT to medication, individual sensitivity of patient to medication, concomitant pathology, age and weight of patient. According to WHO recommendations, patients with negative MBT cultures might not be hospitalized but might be given controlled chemotherapy on an outpatient basis.

Individual approach foresees changes into primary regimen of treatment. This may be necessary due to development of drug resistance to prescribed medications, little effect of therapy (continuing of bacterial seeding, slow dissolution of inflammatory alteration and absence of positive dynamics of the destruction cavity). Change of regimen might be due to change of medication or the way of their introduction.

- 5) ***Long-term and continued treatment***, which should last for several (often 6-8) months. In caseation necrotic masses and in caverns with MBT there is obliteration of vessels with cheese-like necrosis or their destruction. Thus adequate concentrations of medications are not achieved in main focus of pathogen collection. One has to consider that involution of tubercular alterations starts soon but it takes long time for reparation to complete. Sometimes treatment lasts for several years.

Continued (regular) intake of medication decreases incidence of drug resistance and promotes effectiveness of treatment. Intermittent therapy first introduced in 1964-1966 is considered continued therapy (intake of antimycobacterial medications 2-3 times a week).

- 6) ***Staged treatment*** includes such stages as in-patient (day care), sanatorium, outpatient, and dispensary follow-up with courses of anti-

relapse treatment. This provides succession of phthisiology service. From 1956 outpatient treatment plays significant role in foreign countries.

7) ***Controlled chemotherapy*** means that all medication should be taken in the presence of medical personnel, close relatives, social workers or volunteers. Purpose of controlled chemotherapy is to provide regular intake of antimycobacterial medications. It has been shown that up to 50% of treatment failure is associated with failure of patient to comply with prescribed treatment.

Availability and adequate number of medication, fully informed patient about gravity of disease, the need for treatment and possible outcomes estimate quality of anti-tubercular service. Economizing on personnel training and lack of state support of realization of anti-tubercular programs lead to increase of expenses for fight with tuberculosis.

8) ***Treatment of tuberculosis should necessarily be free of charge, available and safe.*** Chemotherapy is aimed at one pathogen, Mycobacterium tuberculosis. Most important factor in choice of antimycobacterial therapy is sensitivity of Mycobacteria to antitubercular medication.

4. DRUGS: STRUCTURE, PHARMACOKINETICS AND TOXICITY

4.1. First line drugs

Isoniazid (H)

Structure and general properties

H is a pro-drug that requires processing by the bacterial catalase-peroxidase to become active. Once activated, it inhibits the biosynthesis of mycolic acids, which are essential components of the mycobacterial cell wall. This drug is bactericidal against metabolically active bacilli and bacteriostatic against resting bacilli. H is active against *M. tuberculosis*, *M. bovis* and *M. kansasii*. Susceptible *M. tuberculosis* strains show minimal inhibitory concentrations (MIC) between 0,02 and 0,2 mg/L.

Pharmacokinetics

H is readily absorbed from the gastrointestinal tract (although absorption is reduced by food) or following intramuscular injections. Peak concentrations of 3-8 mg/L appear in blood between 1-2 hours after ingestion of 300 mg of H. It diffuses into all body tissues, including cerebrospinal fluid. The plasma half-life ranges from 1 to 6 hours. H is metabolized in the liver and the small intestine: first, an N-acetyltransferase acetylates H producing acetylisoniazid; this product is hydrolyzed to isonicotinic acid and monoacetylhydrazine, and the latter compound is further acetylated to diacetylhydrazine. None of these H-derived metabolites have any antituberculosis activity. Within the population, there are two groups of patients, depending on whether H is acetylated slowly or rapidly, a characteristic that is genetically determined. Plasma H concentrations are lower in rapid acetylators than in slow acetylators, although this difference does not affect the efficacy of the treatment. H and its metabolites are excreted in the urine.

Toxicity

H is well tolerated at recommended doses, although slow acetylators can accumulate higher H concentrations and then have a higher risk of developing adverse effects. Between 10 % and 20 % of patients may develop transient increases in liver enzymes at the beginning of treatment, and sometimes develop hepatic damage. In these cases, administration of H should be stopped. Liver function should be monitored before and during treatment, especially in those patients with a history of hepatic or renal dysfunction, in whom doses of H should be reduced to prevent further damage. Neurological or hematological adverse effects and hypersensitivity reactions occur less frequently. A daily dose of 10 mg of pyridoxine hydrochloride is recommended to reduce neurotoxicity and to treat adverse effects caused by H.

Rifampicin (R)

Structure and general properties

R inhibits gene transcription, by interacting with the beta subunit of the ribonucleic acid polymerase enzyme. It is bactericidal against dividing mycobacteria and also has some activity against non-dividing bacilli. M. tuberculosis strains are normally susceptible to 0,1-2 mg/L. The introduction of R, thus, allowed reduction of the duration of standard antituberculosis treatments from one year to nine months. R is also active against a wide range of microorganisms, including staphylococci, Neisseria spp. Haemophilus influenza and Legionella spp.

Pharmacokinetics

This drug is readily absorbed from the gastrointestinal tract (food may delay or decrease R absorption); within 2 to 4 hours after ingestion of a dose of 600 mg, peak plasma concentrations may reach 7-10 mg/L. It also can be given intravenously. In blood, R is bound to plasma proteins, and distributes into body

tissues and fluids, including cerebrospinal fluid and breast milk, and crosses the placenta. The half-life of R ranges from 2 to 5 hours. R is metabolized in the liver, and excreted in the bile, feces and urine.

Toxicity

R is well tolerated, although adverse effects may arise during intermittent therapy or when restarting an interrupted treatment. Adverse effects include diverse alterations in the gastrointestinal tract, skin, kidney and nervous system. It may also produce thrombocytopenia. R will cause a red-orange coloration of body fluids such as urine, tears, saliva, sweat, sputum and feces; it may result in the coloration of soft contact lens. Since it is metabolized in the liver, hepatic functions should be controlled before starting treatment and monitored regularly until the therapy ends. Special care should be taken in patients with pre-existing liver diseases. A moderate increase in alkaline phosphatase can be observed.

Pyrazinamide (Z)

Structure and general properties

Z is a bactericidal drug active only against *M. tuberculosis*, having no in vitro activity against other mycobacteria or any other microorganism. Susceptible strains have MICs of 20 mg/L at pH 5,6. It is active against persisting and non-dividing bacilli, even against those residing intracellular, being almost inactive at neutral pH. The introduction of Z into treatment regimens for TB allowed reduction of the duration of such regimens to six months. Z is a pro-drug that requires conversion into pyrazinoic acid to be effective; this is done by mycobacterial pyrazinamidases.

Pharmacokinetics

Z is given orally and is readily absorbed from the gastrointestinal tract. Serum concentrations reach a peak level of about 66 mg/L two hours after

administration of a dose of 3 g. It is distributed in all body tissues and fluids, including the cerebrospinal fluid and breast milk. The half-life of Z is about 9-10 hours. Z is hydrolyzed in the liver, being converted to pyrazinoic acid, which is further hydroxylated and finally excreted in the urine.

Toxicity

Z is hepatotoxic in a dose-dependent manner. Following a daily dose of 3 g of PZA, 15 % of patients may develop liver alterations, such as transient increases in liver enzymes, hepatomegaly, splenomegaly and jaundice. Hepatitis has been reported in less than 3 % of cases. It may also produce hyperuricaemia, leading to attacks of gout. Therefore, it is contra-indicated in patients with liver damage, and it is advisable to test liver function before and regularly during treatment. It also should not be given to patients having a history of gout or hyperuricaemia.

Ethambutol (E)

Structure and general properties

This drug is used to treat TB and other opportunistic infections caused by nontuberculosis mycobacteria such as *Mycobacterium kansasii*. The MICs of sensitive *M. tuberculosis* strains range from 0,5 to 8 mg/L. E is only active against dividing mycobacteria, being bacteriostatic. Since E affects the biosynthesis of the cell wall, it has been suggested that it contributes towards increasing the susceptibility of *M. tuberculosis* to other drugs.

Pharmacokinetics

E is given orally, as it is well absorbed in the gastrointestinal tract (and not affected significantly by food), although a part is excreted in the feces. After absorption, it is distributed in most tissues and diffuses into the cerebrospinal fluid and breast milk; it also crosses the placenta. Following a dose of 25 mg/kg

body weight a peak concentration of 5 mg/L in serum is reached after 4 hours. The half-life is about 3 to 4 hours. Only a fraction of E is metabolized in the liver; the unchanged drug and its metabolites are excreted in the urine.

Toxicity

E produces retrobulbar neuritis with a reduction in visual acuity, constriction of visual field, central or peripheral scotoma, and green-red color blindness. This may affect one or both eyes. The severity of these effects depends on the dose and duration of treatment. Usually, normal vision is recovered a few weeks after the end of the treatment, although in some cases, this recovery may not occur until some months after the completion of treatment. Consequently, E is contraindicated in patients with optic neuritis, and should be used with care in patients with visual disorders. Optical examinations are advisable before and during treatment. E is not usually given to children under six years of age because of the difficulty in monitoring visual acuity, unless resistance to H or R is highly suspected.

Other adverse effects include a reduction of urate excretion (hence producing gout), gastrointestinal disorders and hypersensitivity skin reactions.

Streptomycin (S)

Structure and general properties

S, an antibiotic produced by some strains of *Streptomyces griseus*, was the first drug with antituberculosis activity to be discovered. It is mainly used in the treatment of TB (most *M. tuberculosis* strains are susceptible to 1-8 mg/L of streptomycin). It can also be used in the treatment of other bacterial infections such as those produced by *Yersinia pestis*, *Francisella tularensis*, and *Brucella* spp.

Pharmacokinetics

S, like most aminoglycosides, is poorly absorbed from the gastrointestinal tract, and therefore it must be administered by intramuscular injection. Because of the toxicity of S and the introduction of other drugs that can be administered orally for the treatment of TB, the use of S has decreased, being relegated to the treatment of infections caused by drug-resistant strains. Two hours after an injection of 1 g SM, drug levels in blood may reach up to 50 mg/L, where one third of it circulates bound to plasma proteins. The half-life for SM is about 2,5 hours.

S and the other aminoglycosides diffuse well into most extracellular fluids, maybe with the exception of the cerebrospinal fluid. They diffuse quite readily into the perilymph of the inner ear, causing ototoxic effects. Aminoglycosides also tend to accumulate in specific body tissues such as the kidneys. Streptomycin does not appear to be metabolized, and is excreted unchanged in the urine. The concurrence of other diseases may affect the pharmacokinetics of S and this may become relevant since there is a relatively small difference between the therapeutic and toxic concentrations of aminoglycosides. For example, patients with renal impairment will have increased plasma concentrations of S, whereas in patients having diseases that cause expanded extracellular fluid volume or increased renal clearance (such as ascites, cirrhosis, heart failure, malnutrition or burns), S concentrations will be reduced.

Toxicity

Like most aminoglycosides, S has ototoxic effects affecting vestibular rather than auditory (cochlear) function, which manifest as dizziness and vertigo. It is less nephrotoxic than other aminoglycosides, although it may produce renal failure when administered with other nephrotoxic agents. Regular assessment of both auditory and renal function is recommended. In case of severe adverse effects, S can be removed by hemodialysis. Paresthesia,

neurological symptoms such as peripheral neuropathies, optic neuritis and scotoma and hypersensitivity skin reactions have also been observed after SM injections.

