Tuberculosis

Practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries
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Authors/Contributors

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**Amikacin (Am)**

**Amoxicillin/clavulanic acid ratio 4:1 (Amx/Clv)**

**Clofazimine (Cfz)**

**Cycloserine (Cs) or terizidone (Trd)**

**Ethambutol (E)**

**Ethionamide (Eto) or prothionamide (Pto)**

**Imipenem/cilastatin (Ipm/Cln)**

**Isoniazid - Standard dose (H)**

**Levofloxacin (Lfx)**

**Linezolid (Lzd)**

**Meropenem (Mpm)**

**Moxifloxacin (Mfx)**

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Hepatotoxicity
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Nausea and vomiting
  Neurotoxicity
Depression
Headache
Optic neuritis
Ototoxicity
Peripheral neuropathy
Psychosis
Seizures
  Endocrine disorders
Gynecomastia
Hypothyroidism
  Dermatological disorders
Alopecia
Fungal infection
Photosensitivity
Skin reactions
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Introduction

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis*. Tuberculosis typically attacks the lungs, but can also affect other parts of the body. The disease has become rare in high income countries, but is still a major public health problem in low- and middle-income countries.

It is estimated that between the years 2000 and 2010, eight to nine million new cases emerged each year. Approximately 1.5 million people die from the disease each year. In adults, tuberculosis is the second leading cause of death due to an infectious disease (after AIDS), with 95% of deaths occurring in low-income countries. Tuberculosis is a major problem of children in poor countries where it kills over 100,000 children each year.

The treatment of tuberculosis remains a constraint for patients and a heavy burden for the healthcare system. Drug-susceptible tuberculosis requires at least six months of therapy under close supervision. A treatment for multidrug-resistant tuberculosis requires nearly two years of treatment with poorly tolerated and less effective drugs. In most places the diagnosis still relies mainly on direct microscopy that is unable to detect a large proportion of patients. The BCG vaccine, developed almost a century ago, confers only partial protection.

After 40 years of minimal progress in the tools to fight tuberculosis there are some reasons for hope. A few new drugs are reaching the final phase of development; a new molecular test that can be decentralized to some extent and allows the rapid diagnosis of tuberculosis and of resistance to rifampicin has been introduced. Though this is undeniable progress, much will be needed to bring the new tools and drugs to the patients in need. Furthermore, a true “point of care” diagnostic test still does not exist and little progress has been made in research for a more effective vaccine.
Case management of patients does not necessarily have to involve a major, vertical programme. It should be incorporated into the framework of other medical activities in order to offer comprehensive and integrated treatment even if the number of patients being treated is relatively small.

This guide has been developed jointly by Médecins Sans Frontières and Partners In Health. It aims at providing useful information to the clinicians and health staff for the comprehensive management of tuberculosis. Forms of susceptible and resistant tuberculosis, tuberculosis in children, and HIV co-infection are all fully addressed.

As treatment protocols are constantly changing, medical staff are encouraged to check this website for updates.

**Abbreviations and acronyms**
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ACH</td>
<td>Air change per hour</td>
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<tr>
<td>AFB</td>
<td>Acid-fast bacilli</td>
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<tr>
<td>AIDS</td>
<td>Acquired immunodeficiency syndrome</td>
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<tr>
<td>Amk</td>
<td>Amikacin</td>
</tr>
<tr>
<td>Amx/Clv</td>
<td>Amoxicillin/clavulanic acid</td>
</tr>
<tr>
<td>ARI</td>
<td>Annual risk of infection</td>
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<tr>
<td>ART</td>
<td>Antiretroviral therapy</td>
</tr>
<tr>
<td>ARV</td>
<td>Antiretroviral</td>
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<tr>
<td>BCG</td>
<td>Bacillus Calmette-Guérin</td>
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<tr>
<td>Bdq</td>
<td>Bedaquiline</td>
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<tr>
<td>CDC</td>
<td>United States Centers for Disease Control and Prevention</td>
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<tr>
<td>Cfz</td>
<td>Clofazimine</td>
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<tr>
<td>Cm</td>
<td>Capreomycin</td>
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<tr>
<td>CMX</td>
<td>Cotrimoxazole</td>
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<tr>
<td>CPC</td>
<td>Cetylpyridinum chloride</td>
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<tr>
<td>CPT</td>
<td>Cotrimoxazole preventive therapy</td>
</tr>
<tr>
<td>Cs</td>
<td>Cycloserine</td>
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<tr>
<td>CXR</td>
<td>Chest X-ray</td>
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<