4.2. Other drugs against tuberculosis

Drugs in this group are interesting for one or more of the following features:

- widely used in the past but in our days its use has been relegated by the incorporation of more effective and/or less toxic drugs
- used when resistance to first-line antituberculosis drugs is suspected or confirmed and are usually denominated second-line drugs
- used when severe adverse effects to other antituberculosis drugs develop
- have been developed recently and, because of their usefulness for the treatment of TB, are potential first-line drugs that could be incorporated soon into standard (and maybe shorter) antituberculosis regimens
- allow intermittent doses, hence facilitating patient's adherence to antituberculosis treatment.

Para-aminosalicylic acid (PAS)

This compound and its salts are active only against *M. tuberculosis*, which can be inhibited by 1 mg/L of this drug. It is bacteriostatic. PAS can be given orally, in a daily dose of 10-12 g divided into two or three doses. It is well absorbed in the gastrointestinal tract and distributes well throughout the body, although it is poorly distributed in the cerebrospinal fluid. It is metabolized in the intestine and in the liver, and it is excreted mainly in the urine. PAS may produce gastrointestinal side effects such as nausea, vomiting, diarrhea, and hypersensitivity reactions, and should be administered with care in patients with

liver or renal impairment. PAS can be used safely during pregnancy but is not recommended because of the gastrointestinal intolerance. The use of PAS has largely decreased since the introduction of R and E; however, due to its low cost, it is still in use in low-resource countries.

Capreomycin (Cm)

This polypeptide is bacteriostatic against several mycobacteria including *M. tuberculosis*; susceptible strains are inhibited by 10 mg/L of capreomycin. Doses, usually of 1 g, must be administered by intramuscular or intravenous injection. Capreomycin is excreted in the urine. It must be given with care to patients with renal, hepatic or auditory dysfunction. Commonly, capreomycin affects the frequency of urination or the amount of urine, increases thirst and may produce loss of appetite, nausea and vomiting. Due to its toxic effects, it must not be given in combination with aminoglycosides such as kanamycin or streptomycin.

Cycloserine (Cs)

This is a broad-spectrum antibiotic that inhibits many microorganisms such as *Escherichia coli*, *Staphylococcus aureus*, *Nocardia* spp., *Chlamydia*, and *M. tuberculosis*. Due to its high toxicity, it is only used against bacilli resistant to the main antituberculosis drugs. It is fairly well absorbed in the gastrointestinal tract, being distributed to most tissues and fluids, including cerebrospinal fluid. Cycloserine is metabolized and excreted in the urine. It should be given with care to patients with renal impairment. It may produce diverse adverse reactions involving the central nervous system, from mild headache or restlessness to severe psychosis and seizures, and is therefore contraindicated in patients with epilepsy, depression or anxiety. Hypersensitivity skin reactions have also been described.

Aminoglycosides (Km, Am)

Amikacin and kanamycin are active against a range of bacteria including *M. tuberculosis*. Amikacin is also active against atypical mycobacteria that cause opportunistic infections, such as those of the *Mycobacterium avium* complex. Both are considered as second-line antituberculosis drugs; other safer drugs are preferred for the treatment of TB. These antibiotics are often combined with E, ciprofloxacin, and macrolides. Like S amikacin and kanamycin must be given by intramuscular injections, usually in doses of 0,5-1 g. They are distributed in body tissues and fluids, and cross the placenta but do not reach the cerebrospinal fluid. Like most aminoglycosides, amikacin and kanamycin affect auditory function and must be given with care to patients with auditory dysfunctions. They are also nephrotoxic, producing renal impairment in approximately 8 % of patients. Kanamycin may also produce some gastrointestinal effects, such as nausea, vomiting, and stomatitis, especially when taken by mouth. Both aminoglycosides are excreted unchanged in the urine.

Thioamides (Et, Pt)

There are two main drugs from the thioamide (or thionamide) family that can be used for the treatment of TB: E ethionamide (Et) and prothionamide. Et is a structural analogue of H and in fact some cross-resistance has been observed between both drugs. Et is active against *M. tuberculosis*, *M. leprae*, *M. kansasii*, and some strains of the *M. avium* complex. Susceptible *M. tuberculosis* strains are inhibited by 0,6-2,5 mg/L of Et. For the treatment of TB, doses of 15-20 mg/kg of body weight are given orally, up to a maximum of 1 g daily. It is well absorbed from the gastrointestinal tract, and diffuses into all body tissues and fluids, including cerebrospinal fluid. Its half-life is 2 hours. Et is metabolized in the liver and excreted in the urine. Thus, it should not be given to patients with

liver dysfunction. Adverse effects associated with Et administration include dose-related gastrointestinal disorders (such as anorexia, excessive salivation, nausea, vomiting, metallic taste, abdominal pain, and diarrhea), diverse mental disturbances (such as depression, anxiety, psychosis, dizziness, drowsiness, and headache) and hypersensitivity skin reactions have also been described. Prothionamide is very similar to Et; complete cross-resistance between these two drugs usually occurs. It can be used orally, at doses similar to those of Et. It is well absorbed from the gastrointestinal tract, and distributes to all body tissues and fluids, including cerebrospinal fluid. Prothionamide is metabolized in the liver and excreted in the urine.

Fluoroquinolones (FQ)

Among the fluoroquinolones, there are drugs with several degrees of activity against *M. tuberculosis*. Whereas norfloxacin has no activity against mycobacteria, ciprofloxacin and ofloxacin have been used for the treatment of TB, especially when caused by drug resistant strains, and also in the treatment of opportunistic mycobacterial infections. Other fluoroquinolones such as sparfloxacin, gatifloxacin, and moxifloxacin are even more active than ciprofloxacin for the treatment of TB, being comparable to H.

Fluoroquinolones are well absorbed from the gastrointestinal tract (presence of food reduces absorption), and peak plasma concentrations are obtained rapidly, usually after 1-2 hours, where they are partially bound to plasma proteins. Half-life is variable, ranging from 4 hours in the case of ciprofloxacin to 10-13 hours in the case of moxifloxacin. They distribute well into all body tissues, and are finally, eliminated in the urine. Fluoroquinolones are generally well tolerated. Adverse effects include disorders of the gastrointestinal tract, nervous system, and skin.

They should not be given to patients having central nervous system disorders such as epilepsy. The use of fluoroquinolones is not recommended in children or during pregnancy. Interactions with other drugs are infrequent.

Rifamycins

The rifamycin family of drugs includes R, one of the most potent first-line antituberculosis drugs. Other members of this family include rifabutin and rifapentine, which share their mode of action and spectrum of antibacterial activity with R. A high degree of cross-resistance among rifamycins has been found. Rifapentine and rifabutin have, however, some distinct properties in comparison to R which makes them very useful in certain situations. The MICs of rifabutin for *M. tuberculosis* susceptible strains are usually eight times lower than those for R. Rifabutin can be used for the treatment of TB at doses of 150-450 mg daily, combined with other drugs to avoid drug resistance. It is also frequently used for the prophylaxis of *M. avium* infections in immunocompromised patients and for the treatment of other opportunistic infections caused by mycobacteria.

In contrast to R, rifabutin is poorly absorbed in the gastrointestinal tract; once it gets into the blood, most of it is bound to plasma proteins, and distributes widely into the body. Rifabutin is metabolized in the liver where it induces microsomal enzymes, although to a lesser extent than RIF. Rifabutin is excreted in the urine.

Rifabutin produces a syndrome of polyarthralgia-arthritis at doses over 1 g daily. Uveitis has been reported in patients also receiving macrolides or azole antifungals. Rifabutin reduces the plasma concentration of several antiretroviral drugs, such as Zidovudine. Despite this, rifabutin (at reduced doses) has been recommended in place of R in the treatment of TB in HIV/AIDS patients, in order to avoid major interactions of R and the antiretroviral drugs.

Rifapentine is considered a long-acting rifamycin, since it can be given orally at doses of 600 mg twice weekly or even once weekly during the initial phase in the treatment of TB. It is well absorbed from the gastrointestinal tract. Rifapentine and R show cross-resistance. Adverse effects of rifapentine are similar to those of R, except for a higher incidence of hyperuricaemia. This drug has not been approved for use in children, since the safety and efficacy of this drug has not yet been established for this age group. Also, rifapentine is not recommended for HIV/AIDS patients because of their risk of developing rifamycin resistance.

Thiacetazone (Thz)

This drug, also spelled thioacetazone, is bacteriostatic against *M. tuberculosis*, with susceptible strains being inhibited by 1 mg/L. Cross-resistance with ethionamide and prothionamide can occur. It may be used in anti-tuberculosis regimens, although these may not be as effective as the standard short-course therapy. It is well absorbed in the gastrointestinal tract and peak concentrations of 1-2 mg/L are obtained four hours after administration of a 150 mg dose. It is excreted in the urine. Thiacetazone produces diverse adverse effects such as gastrointestinal disorders, and hypersensitivity reactions (including skin rashes) that may be more frequent in HIV/AIDS patients. Other frequent adverse effects include conjunctivitis, vertigo, toxic epidermal necrolysis, exfoliative dermatitis, hemolytic anemia, and hepatotoxicity with jaundice. It should not be given to patients with liver impairment, or to HIV/AIDS patients because of the risk of increased adverse reactions. Some low-income countries still use thiacetazone because of its low cost.

Linezolid (Lzd)

Linezolid injection, tablets and oral suspension contain linezolid, which is a synthetic antibacterial agent of the oxazolidinone class. The chemical name is

(S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl] methyl]-acetamide. Tablets for oral administration contain 400 mg or 600 mg linezolid as film-coated compressed tablets. Inactive ingredients are corn starch, microcrystalline cellulose, hydroxypropylcellulose, sodium starch glycolate, magnesium stearate, hypromellose, polyethylene glycol, titanium dioxide, and carnauba wax. The sodium (Na⁺) content is 1.95 mg per 400-mg tablet and 2.92 mg per 600-mg tablet (0.1 mEq per tablet, regardless of strength). Linezolid is not an inducer of cytochrome P450 (CYP450) in rats. In addition, linezolid does not inhibit the activities of clinically significant human CYP isoforms (e.g., 1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Therefore, linezolid is not expected to affect the pharmacokinetics of other drugs metabolized by these major enzymes. Concurrent administration of linezolid does not substantially alter the pharmacokinetic characteristics of (S)-warfarin, which is extensively metabolized by CYP2C9. Drugs such as warfarin and phenytoin, which are CYP2C9 substrates, may be given with linezolid without changes in dosage regimen. Linezolid is a synthetic antibacterial agent of a new class of antibiotics, the oxazolidinones, which has clinical utility in the treatment of infections caused by aerobic Gram-positive bacteria. The in vitro spectrum of activity of linezolid also includes certain Gram-negative bacteria and anaerobic bacteria. Linezolid inhibits bacterial protein synthesis through a mechanism of action different from that of other antibacterial agents; therefore, cross-resistance between linezolid and other classes of antibiotics is unlikely. Linezolid has not been tested in large clinical trials of people with TB, but information from observational studies and small trials supports the use of linezolid in highly resistant TB strains and cases that are otherwise complicated to treat (e.g., when someone with MDR-TB cannot tolerate other drugs in his or her regimen). A meta-analysis of 12 nonrandomized studies of linezolid's role in MDR- and XDR-TB treatment found that 82 percent of patients treated with linezolid were cured or completed treatment—higher than in previously reported XDR-TB treatment outcomes.

5. DRUG INTERACTIONS

In general, when two or more drugs are administered simultaneously to a patient, there is a possibility that the drugs involved may interact between them. This interaction may result in changes (increase or decrease) of the effective concentration of one or more of the drugs involved, which most can usually be solved by adjusting the doses of the affected drug.

The interaction may also produce an enhancement in adverse effects produced by any of the drugs, which is frequently solved by using alternative drugs that are not affected by the interaction. Since the antituberculosis treatment itself consists of the administration of two or more drugs, and in some occasions it is given simultaneously with other drug regimens (i.e. the antiretroviral treatment) it is very important to consider those drug interactions affecting the TB drugs.

Few drugs interact to alter the concentration of the antituberculosis drugs. More frequently, antituberculosis drugs affect the other drugs. Most of the clinically relevant interactions involve the rifamycin drugs (R, rifapentine and rifabutin). Other interactions affecting first-line antituberculosis drugs and the fluoroquinolones will also be described in this section.

Rifamycins

The rifamycins are metabolized mainly in the liver, and to a lesser extent in the intestine wall, where they induce several pathways involving isoenzymes of the cytochrome P450 system, such as the isoenzyme CYP3A4. The extent of the induction of the isoenzyme CYP3A4 depends on the particular rifamycin drug that is being used, and so, R is the most potent inducer, whereas rifapentine is a moderate inducer and rifabutin is the least potent inducer of the isoenzyme CYP3A4. Rifabutin, but not R or rifapentine, is also a substrate of CYP3A4.

Then, other drugs that share or interact with the cytochrome P450 system may have significant levels of interaction with the rifamycins.

Drugs affecting the rifamycins

Ritonavir, a protease inhibitor that is combined with inhibitors of reverse transcriptase during anti-HIV therapy, is a potent inhibitor of the isoenzyme CYP3A4, which is the isoenzyme that metabolizes rifabutin. As a consequence, rifabutin levels may increase up to four-fold, and other rifabutin-derived metabolites may also reach higher levels. This produces a higher probability of having leucopenia and other adverse effects. R can be used instead of rifabutin in order to avoid this interaction.

Efavirenz, another antiretroviral drug, is an inducer of the CYP3A4. Its administration may result in a decrease in the concentration of rifabutin to one third of its normal serum concentrations.

Clofazimine, a drug used in the treatment of leprosy, may reduce the absorption of R.

Drugs affected by the rifamycins

Since rifamycins induce microsomal liver enzymes, they accelerate the metabolism of some other drugs reducing their half-lives and their concentrations, sometimes to sub-therapeutic levels. This problem can be solved easily by increasing the dosage of the drugs affected, which have to return to normal doses two weeks after completion of the rifamycin treatment. One exception to this general rule can be the case of oral contraceptives in women, and other contraceptive methods should be recommended.

Maybe, the most important family of drugs affected by the rifamycins is the antiretroviral agents, both the protease inhibitors and the non-nucleoside reverse transcriptase inhibitors. R should not be administered simultaneously with anti-HIV drugs such as zidovudine, non-nucleoside reverse transcriptase inhibitors, and HIV protease inhibitors, since it may induce the metabolism of

these drugs in the liver. Rifabutin can be used instead of R in some situations. The nucleoside reverse transcriptase inhibitors, which are not metabolized by CYP3A4, can be co-administered with rifamycins.

Other drugs, whose concentrations can be decreased by the use of rifamycins include atovaquone, azathioprine, chloramphenicol, cyclosporine, cimetidine, clofibrate, corticosteroids, coumarin anticoagulants, dapsone, diazepam and other benzodiazepines, doxycycline, fluconazole, haloperidol, hexobarbital, itraconazole, ketoconazole, lamotrigine, methadone, ondansetron, oral hypoglycemics, phenytoin, quinine, rofecoxib, statins, sulphasalazine, tacrolimus, the bronchodilator theophylline, thyroid hormones, and several cardiovascular drugs including beta blockers, digitalis alkaloids and antiarrhythmics such as disopyramide, lorcaïnide, mexiletine, propafenone, quinidine, tocainide, and verapamil and other calciumchannel blockers.

Isoniazid

Drugs affecting isoniazid

Chronic alcoholism may increase liver metabolism of H. Aluminum-containing antacids reduce the absorption of H. Food such as cheese and fish, and also red wine may produce H-associated adverse effects.

Drugs affected by isoniazid

H is a potent inhibitor of several cytochrome P450 isoenzymes, and then, it interferes with and inhibits the hepatic metabolism of a large number of drugs (such as, R), thus increasing their half-life and therefore their potential toxicity. The main drugs interacting with H include anti-epileptics such as carbamazepine, ethosuximide and phenytoin, benzodiazepines, and chlorzoxazone.

Combination of isoniazid and rifamycins

In the standard anti-tuberculosis regimes, R is administered simultaneously with H during the complete treatment (initial and continuation phases). Since both drugs are metabolized in the liver, the incidence of hepatotoxicity can be increased and liver function should be monitored regularly. The risk of hepatotoxicity can also increase when other potentially hepatotoxic drugs are taken.

There is an important number of drugs for which both H and R interact producing opposite effects: H may increase drug concentrations whereas R decreases such concentrations. When both drugs are administered simultaneously, the effect of R is more important than that of H, resulting in a decrease in the concentration of the drugs affected.

Pyrazinamide

Probenecid, a drug used for the treatment of gout, may block the excretion of Z and co-administration of both drugs also affects excretion of urate. In some cases, patients receiving zidovudine as anti-HIV treatment may have diminished levels of Z.

Ethambutol

Aluminum hydroxide-containing antacids may reduce the absorption of E up to a 20 %. These compounds should be taken at least two hours after the ingestion of E to avoid interaction.

Streptomycin

The administration of S with other nephrotoxic drugs, including other aminoglycosides, vancomycin, and some of the cephalosporins, or potentially

ototoxic drugs such as ethacrynic acid or frusemide should be avoided since this could increase the risk of toxicity.

Fluoroquinolones

Several drugs (such as those containing divalent cations, including antacids or vitamin supplements) decrease the absorption of fluoroquinolones. Taking these medications at least two hours after the dose of fluoroquinolones circumvents this problem.

Some fluoroquinolones can inhibit the metabolism of other drugs, such as the bronchodilator theophylline, therefore enhancing its toxic effects. The most recently developed fluoroquinolones (moxifloxacin, gatifloxacin, etc) lack this effect.

6. STANDARD REGIMENS FOR PULMONARY TUBERCULOSIS

WHO definitions of TB cases recommended for use since March 2013 and that were used in the 2014 round of global TB data collectiona

Bacteriologically confirmed case of TB A patient from whom a biological specimen is positive by smear microscopy culture or WHO-approved rapid diagnostic test (such as Xper MTB/RIF). All such cases should be notified, regardless of whether TB treatment is started.

Clinically diagnosed case of TB A patient who does not fulfil the criteria for bacteriologically confirmed TB but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. This definition includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extrapulmonary cases without laboratory confirmation. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

Case of pulmonary TB Any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Miliary TB is classified as pulmonary TB because there are lesions in the lungs. Tuberculous intra-thoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitute a case of extrapulmonary TB. A patient with both pulmonary and extrapulmonary TB should be classified as a case of pulmonary TB.

Case of extrapulmonary TB Any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges.

New case of TB A patient who has never been treated for TB or has taken anti-TB drugs for less than one month.

Previously treated case of TB A patient who has been treated for one month or more with anti-TB drugs in the past. Retreatment cases are further classified by the outcome of their most recent course of treatment into four categories.

1. *Relapse* patients have previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).

2. *Treatment after failure* patients have previously been treated for TB and their most recent course of treatment failed i.e. they had a positive sputum smear or culture result at month 5 or later during treatment.

3. *Treatment after loss to follow-up* patients have previously been treated for TB and were declared 'lost to follow-up' at the end of their most recent course of treatment.

4. *Other previously treated* patients are those who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.

Case of multidrug-resistant TB (MDR-TB) TB that is resistant to two first-line drugs: isoniazid and rifampicin. For most patients diagnosed with MDR-TB, WHO recommends treatment for 20 months with a regimen that includes secondline anti-TB drugs.

Case of rifampicin-resistant TB (RR-TB) A patient with TB that is resistant to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, whether mono-resistance, multidrug resistance, polydrug resistance or extensive drug resistance.

The standard short course treatment of tuberculosis has a strong evidence base. A series of trials conducted under the auspices of the British Medical

Research Council (BMRC) in Singapore, Hong Kong, India and East Africa underpin the regimens below.

FOR ALL NEW CASES OF TB AND PREVIOUSLY TREATED CASES OF TB: THE TREATMENT REGIMEN CONTAINING 4 FIRST-LINE DRUGS: 2HRZE/4HR

Length of the intensive phase and continuation phase in initial tuberculosis treatment.

With the previously discussed initial treatment (2 months H+R+Z+E followed by 4 months H+R), the majority of patients will be cured with a minimum of adverse side effects. However, this regimen is already 30 years old, and while it continues to be effective, resistance around the world has noticeably changed over this period. This can raise questions about the length of the intensive and continuation phases.

If there are negative AFB smears at the end of the second month of treatment, the length of the intensive phase should be unchanged because the TB patient could very possibly be sensitive to the entire administered drug regimen. In any event, the bacillary load will be so low that nothing will happen by moving to the continuation phase. However, if Z+E are systematically suspended when the intensive phase ends, regardless of the AFB smear result, questions arise about the fate of the more than 10 % of patients who still have positive smears at the end of the intensive phase. It is possible that some patients will have positive AFB smears due to non-viable, dead bacilli or totally susceptible bacilli (delayed conversion). In both cases, there would be no effects. Another cause of such a presentation may be viable bacilli with initial resistance to H. These patients may be more likely to have a positive AFB smear at the end of the second month, because this drug has not been able to act with its powerful early bactericidal activity. However, the cause of the presentation would not be known until culture results became available, which can take several weeks. It is therefore advisable that, for this group of patients with

positive AFB smears at the end of the intensive phase, the same treatment be maintained with the four drugs throughout the entire period of treatment. This ensures protection of R in all patients with initial resistance to H, a condition that customarily is not known until several weeks or months after treatment is started. Although this strategy can be controversial because there are no studies addressing the issue, adding E and Z (or at least E) for these patients is hardly ill-advised because R will always be protected. Although Z would not be necessary in the continuation phase for those with positive bacilloscopies at the end of the second month (E could be prolonged to protect R), the best way to facilitate management on the ground is 6 months of H+R+Z+E.

Ideally, a DST for H and R should be performed on patients who still have positive AFB smears at the end of the second month of initial treatment and a decision made when the results are received. If the culture is negative (indicating that the positive AFB smear is due to dead or non-viable bacilli), or if it is positive but the isolated bacilli are sensitive to H+R (indicating delayed conversion), the choice could be made to suspend the intensive phase and move to continuation with 4 months of H+R. For such patients, information provided by Xpert would not be valid because it only addresses possible R resistance, while the patient may be sensitive to R but resistant to H. In this case, we run the same risk of amplifying resistance to R by moving to the continuation phase with only H+R.

Although the continuation phase with 4–6 months of H+R usually suffices to cure most patients, several conditions have been identified in recent years that may facilitate relapses if the treatment lasts only 6 months. This has notably been seen with HIV infection, where it is more and more widely accepted that to reduce the chance of relapse, the continuation phase should consist of at least 8–9 months of treatment with H+R. Other conditions, such as extensively advanced or cavitory TB or delayed smear and/or culture conversion even in sensitive patients, seem to benefit from prolonged continuation phases. Standardised plans should always be administered under controlled programmed

conditions but, in cases of delayed bacteriological conversion, it may be best to maintain the continuation phase for a minimum of 4 months after smear conversion.

Intermittent treatment regimens.

Though daily treatment is the ideal scenario to ensure maximum effectiveness, numerous trials have demonstrated similar efficacy with intermittent treatments. As noted above, *M. tuberculosis* multiplies very slowly (approximately once every 14–24 hours), enabling efficacy when the anti-TB drug is administered in a single daily dose. It is known that a single dose of H inhibits bacterial growth for several days, meaning it is equally effective to administer either two weekly doses or one daily dose. However, efficacy decreases when the interval between doses exceeds 4 days. With R and E, growth inhibition also persists for several days, though the bactericidal behaviour of R makes the latter much more effective. In any case, the efficacy of these two drugs is similar whether administered daily or once a week.

Similar considerations apply to Z, which at a pH of 5.6 inhibits mycobacterial growth for 9 days following 24 hours of bacterial exposure to the drug. These circumstances apply to H, R, E and Z but not to FQ, ethionamide or thiacetazone. Therefore, if regimens with H, R, E and Z are recommended, intermittent administration in the form of twice-weekly doses can be used with the same therapeutic safety margin as a daily dose, the only requirement being an increase in the amount of H, E and Z contained in each dose. The dose of R should not be increased. In order to achieve satisfactory efficacy, a minimum of two doses a week is required. Consequently, national tuberculosis programmes (NTPs) that recommend intermittent regimens should first ensure strict supervision of medication administration.

Some programmes recommend administration three times a week (even though it has been reasoned that twice is enough) for operative reasons only, because this recommendation also applies to the second phase of therapy when adherence to treatment decreases. No problems should be expected if a single

dose is missed in the context of the thrice-weekly treatment scheme, because two weekly administrations effectively suffice to ensure therapeutic efficacy. However, if a dose is missed in a twice-weekly treatment scheme, the patient will in effect receive only a single weekly dose, creating a dangerous situation because R may inhibit mycobacterial growth for 3–4 days but H does so for 7–8 days. From a bacteriological perspective, a single weekly dose of these two drugs means that the patient is actually receiving sequential monotherapy with H, with the risk of selecting for mutants resistant to H.

Use of these drugs in intermittent treatment regimens makes supervising administration more practicable (supervision is only needed twice a week instead of daily), the option is much less expensive (for R, the most costly drug, it is not necessary to increase the dose at each administration) and toxicity is similar to that associated with daily dosing. Moreover, it has been suggested that greater peak concentrations in blood make the selection of resistant mutants less likely. Although the drugs could be administered intermittently from the start (mycobacterial growth inhibition being achieved from the first dose), it is normally advised to commence therapy with a daily administration phase lasting 1–2 months, because maximum bactericidal action takes place in the first days of chemotherapy. Nevertheless, some studies have shown intermittent administration to be effective from the start, though four drug substances are used in the initial phase in such cases.

There has been controversy recently about whether these intermittent treatments cause more failures, relapses or amplification of resistance. Although the evidence is not very strong, if intermittent treatments are initiated at the beginning of therapy, the result may be more relapses in specific patient groups, such as those co-infected with HIV, with cavitation on chest X-rays or with initial resistance to H. The likelihood that more failures and amplifications of resistance in these three patient groups will occur is somewhat more controversial, but some trials have shown just such results. The best way to avoid these unfortunate occurrences is daily treatment for all phases. If this is

not possible at field-level conditions, the intensive phase should be administered daily with the goal of moving to administration three times a week in the continuation phase. Patients infected with HIV should have daily treatments in both phases.

Additional considerations for children (age 0-14 years):

a) Weight based dosing

Anti-tuberculosis drugs are dosed in children according to weight. Significant weight gain may occur as the child responds to treatment. The child's weight should be monitored monthly during treatment and doses adjusted in line with any significant changes in weight.

b) Ethambutol

Previous local and international guidelines have recommended against using ethambutol in young children unless resistance to isoniazid and/or rifampicin is known or suspected. This is because it is not possible to screen with Snellen and Ishihara tests in young children.

Initial treatment for young children with uncomplicated disease from areas with a low prevalence of isoniazid resistance can be with three drugs (HRZ). However, recent WHO guidelines recommend the addition of ethambutol 20mg/kg to this regimen in children who have HIV, non-pulmonary TB or extensive or cavitary lung disease or who are from areas with a high prevalence of isoniazid resistance (World Health Organisation, 2010). Optic neuritis is unlikely to develop, provided that the recommended dose and duration are not exceeded. The decision whether to cease ethambutol in the intensive phase will depend on demonstration of susceptibility to isoniazid and rifampicin (if culture positive), HIV status and, if culture negative, an assessment as to the epidemiological likelihood of drug resistance.

c) Pyridoxine

Pyridoxine is not routinely recommended for children taking isoniazid but should be considered in exclusively breast feeding infants and children with HIV infection or nutritional deficiencies.

Table 1. Drug dosages

Drug Name	Adult Dosages		Dosages in children	Parenteral Product Availability
	<i>Daily</i>	<i>Thrice-Weekly</i>	<i>Daily</i>	
Isoniazid (H)	5 mg/kg to 300 mg	15 mg/kg to 900 mg	10 mg/kg (range 10–15 mg/kg) to maximum 300 mg	IV Ampoule 50mg in 2mL (via Special Access Scheme)
Rifampicin (R)	10 mg/kg to maximum 600 mg (in practice 450 mg if <50 kg, 600 mg if ≥50 kg)	600 mg	15 mg/kg (range 10–20 mg/kg) to maximum 600 mg	IV Vial 600mg
Ethambutol (E)	15–25 mg/kg to 1200 mg	30 mg/kg	20 mg/kg (range 15–25 mg/kg)	None Available
Pyrazinamide (Z)	30–40 mg/kg to max 2 g (in practice 1.5 g if <50 kg, 2 g if ≥50 kg)	2 g if <50 kg, 2.5g if ≥50 kg	35 mg/kg (range 30–40 mg/kg) to maximum 2 g	None Available
Pyridoxine (B6)	25mg	50mg	Not routine; Not routine; 1-2mg/kg; Typically 5-10mg in neonates	IV Ampoule 100mg in 1mL (via Special Access Scheme)

Recommended drug dosages

Although dosing is weight based, many adults will weigh more than 50kg and be eligible for standard doses of isoniazid (300mg/day) and rifampicin (600mg/day).

Doses of ethambutol are more likely to vary between adult patients. Combination tablets are not available but may be used for patients who have commenced therapy in overseas countries.

Definitions of treatment outcomes recommended for use since March 2013 and that were used in the 2014 round of global TB data collection

Cured A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.

Completed treatment A TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.

Died A TB patient who died from any cause during treatment.

Failed A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.

Lost to follow-up A TB patient who did not start treatment or whose treatment was interrupted for two consecutive months or more.

Not evaluated A TB patient for whom no treatment outcome is assigned. This includes cases 'transferred out' to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.

Successfully treated A patient who was cured or who completed treatment.

Cohort A group of patients in whom TB has been diagnosed, and who were registered for treatment during a specified time period (e.g. the cohort of new cases registered in the calendar year 2012). This group forms the denominator for calculating treatment outcomes. The sum of the patients included in the above treatment outcome categories should equal the number of cases registered. It should be highlighted that in the new definitions recommended since March 2013 *any patient found to have drugresistant TB and*

placed on second-line treatment should be removed from the drug-susceptible TB outcome cohort. This means that management of the standard TB register and of the second-line TB treatment register needs to be coordinated to ensure proper accounting of the outcomes of treatment.

7. DRUG RESISTANCE OR INTOLERANCE

Detection of drug resistance

All strains of *Mycobacterium tuberculosis* must be referred to the Laboratory for confirmation of identification and drug susceptibility testing (DST).

a) Rapid detection of resistance

The Gene Xpert instrument, using the Xpert MTB/RIF assay can be used to detect *M. tuberculosis* DNA from respiratory samples using real time PCR technology. The assay also detects mutations which confer rifampicin resistance. For patients likely to have acquired TB in settings where the risk of multidrug resistance (resistant to isoniazid and rifampicin) is significant, the detection of rifampicin resistance by Xpert MTB/RIF is highly predictive of MDRTB detection. Some extrapulmonary specimens may also be tested with the Xpert assay – such testing should be discussed with the laboratory.

b) Conventional DST

This is performed using the BACTEC 960 MGIT liquid culture system. All *M. tuberculosis* strains receive first line DST (isoniazid, rifampicin, ethambutol, streptomycin and pyrazinamide). Drug resistant strains receive supplementary DST to the second line agents. First and second line testing each requires 10-14 days for a result. Slow growing strains may need repeat testing before a reportable result is obtained.

Drug intolerance

In the event of an adverse drug reaction, careful assessment is required and clinical liaison with a clinician experienced in managing such issues is recommended. Some adverse events may represent an absolute contra-indication

to continued use of an agent whereas others may be managed symptomatically without necessarily abandoning the use of the drug. Comments below on mono-resistance also apply to intolerance where ongoing use of the particular agent is contra-indicated.

Treatment of mono- or poly-resistant non-multidrug-resistant tuberculosis

The therapy focus for patients carrying mono- or poly-resistance who are not MDR is completely different than cases where the drug involved in the resistance is H or R.

Patients with H mono- or poly-resistance but who retain susceptibility to R are fairly common in all NTPs. These patients are relatively easy to treat and cure with a drug combination regimen of 9–12 months that includes R and three other drugs, including an FQ. These three other drugs should be selected based on the rational categorisation. The ideal treatment for a patient with H mono-resistance would be treatment length of 9 months with R+FQ+E and the initial support of Z during the first 2 months.

In Ukraine used the next regimen for H-mono-resistance or H+S or H+E poly-resistance:

2RZK_mLfx10RZLfx.

If there is H+Z poly-resistance:

2REK_mLfx10RELfx.

A completely different situation exists **in patients with R mono- and poly-resistance** retaining susceptibility to H. This situation is very rare because over 90 %–95 % of cases with R resistance are actually MDR-TB. Further, it must be remembered that while DST reliability for H is high, it is not 100 %. So, under field conditions, *all R mono- or poly-resistant cases must be managed like MDR-TB patients*, of course adding H for its potential helpful effect. Accordingly, an MDR-TB plan must be designed following all the premises

discussed in this chapter. H must be added, but preferably not counted among the four drugs forming the core of treatment. The patient will then have a high likelihood of cure, whether he is MDR-TB or R mono or poly-resistant but with susceptibility to H. Because R cannot be used on these patients, treatment should last at least 18-20 months.

Multi-drug resistance (MDR-TB)

MDR-TB is TB resistant to at least isoniazid and rifampicin (and possibly other drugs). MDR-TB should only be treated by clinicians experienced in managing TB.

Treatment must be individualized based on drug susceptibility results, but is usually as many first-line drugs as possible (ethambutol and/or pyrazinamide), an injectable agent (usually amikacin, a fluoroquinolone, moxifloxacin), and other second-line drugs as appropriate. A regimen should include a minimum of three (preferably five) drugs to which the organism is known to be susceptible. Despite laboratory resistance, isoniazid may be kept in the treating regimen and is recommended in most cases where isoniazid resistance is documented to be at a low level only.

Recommendations on pyrazinamide dosage

Queensland Health recommends 30–40 mg/kg of pyrazinamide to a maximum of 2g per day. This dose is higher than recommended by other authorities. This is because the original randomized controlled trials conducted by the BMRC used dosages of 1,5g daily for participants less than 50kg, and 2g for those 50kg and over.

GROUPS OF DRUGS TO TREAT MDR-TB

For MDR treatment, TB drugs are grouped according to efficacy, experience of use and drug class. All the first-line TB drugs are in Group 1,

except streptomycin, which is classified with the other injectable agents in Group 2. All the drugs in Groups 2–5 (except streptomycin) are second-line, or reserve, drugs. The features of the drugs within each group, including cross-resistance are discussed in more detail below. Cross resistance means that resistance mutations (in *M. tuberculosis* bacteria) to one anti-TB drug may confer resistance to some or all of the members of the drug family and, less commonly, to members of different drug families.

Group 1. Group 1 drugs are the most potent and best tolerated. If there is good laboratory evidence and clinical history that suggests that a drug from this group is effective, it should be used. If a Group 1 drug was used in a previous regimen that failed, its efficacy should be questioned even if the DST result suggests susceptibility. Then newer rifamycins, such as rifabutin, have very high rates of cross-resistance to rifampicin.

Group 2. All patients should receive a Group 2 injectable agent if susceptibility is documented or suspected. Among aminoglycosides, kanamycin or amikacin is the first choice of an injectable agent, given the high rates of streptomycin resistance in drug-resistant TB. In addition, both these agents are inexpensive, cause less ototoxicity than streptomycin, and have been used extensively for the treatment of drug-resistant TB. Amikacin and kanamycin are considered to be very similar and have a high frequency of cross-resistance. If an isolate is resistant to both streptomycin and kanamycin, or if DRS data show high rates of resistance to amikacin and kanamycin, capreomycin (a polypeptide) should be used.

Group 3. All patients should receive a Group 3 medication if the *M. tuberculosis* strain is susceptible or if the agent is thought to have efficacy. One of the higher generation fluoroquinolones, such as levofloxacin or moxifloxacin,

is the fluoroquinolone of choice. Ciprofloxacin is no longer recommended to treat drug-susceptible or drug-resistant TB.

Table 2. Groups of drugs to treat MDR-TB

Group	Drugs (abbreviations)
Group 1: First-line oral agents	<ul style="list-style-type: none"> •pyrazinamide (Z) •ethambutol (E) •rifabutin (Rfb)
Group 2: Injectable agents	<ul style="list-style-type: none"> •kanamycin (Km) •amikacin (Am) •capreomycin (Cm) • streptomycin (S)
Group 3: Fluoroquinolones	<ul style="list-style-type: none"> • levofloxacin (Lfx) • moxifloxacin (Mfx) • ofloxacin (Ofx)
Group 4: Oral bacteriostatic second-line agents	<ul style="list-style-type: none"> • para-aminosalicylic acid (PAS) • cycloserine (Cs) • terizidone (Trz) • ethionamide (Et) • protionamide (Pt)
Group 5: Agents with unclear role in treatment of drug resistant-TB	<ul style="list-style-type: none"> •clofazimine (Cfz) •linezolid (Lzd) •amoxicillin/clavulanate (Amx/Clv) •thioacetazone (Thz) •imipenem/cilastatin (Ipm/Cln) • high-dose isoniazid (high-dose H)¹ • clarithromycin (Clr)

¹High-dose isoniazid is defined as 16–20mg/kg/day. Some experts feel that high-dose isoniazid can still be used in the presence of resistance to low concentrations of isoniazid (>1% of bacilli resistant to 0.2 µg/ml but susceptible to 1 µg/ml of isoniazid), whereas isoniazid is not recommended for high-dose resistance (>1% of bacilli resistant to 1 µg/ml of isoniazid).

Group 4. Ethionamide (or protionamide) is often added to the treatment regimen because of low cost. If cost is not a constraint, p-aminosalicylic acid (PAS) may be added first, given that the enteric-coated formulas are relatively well tolerated and that there is no cross-resistance to other agents. When two agents are needed, cycloserine can be added. Since the combination of ethionamide (or protionamide) and PAS often causes a high incidence of gastrointestinal side-effects and hypothyroidism, these agents are usually used together only when three Group 4 agents are needed: ethionamide (or protionamide), cycloserine and PAS. Terizidone can be used instead of cycloserine and is assumed to be equally efficacious.

Group 5. Group 5 drugs are not recommended by WHO for routine use in drug-resistant TB treatment because their contribution to the efficacy of multidrug regimens is unclear.

They can be used in cases where it is impossible to design adequate regimens with the medicines from Groups 1–4, such as in patients with XDR-TB. They should be used in consultation with an expert in the treatment of drug-resistant TB.

8. COMMON DRUG SIDE EFFECTS

Regimens used in the treatment of new TB patients consist of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E). In general, first-line anti-TB drugs (FLDs) are well tolerated with a relatively low frequency of major adverse effects that result in withdrawal of drugs from the regimens.

Gonzalez Montaner and colleagues reported that the frequency of interruption of treatment due to adverse effects was 0,9 % for H, 2,3 % for R and 4,9 % for Z. Ormerod and Horsfield assessed 1317 patients and reported that 5,1 % of patients had adverse reactions to anti-TB drugs requiring modification of treatment regimens. Reactions occurred in 4,9 % of patients treated with Z, 4,5 % with streptomycin (S), 1,8 % with R, 0,5 % with H and 0,2 % with E. A meta-analysis reported that the overall proportion of adult patients treated with regimens containing both H and R who developed clinical hepatitis was 2,7 %, but there was substantial variation between settings.

Yee and colleagues reported that 9 % of patients had major adverse drug effects and that overall incidence of major adverse effects of Z (6 %) was higher than H (4 %) or R (3 %). The proportion of patients with MDR-TB who experienced one or more adverse drug reactions was 69,2 % in Turkey, 71 % in Bangladesh, 72 % in Nepal and 79 % in Latvia. The proportion of MDR-TB patients who required discontinuation of one or more anti-TB drugs during treatment was substantial: 21,4 % in Taiwan (Taipei), 28,7 % in Russia (Tomsk), 30 % in the United States (Denver), 34,2 % in Peru (Lima), 42,6 % in Estonia, 43,5 % in Latvia, 49,4 % in the Philippines (Manila) and 55,5 % in Turkey (Istanbul). Several factors are associated with increased risk of hepatotoxicity during anti-TB treatment: old age, extensive TB disease, malnutrition, excessive use of alcohol, chronic hepatitis B infection, chronic hepatitis C infection and human immunodeficiency virus (HIV) infection.

Table 3. Common drug side effects

Drug	Adverse effects	Comments
Isoniazid	<ul style="list-style-type: none"> * Raised transaminases (10-20%) * Hepatitis (0.6% monotherapy, 2.6% H+R) * Peripheral neuropathy * CNS effects (fatigue, drowsiness, headache, depression/neuropsychiatric_) * Acne (especially in SE Asian subjects) * Nausea, vomiting, diarrhoea. 	<ul style="list-style-type: none"> * Risk of hepatotoxicity increases with age¹, heavy alcohol consumption, liver disease. * Rarely neuropathy may affect optic nerve.
Rifampicin	<ul style="list-style-type: none"> * Red-orange discolouration of urine and body fluids * Nausea, vomiting, diarrhoea * Thrombocytopenia * Flu like syndrome. 	<ul style="list-style-type: none"> * Flu like syndrome (myalgia, arthralgia, fever malaise, mild hemolysis) more likely with intermittent therapy. * Interrupted therapy may be associated with shock, acute renal failure, haemolytic anaemia and thrombocytopenic purpura – these features are an absolute contraindication to re-challenge. * Liver enzyme abnormalities may be cholestatic or transaminitis.
Pyrazinamide	<ul style="list-style-type: none"> * Arthralgia * Gout * Nausea, vomiting, diarrhoea * Hepatitis * Facial flushing * Rash * Photosensitivity * Difficulty with diabetic control. 	<ul style="list-style-type: none"> * Elderly are more prone to GI side-effects and to hepatitis. * Avoid pyrazinamide if pre-existing history of clinical gout.
Ethambutol	<ul style="list-style-type: none"> * Rash * Nausea * Optic neuritis (retrobulbar) * Increased serum urate / gout * Hypersensitivity reactions are rare. 	<ul style="list-style-type: none"> * Visual disturbance risk is increased with longer duration and higher dose². Usually occurs after months of therapy but rarely within days. Typically is a central (axial neuritis) and manifest by blurred vision, decreased acuity, central scotomas, loss of ability to detect green and sometimes red colour. More rarely optic neuritis affects peripheral nerve fibres: visual field constriction but acuity and colour vision intact. * Visual acuity, colour vision and fields should be checked monthly. * Risk of ocular toxicity is

		<p>increased in renal impairment. * Patients should undergo an ophthalmology review if their ethambutol treatment extends for two months or longer. Patients need to be educated at the commencement of treatment about visual symptoms.</p>
--	--	---

¹ In IPT recipients ALT >5 x normal found in 0.45% age <35, 0.85% age 35-49 and 2% age 50 and over (Fountain, 2005).

² Tb patients taking ethambutol for greater than 2 months: risk of optic neuritis [15mg/kg/day - <1%], [25mg/kg/day – 5-6%] [>35mg/kg/day – 18%].

Isoniazid

Abnormally high liver enzymes (transaminase) are relatively frequent among patients treated with H. Hepatitis and peripheral neuropathy occur occasionally. Seizures, hallucinations, psychosis, optic neuropathy, pellagra, anaemia, metabolic acidosis, lupus erythematosus, agranulocytosis, alopecia, asthma and dermatitis are rare.

Rifampicin

Among patients treated with R, transient elevation of bilirubin, orange discolouration of urine and tears and increased liver enzymes are relatively frequent. Hepatitis, pruritus and drug fever occasionally occur. Interstitial nephritis, glomerulonephritis, renal failure, toxic epidermal necrolysis, oligomenorrhoea, amenorrhoea, anaphylactic shock, thrombocytopenia, neutropenia, hemolytic anaemia, pseudomembranous colitis, lupus erythematosus and myopathy are rare.

Pyrazinamide

Among patients treated with Z, arthralgia and hyperuricemia are relatively common. Z interferes with the metabolism of purine, resulting in decreased excretion of uric acid. Allopurinol is not recommended in the management of Z-induced hyperuricemia because it increases plasma concentration of pyrazinoic

acid, which inhibits renal urate secretion. Hepatitis, nausea and rash occasionally occur. Anaemia, lupus erythematosus, convulsions and photodermatitis are rare. Among the first-line anti-tuberculosis drugs, Z is the most frequent offending drug in cases of drug-induced hepatitis.


Ethambutol

Among those treated with E, the most important adverse effect is ocular toxicity, which fortunately is uncommon. Aplastic anaemia, eosinophilic pneumonia, thrombocytopenia and hyperuricemia are rare.

Streptomycin

The main adverse drug effects of S are vestibular-cochlear toxicity and renal toxicity, both of which are typically dose-dependent. Hypersensitivity reaction occurs relatively frequently. S may in rare cases cause neuromuscular blockade.

Table 4. Which agent is most likely to cause a given symptom or adverse effect?

	Most likely cause			Least likely cause
Hepatitis – ALT/AST predominant	Isoniazid	Pyrazinamide	Rifampicin	Ethambutol (very rare)
Hepatitis - cholestatic	Rifampicin			
Upper GIT symptoms	Rifampicin	Pyrazinamide	Isoniazid	Ethambutol
Arthralgia	Pyrazinamide	Rifampicin (flu like syn.)	Isoniazid (drug induced lupus)	Ethambutol
Hypersensitivity (fever plus rash plus other)	Isoniazid	Rifampicin	Pyrazinamide	Ethambutol

9. MANAGEMENT OF SIDE EFFECTS

Management of cutaneous reactions

If a patient develops itching without a rash and there is no other obvious cause, the recommended approach is to try symptomatic treatment with antihistamines and skin moisturizing, and continue TB treatment while observing the patient closely. If a skin rash develops, however, all anti-TB drugs must be stopped.

Once the reaction has resolved, anti-TB drugs are reintroduced one by one, starting with the drug least likely to be responsible for the reaction (rifampicin or isoniazid) at a small challenge dose, such as 50 mg isoniazid (3). The dose is gradually increased over 3 days.

This procedure is repeated, adding in one drug at a time. A reaction after adding in a particular drug identifies that drug as the one responsible for the reaction.

Management of drug-induced hepatitis

Of the first-line anti-TB drugs, isoniazid, pyrazinamide and rifampicin can all cause liver damage (drug-induced hepatitis). In addition, rifampicin can cause asymptomatic jaundice without evidence of hepatitis. It is important to try to rule out other possible causes before deciding that the hepatitis is induced by the TB regimen.

The management of hepatitis induced by anti-TB treatment depends on:

whether the patient is in the intensive or continuation phase of TB treatment;

the severity of the liver disease;

the severity of the TB; and

the capacity of the health unit to manage the side-effects of TB treatment.

If it is thought that the liver disease is caused by the anti-TB drugs, all drugs should be stopped. If the patient is severely ill with TB and it is

considered unsafe to stop anti-TB treatment, a non-hepatotoxic regimen consisting of streptomycin, ethambutol and a fluoroquinolone should be started.

If anti-TB treatment has been stopped, it is necessary to wait for liver function tests to revert to normal and clinical symptoms (nausea, abdominal pain) to resolve before reintroducing the anti-TB drugs. If it is not possible to perform liver function tests, it is advisable to wait an extra 2 weeks after resolution of jaundice and upper abdominal tenderness before restarting TB treatment. If the signs and symptoms do not resolve and the liver disease is severe, the non-hepatotoxic regimen consisting of streptomycin, ethambutol and a fluoroquinolone should be started (or continued) for a total of 18–24 months.

Once drug-induced hepatitis has resolved, the drugs are reintroduced one at a time. If symptoms recur or liver function tests become abnormal as the drugs are reintroduced, the last drug added should be stopped. Some advise starting with rifampicin because it is less likely than isoniazid or pyrazinamide to cause hepatotoxicity and is the most effective agent. After 3–7 days, isoniazid may be reintroduced. In patients who have experienced jaundice but tolerate the reintroduction of rifampicin and isoniazid, it is advisable to avoid pyrazinamide.

Alternative regimens depend on which drug is implicated as the cause of the hepatitis. If rifampicin is implicated, a suggested regimen without rifampicin is 2 months of isoniazid, ethambutol and streptomycin followed by 10 months of isoniazid and ethambutol.

If isoniazid cannot be used, 6–9 months of rifampicin, pyrazinamide and ethambutol can be considered.

If pyrazinamide is discontinued before the patient has completed the intensive phase, the total duration of isoniazid and rifampicin therapy may be extended to 9 months.

If neither isoniazid nor rifampicin can be used, the non-hepatotoxic regimen consisting of streptomycin, ethambutol and a fluoroquinolone should be continued for a total of 18 – 24 months.

Reintroducing one drug at a time is the optimal approach, especially if the patient's hepatitis was severe. National TB programs using FDC tablets should therefore stock limited quantities of single anti-TB drugs for use in such cases. However, if the country's health units do not yet have single anti-TB drugs, clinical experience in resource-limited settings has been successful with the following approach, which depends on whether the hepatitis with jaundice occurred during the intensive or the continuation phase.

- When hepatitis with jaundice occurs during the intensive phase of TB treatment with isoniazid, rifampicin, pyrazinamide and ethambutol: once hepatitis has resolved, restart the same drugs except replace pyrazinamide with streptomycin to complete the 2-month course of initial therapy, followed by rifampicin and isoniazid for the 6-month continuation phase.

- When hepatitis with jaundice occurs during the continuation phase: once hepatitis has resolved, restart isoniazid and rifampicin to complete the 4-month continuation phase of therapy.

10.TREATMENT OF EXTRAPULMONARY TUBERCULOSIS

Bone and joint TB

Standard course therapy (5EHRZ, 4 HR) is sufficient in most cases where TB is known to be susceptible to first line drugs. The continuation phase is sometimes extended to 10 months but this regimen is not supported by published evidence unless infection is disseminated, treatment interruption or drug resistance is suspected or proven.

Central nervous system TB

Standard treatment is extended to twelve months (2EHRZ/10HR). Adjunctive corticosteroids are usually recommended to prevent clinically dangerous paradoxical reactions.

Disseminated or miliary TB

Standard treatment is extended to twelve months (2EHRZ/10HR). Smear positive pulmonary TB with extensive cavitation on plain radiography of the chest.

Standard treatment is extended to nine months (2EHRZ/7HR) unless there has been documented culture conversion at two months, because there is a higher risk of relapse with six months of treatment.

11. TREATMENT REGIMENS IN SPECIAL SITUATIONS

The treatment of TB in pregnancy and breastfeeding, liver disorders, and renal failure is discussed below.

Pregnancy and breastfeeding

Women of childbearing age should be asked about current or planned pregnancy before starting TB treatment. A pregnant woman should be advised that successful treatment of TB with the standard regimen is important for successful outcome of pregnancy. With the exception of streptomycin, the first line anti-TB drugs are safe for use in pregnancy: streptomycin is ototoxic to the fetus and should not be used during pregnancy.

A breastfeeding woman who has TB should receive a full course of TB treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to the baby. Mother and baby should stay together and the baby should continue to breastfeed. After active TB in the baby is ruled out, the baby should be given 6 months of isoniazid preventive therapy, followed by BCG vaccination.

Pyridoxine supplementation is recommended for all pregnant or breastfeeding women taking isoniazid.

Liver disorders

Patients with the following conditions can receive the usual TB regimens provided that there is no clinical evidence of chronic liver disease: hepatitis virus carriage, a past history of acute hepatitis, current excessive alcohol consumption. However, hepatotoxic reactions to anti-TB drugs may be more common among these patients and should therefore be anticipated.

In patients with unstable or advanced liver disease, liver function tests should be done at the start of treatment, if possible. If the serum alanine

aminotransferase level is more than 3 times normal before the initiation of treatment, the following regimens should be considered.

The more unstable or severe the liver disease is, the fewer hepatotoxic drugs should be used.

Possible regimens include:

- Two hepatotoxic drugs (rather than the three in the standard regimen):

9 months of isoniazid and rifampicin, plus ethambutol (until or unless isoniazid susceptibility is documented);

2 months of isoniazid, rifampicin, streptomycin and ethambutol, followed by 6 months of isoniazid and rifampicin;

6–9 months of rifampicin, pyrazinamide and ethambutol.

- One hepatotoxic drug:

2 months of isoniazid, ethambutol and streptomycin, followed by 10 months of isoniazid and ethambutol.

- No hepatotoxic drugs:

18–24 months of streptomycin, ethambutol and a fluoroquinolone.

Expert consultation is advisable in treating patients with advanced or unstable liver disease.

Clinical monitoring (and liver function tests, if possible) of all patients with pre-existing liver disease should be performed during treatment.

Renal failure and severe renal insufficiency

The recommended initial TB treatment regimen for patients with renal failure or severe renal insufficiency is 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol, followed by 4 months of isoniazid and rifampicin. Isoniazid and rifampicin are eliminated by biliary excretion, so no change in dosing is necessary. There is significant renal excretion of ethambutol and metabolites of pyrazinamide and doses should therefore be adjusted. Three times per week administration of these two drugs at the following doses is

recommended: pyrazinamide (25 mg/kg), and ethambutol (15 mg/kg). These are the same mg/kg doses as those listed under “Daily”.

While receiving isoniazid, patients with severe renal insufficiency or failure should also be given pyridoxine in order to prevent peripheral neuropathy.

Because of an increased risk of nephrotoxicity and ototoxicity, streptomycin should be avoided in patients with renal failure. If streptomycin must be used, the dosage is 15 mg/kg, two or three times per week, to a maximum of 1 gram per dose, and serum levels of the drug should be monitored.

12. MONITORING THE PATIENT

All patients should be monitored to assess their response to therapy. Regular monitoring of patients also facilitates treatment completion and allows the identification and management of adverse drug reactions. All patients, their treatment supporters and health workers should be instructed to report the persistence or reappearance of symptoms of TB (including weight loss), symptoms of adverse drug reactions, or treatment interruptions.

Patient weight should be monitored each month, and dosages should be adjusted if weight changes. Additional monitoring and the actions it triggers are discussed below for pulmonary and extrapulmonary cases treated with first-line drugs for monitoring of patients receiving second-line drugs.

A written record of all medications given, bacteriological response and adverse reactions should be maintained for every patient on the TB Treatment Card.

13. SURGICAL TREATMENT

A recent systematic review reported that pulmonary resection combined with anti-TB chemotherapy for MDR-TB has achieved treatment success rates in some settings of up to 88–92% of cases, as well as reduced odds of all-cause mortality. Despite these favourable results, the role of surgery remains rather controversial in the most recently published MDR-TB treatment guidelines. Its indication is limited to the management of complicated forms of TB (including massive haemoptysis, bronchiectasis, bronchial stenosis, bronchopleural fistula and aspergilloma) and, mostly, to cases in which medical treatment is failing.

Among studies assessing surgery for all forms of TB, several authors have postulated the following *absolute indications for surgery in TB treatment*:

- a high probability of failure of medical therapy in MDR-TB patients (due to persistent cavitory disease and lung or lobar destruction) and massive haemoptysis or tension pneumothorax;
- persistent positivity of sputum-smear or sputum-culture despite adequate chemotherapy;
- a high risk of relapse (based on the drug-resistance profile and radiological findings);
- localized lesion;
- progression of TB despite adequate chemotherapy;
- repeated haemoptysis or secondary infection;
- localized disease amenable to resection;
- polyresistant and MDR-TB;
- absence of any radiological and/or bacteriological improvements during the initial three to four months of chemotherapy;
- allergic, toxic and mixed side-effects of drugs;
- chronic diseases of the gastrointestinal organs hindering effective chemotherapy.

Emergency indications (that is, without surgery death is imminent and unavoidable) include:

- profuse lung haemorrhage
- tension spontaneous pneumothorax.

Urgent indications include:

- irreversible TB progression, despite adequate anti-TB chemotherapy
- recurrent haemoptysis that cannot be stopped by other treatment methods.

Although there is not enough evidence to define the characteristics of cavities and other irreversible changes in M/XDR-TB patients that can lead to a high probability of failure of TB chemotherapy and relapse, the majority of authors define ***the elective indications*** listed here:

- localized forms of cavitory TB with continuous *M. tuberculosis* excretion confirmed by bacteriological examination and DST after four to six months of supervised anti-TB chemotherapy;

- M/XDR-TB characterized by failure of anti-TB chemotherapy;

- complications and sequelae of the TB process (including M/XDR-TB), including:

- spontaneous pneumothorax and pyopneumothorax

- pleural empyema with or without bronchopleural fistula

- aspergilloma

- nodular-bronchial fistula

- broncholith

- pachypleuritis or pericarditis with respiratory and blood circulation insufficiency

- post-TB stenosis of trachea and large bronchi

- symptomatic and chronic post-TB bronchiectasis;

– other indications such as the elimination of complications of previous surgery.

Conditions for and timing of surgery

Proper patient selection and the timing of operations are crucial to avoid relapses and to provide a higher chance of cure. Good cooperation between treating physicians and thoracic surgeons, as well as patients' adherence to pre- and postoperative intervention chemotherapy, can increase the success rate of MDR-TB treatment.

For patients to be considered as candidates for surgery, three major criteria need to be met: the patient must have localized disease amenable to resection and with an adequate respiratory reserve; the patient must have extensive drug resistance, making the likelihood of treatment failure or relapse very high; and a sufficient quantity of second-line drugs must be available to ensure healing after surgery. In the case of bilateral lesions, resection should be performed on the side with the greater lesions.

Surgery should be seriously considered when:

- the disease is sufficiently localized to allow surgery;
- the remaining lung tissue around the resection margins is estimated to be free of TB;
- the patient's surgical risk level is acceptable, with sufficient pulmonary reserve to tolerate the resection.

In any case, irreversible pathomorphological changes in the affected lung(s) are a significant additional indication for surgery. In all cases, surgery is only indicated if it is possible to perform surgery (resection of the lung or other type of operation) without significant damage to the patient's lung function.

Types of operation

The following are the types of operation currently performed:

*** lung resections of different size:**

- wedge resection

- segmentectomy
- lobectomy and bilobectomy
- combined resection (lobectomy plus minor resection)
- pneumonectomy or pleuropneumonectomy
- lung resections with different correction methods of the haemithorax's volume;

- * extrapleural thoracoplasty;

- * extrapleural pneumolysis;

- * thoracomyoplasty;

- * pleurectomy and decortications of the lung;

- * **operations on the bronchi:**

- occlusion

- resection

- bronchoplasty

- re-amputation of the stump;

- * thoracocentesis and thoracostomy (drainage of the pleural space);

- * artificial pneumothorax and pneumoperitoneum;

- * operations on both lungs.

According to the literature analysed, the principal types of operation to treat TB today are lung resections of different sizes, using posterolateral thoracotomy under general anaesthesia with double-lumen endotracheal tube and artificial ventilation of the lung. Mobilization of the lung (or the part of it to be resected) is approached in such a way as to avoid contamination of the pleural space. It should be mentioned, however, that anatomical resections are preferable.

It is also worth mentioning that in Kazakhstan, the Russian Federation and Ukraine, thoracoplasty is still widely used when lung resection is contraindicated. For instance, in the Novosibirsk Tuberculosis Research Institute, osteoplastic thoracoplasty (a variant of extrapleural thoracoplasty) has been used for the last 50 years for patients with complicated cavitary forms of

TB for whom lung resection is contraindicated. This type of surgery allows the TB process to be stabilized so that lung resection can be performed later with a lower risk of postoperative complications. Thoracoplasty is also used in other countries to reduce the space in the chest cavity resulting from lung resection.

The operations for TB and M/XDR-TB patients listed above need to be managed in well-equipped and well-staffed clinics (that is, with experienced surgeons, anaesthesiologists and other specialists) with modern preoperative examinations, operating theatres and efficient postoperative care units, because of the associated high perioperative morbidity and mortality. Appropriate infection control measures should also be in place. In addition, it is of the utmost importance to remember that TB is an infectious disease and, therefore, the basic principles for TB control listed below should be followed:

- priority should be given to prevention (that is, full implementation of the Stop TB Strategy);
- a specialized unit should be used;
- reliable DST should be carried out for first- and second-line drugs, or a WHO-endorsed rapid molecular diagnostic test should be carried out;
- a reliable anti-TB drugs supply should be available;
- staff should be involved long-term and financial resources should be available.

The conditions listed above do not exist everywhere. A study from the Russian Federation published in 2012 revealed that surgery does not substantially cure TB, including new cases. The material and technical capacities of TB care facilities (such as equipment and staff skills) do not allow indications for surgery to be adequately determined. Furthermore, computed tomography (CT) scanning technology is only available in 15% of the institutions that have surgical units, and only 12% of operations on respiratory organs are carried out using such high technologies. The authors of the study concluded that substantial changes in the surgical treatment of TB are needed. Each federal district in the Russian Federation should set up two or three

thoracic surgery departments and ensure that they have the necessary equipment and appropriately skilled staff.

**Contraindications for elective surgical treatment of pulmonary TB
and M/XDR-TB**

In the majority of cases, contraindications for the surgical treatment of TB patients depend on how extensive the process is to be, assessment of the patients' cardiopulmonary function and their general state of health.

The following **contraindications can be considered for lung resection:**

- extensive cavitory lesion of the both lungs;
- impaired pulmonary function test; that is forced expiratory volume in one second less than 1.5 L in cases of lobectomy and less than 2.0 L where pneumonectomy is planned;
- pulmonary-heart failure III–IV (functional classification of the New York Hart Association);
- body mass index up to 40–50% of the normal range;
- severe co-morbidity (decompensation in diabetes, exacerbation of stomach and duodenum ulcers, hepatic or renal impairment);
- active bronchial TB.

It should be emphasized, however, that a multidisciplinary approach should be taken when a patient is being considered for surgery and the decision must be made together by physicians, surgeons, anaesthesiologists and other specialists.

Surgery is a very serious step for patients with TB, in particular for those with M/XDR-TB, given the history of their long and difficult-to-treat disease. For many of these patients, their disease will be too extensive and characterized by lung destruction and/or lung function that is too poor, making them unsuitable for surgery. In addition, each operation is rather dangerous and carries certain risks. It is, therefore, crucial to discuss individually with each

patient and his/her family all details about the planned surgery and to perform all necessary preoperative examinations and treatments. *The following steps* are crucial.

– A comprehensive and open discussion should be carried out with patients and their relatives about the nature of their TB and the necessity of surgical intervention, as well as the risks and benefits of surgery, and the short- and long-term prognosis with and without surgical intervention. Possible complications in terms of anaesthesia and the operation must be discussed with all patients and their relatives. Consent for surgery must be obtained for all patients who are to undergo surgery.

– The following preoperative investigations need to be carried out: full blood analysis, biochemistry tests (liver and kidney, blood sugar, electrolytes and coagulation), HIV testing, sputum-smear microscopy, sputum-culture testing and DST, standard chest X-ray and CT scan, and fibre-optic bronchoscopy (to rule out endobronchial TB, contralateral disease and malignancy).

– The patient's cardiorespiratory reserve must be carefully evaluated based on pulmonary function testing: body plethysmography (to evaluate vital capacity, forced expiratory volume in one second and diffusion of the lung(s)), electrocardiogram and echocardiogram (to rule out heart failure and pulmonary hypertension), perfusion lung scintigraphy (in patients with marginal spirometric results and diffusion of the lung(s)), arterial blood gas analysis and routine cardiological consultation.

– Nutritional assessment (body mass index) should be carried out to ensure the patient can tolerate and recover from surgery.

– Airways should be sanitized: respiratory exercises, postural drainage and routine aerosol inhalation should be carried out, or nebulized bronchodilators and antibiotics used.

– Smoking cessation must be encouraged.

Adequate anti-TB chemotherapy before and after surgery is essential in the management of TB (especially M/XDR-TB) patients. All TB cases referred for surgery (except in emergencies) should, therefore, have documented DST results.

The individual preoperative assessment of each patient is crucial and consists of the following criteria:

- which anti-TB chemotherapy regimen(s) a patient has previously received;
- whether the patient took all the drugs in each regimen prescribed and for how long;
- measurement of the bacteriological, clinical and radiological progress or deterioration during and since the administration of each regimen;
- evaluation of the current treatment strategy, including the indications for surgery.

Anti-TB chemotherapy before surgery should be at least four months (and between four and six months) in duration. Individual drug regimens (including at least five drugs for M/XDR-TB patients) should be administered in proper doses. In order to avoid serious and potentially fatal complications of TB surgery, it is recommended to perform the operation when the *M. tuberculosis* population is likely to be at its lowest level.

Postoperative management

The short- and long-term outcomes of surgery largely depend on the meticulous postoperative management of TB patients, beginning in the intensive care (high-dependency) unit immediately after the operation. This includes:

- using proper analgesia, including opioids;
- carrying out physiotherapy and respiratory exercises, including incentive spirometry;
- performing daily chest X-rays for the first three days;
- carrying out diagnostic and/or curative bronchoscopies if needed;
- removal of chest drains when their output has stopped;

– after the lung resections (in particular, after lobectomy and pneumonectomy), watching carefully for the early and late development of postoperative complications, such as air leaks, bronchopleural fistulas, residual pleural space and pleural empyema, and undertaking treatment procedures as necessary (including surgical interventions in the case of clear indications);

– transferring patients from the intensive care unit to the thoracic surgical ward once they are haemodynamically stable.

Postoperative management, including decisions relating to types of analgesia and timing of the removal of chest drains, does, of course, depend very much on the practices of the clinic concerned.

Anti-TB chemotherapy after surgery

Patients in all relevant studies recommenced their preoperative anti-TB chemotherapy regimen as soon as they resumed oral intake after surgery, with the possible adjustment of chemotherapy after analysis of the bacteriological results of the surgical material (resected lung tissue). Postoperative chemotherapy is as indispensable as preoperative chemotherapy because after resection of the main lung lesion, scattered nodular lesions and tiny cavities may be left behind. It is, therefore, vital to ensure that all patients (in particular those with M/XDR-TB) remain on multidrug anti-TB regimens for a sufficiently long period to kill the bacilli present at the remaining lesions.

Based on the analysis of the literature cited above, the following durations of anti-TB chemotherapy are recommended, depending on whether patients are culture-positive or culture-negative at the time of surgery and the type of TB involved:

*** culture-positive patients at the time of surgery:**

- with susceptible TB, four to six months after culture conversion
- with MDR-TB, at least 18 months after culture conversion
- with XDR-TB, at least 24 months after culture conversion;

*** culture-negative patients at the time of surgery:**

- with susceptible TB, at least four months after surgery
- with M/XDR-TB, six to eight months after surgery (depending on postoperative recovery).

It should be emphasized, however, that duration of postoperative chemotherapy also depends on the individual clinical condition of each patient (for example, whether the patient also has diabetes, the acute progression of the TB prior to surgery or the extent of the surgery carried out).

14. PATHOGENETIC TREATMENT OF TUBERCULOSIS

It is aimed at solving the following tasks:

1. Decreasing exudative pneumonic phenomena in a lesion nidus, speeding up its resolution and healing with minimum residual changes;
2. Correction of metabolic processes and disfunctions of various organs and systems disturbed by tuberculous intoxication and antimycobacterial drugs;
3. Strengthening of feebly-expressed inflammatory reactions and stimulation of repairing processes.

The following methods of rational therapy are applied to realize these tasks:

I. Common means of pathogenetic therapy, which include:

1. Hygienic-dietary regimen, which from strict bed care widens to spare diet, training and to labour adaptation regimen;
2. Rational high calory and vitaminized diet (No 11 diet according to Peuzner);
3. Physical metods: aero-, helio-, hydrotherapy, climatotherapy;
4. Psychotherapy and autogenous training;
5. Means of metabolic detoxication and correction, in particular protein and water- electrolytic metabolism; oxidation-reduction processes, acidicalkaline equilibrium, regulation of hemodynamics and diuresis.

II. Immunocorrecting therapy. It is performed after studying the function of T-lymphocytes system (cell immunity), B-lymphocytes (humoral immunity), unspecific defence factors. Among immunocorrectors the following drugs are used: thymalin, tactivin, sodium nucleinat, splenin, levamisol or decaris, interferon.

Of unmedicamental treating methods for immunocorrection and as antiinflammatory methods enterosorption, hemosorption, speleotherapy, magnetotherapy, laser-therapy etc. are applied.

Laser Therapy

This has also been tried as an adjunct to chemotherapy in some countries such as Russia for the treatment of drug resistant TB. This is effective in multicavitary disease with heavy bacterial loads particularly when there is an increased chance of failure of medical treatment. It is thought to have a role in the rapid killing of bacteria, increases and improves penetration of antitubercular drugs in walled off lesions and helps in early closure of cavities and is of proven benefit in tracheal and bronchial stenosis due to endobronchial growth. It also reduces the trauma of surgery and post-operative complications.

Immunotherapy or Immunomodulation

Therapeutic modulation of the immune system to enhance the host's immunity to control tuberculosis and to shorten the durations of chemotherapy required to «cure» patients with drug susceptible disease has been tried with some success. *Mycobacterium vaccae* have shown transiently favourable results when given to drug resistant tuberculosis who had failed chemotherapy. Immune modulation can be affected by enhancing proinflammatory cytokines such as IL-2, IL-12, IFN- γ , TNF- α , inhibiting the antiinflammatory cytokines such as IL-4, IL-5, IL-10, addition of serum to enhance humoral factors or diverting the harmful Th2 immune pathway to the beneficial Th1 response by vaccination utilizing *M. vaccae*.

However these therapies are adjuncts and have proved useful in selected cases of drug resistant tuberculosis and randomized control trials, have failed to confirm the utility of this therapy. Beneficial effect of parenterally used IFN- γ have been reported in disseminated disease attributable to mycobacteria other than tuberculosis that was refractory to chemotherapy. Favourable results were reported following one month use of inhaled IFN- γ , 500 microgram thrice weekly. Cytokine therapy has been shown to have clinical utility in modifying the inflammatory manifestation of the lepromatous type of disease. IL-2 was used to restore antigen responsiveness, presumably via enhancing IFN- γ

production. Thalidomide has been shown to inhibit the in-vitro release of TNF- α from peripheral blood monocytes.

In patients with active tuberculosis it induces a significant gain in weight. However the possibility that thalidomide agents may ameliorate tissue injury in tuberculosis needs further study. The potential role of diverse agents such as transfer factor, indomethacin, and levamisole is yet to be established. Levamisole as adjunct to drug treatment has been reported to cause more rapid radiological clearing in the treated group. However it did not significantly affect the clinical outcome. *Mycobacterium w* (commercially available as Immuvac) has been extensively studied as an effective immunomodulator for treatment of leprosy. It enhances bacterial killing and lesion clearance when used as an adjuvant to multi-drug therapy for leprosy. *Mycobacterium w* shares antigens with *M. leprae* as well as *M. tuberculosis* suggesting its application in treatment of drug resistant tuberculosis. A randomised control study has demonstrated that this drug may be responsible for overall reduction of duration of therapy, with no change in sputum conversion rate compared with the traditional short course chemotherapy in new as well as re-treatment cases of tuberculosis. Another advantage though not proven, may be that Immuvac effect would be longer lasting and could take care of defaulters more meaningfully than chemotherapy alone, leading to a reduction in relapse rate and the emergence of MDR TB. Recently, a randomised control trial has been initiated in 2007 and is under progress in order to establish its efficacy and safety as an adjunct therapy in New Pulmonary Tuberculosis (Category I) Patients.

Glutoxim (a commercial immunostimulator) fully converts Isoniazid into its active form in the presence of hydrogen peroxide. Glutoxim lowered the H MIC by a factor of 1,6-2 in sensitive MBT H37Rv, and also in clinical isolates with strong/weak drug-resistance caused by various genetic mutations.

Gene Therapy

The decoding of the human genome provides another fascinating aspect in the future therapeutic intervention of tuberculosis. By identifying resistance

genes, it will be possible to detect drug resistance before start of therapy and also to develop drugs that target these specific genes, enabling us to considerably reduce the duration of therapy.

Role of Steroids

The adjuvant use of corticosteroids in DR-TB patients has been shown not to increase mortality and can be beneficial in conditions such as severe respiratory insufficiency, severe drug induced rashes and central nervous system or pericardial involvement. Prednisone is commonly used, starting at approximately 1 mg/kg and gradually decreasing the dose to 10 mg per week when a long course is indicated.

Corticosteroids may also alleviate symptoms in patients with an exacerbation of obstructive pulmonary disease or when patient is in a very low general condition. In these cases, prednisone may be given in a short course, tapering over 1–2 weeks, starting at approximately 1 mg/kg and decreasing the dose by 5–10 mg per day. Injectable corticosteroids are often used initially when a more immediate response is needed.

Other drugs

Inhibitors of proteolytic enzymes (Contrical 10000 in 200ml of the physiological solution of sodium chloride intravenously drop by drop once a day). Stimulators of repairing processes and cavern healing. The tracheobronchial tree sanitation occupies one of the most prominent places in a complex treatment of respiratory organs tuberculosis patients. The sanative methods may be passive and active. To the former belong postural drainage, administering expectorants, to the latter ones – all methods that consist in aspiration of the tracheobronchial tree contents and immediate administration of medicines into it. With a view to increase sputum excretion the following preparations are applied: preparations stimulating expectoration on account of passive secretion of bronchial glands, decreasing sputum tenacity, increasing activity of twinkling epithelium and peristalsis of bronchioles.

15. REFERENCES

1) Уніфікований клінічний протокол первинної, вторинної (спеціалізованої) та третинної (високоспеціалізованої) медичної допомоги дорослим. Туберкульоз. – Київ. – 2014. – 139 с.

2) Antituberculosis chemotherapy-general and hepatic toxicity revisited [Text] / A.A. Sial [et al.] // Journal of Applied Pharmaceutical Science. – 2014. – Vol 4(1). – P. 148-152.

3) Antituberculosis drugs: Drug interactions, adverse effects, and use in special situations. Part 2: Second-line drugs [Text] / M.A. Arbex, M.de Castro Lima Varella, H.R. de Siqueira, F.A.F. de Mello // Journal Brazilian pneumology. – 2010. – Vol. 36 (5). – 641-656 p.

4) Association between weight change during treatment outcome in patients with smear positive pulmonary tuberculosis [Text] / M. Khajedaluee [et al.] // Open J of Preventive Medicine. – 2014. – Vol. 4. – 446-453 pp.

5) Bottger, E.C. Drug resistance in Mycobacterium tuberculosis: molecular mechanisms and laboratory susceptibility testing [Text] / E.C. Bottger // Antituberculosis chemotherapy. Prog Respir Res Basel, Karger. – 2011. – Vol. 40. – 128-144 pp.

6) Chang, K. A systematic review of rapid drug susceptibility tests for multidrug-resistant tuberculosis using rifampicin-resistance as a surrogate [Text] / K. Chang, W. Yew, Y. Zhang // Expert Opin Med Diagn. – 2009. – Vol. 3. – 99-122 p.

7) Frydenberg, A.R. Toxicity of first-line drugs for treatment of tuberculosis in children: review [Text] / A.R. Frydenberg, S.M. Graham // Tropical medicine and international health. – 2009. – Vol 14, № 11. – 1329-1337.

8) Global tuberculosis report: 2014 [Text]: guideline. – Geneva.: WHO, 2014. – 169 p.

9) Guidelines for clinical and operational management of drug-resistant tuberculosis [Text]: guideline. – Paris.: International union against tuberculosis and lung disease, 2013. – 256 p.

10) Guidelines for the programmatic management of drug-resistant tuberculosis [Text]: guideline. – Geneva.: WHO, 2011. – 33 p.

11) National Tuberculosis Management guidelines [Text]: guideline. – Department health Republic of South Africa, 2014. – 116 p.

12) Patel, N. Effect of an immunomodulator containing Mycobacterium w on sputum conversion in pulmonary tuberculosis [Text] / N. Patel, M.M. Deshpande, M. Shah // J Indian Med Assoc. – 2002. – Vol. 100. – 191-193 pp.

13) Prasad, R. Management of drug resistant and multidrug resistant tuberculosis [Text] / R. Prasad // Medicine update. – 2012. – Vol. 22. – 42-53 pp.

14) The effectiveness of surgical methods of treatment of pulmonary tuberculosis for patients with multidrug resistant at adequate chemotherapy (retrospective, case control, comparative research) [Text] / K.D. Yerimbetov [et al.] // Surgical science. – 2014. – Vol. 5. – 164-169 pp.

15) The influence of Glutoxim on the resistance of Mycobacterium tuberculosis (MTB) strains to Isoniazid [Text]: abstract / O. Manicheva [et al.] // Scientific program including abstracts of Annual Congress of the European Society of Mycobacteriology: 30th june – 03d july 2013. – Florence, Italy. – 88-89 p.

16) Treatment of tuberculosis: GUIDELINES, fourth edition [Text]: guideline. – Geneva.: WHO, 2010. – 147 p.

17) Treatment of tuberculosis in adults and children [Text]: guideline, version 2.0. – Communicable diseases Unit. Department of health, 2014. – 12 p.

18) Tuberculosis: from basic science to patient care [Text]: textbook / edited by J.C. Palomino, S.C. Leao, V. Ritacco. – Antwerp, Sao Paulo, Buenos Aires, 2007. – 686 p.

19) Tuberculosis: practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries [Text]: guide. – Paris.: Medecins Sans Frontieres, Partners in Health, 2013. – 297 p. – ISBN 2-906498-89-0.

20) Tuberculosis: selected internet resources [Text]: compilation / compiled and edited by N.G. Gotera, A.A. Dominguez, M.E.S. Garsia-San Miguel. – Havana City: Finlay Ediciones, 2005. – 353 p. – ISBN 959-7076-12-8.

21) Understanding and using tuberculosis data [Text]: handbook. – Geneva.: WHO, 2014. – 205 p.

22) Understanding tuberculosis – new approaches to fighting against drug resistance [Text]: compilation / edited by Dr. Pere-Joan Cardona. – INTECH, 2012. – 376 p. – ISBN 978-953-307-948-6.

23) Zhang, Y. Mechanisms of drug resistance in Mycobacterium tuberculosis [Text] / Y. Zhang, W.W. Yew // International journal tuberculosis lung diseases. – 2009. – Vol. 13(11). – P. 1320-1330.

24) Zhang, Y. The curious characteristics of pyrazinamide: a review [Text] / Y. Zhang, D. Mitchinson // Int J Tuberc Lung Dis. – 2003.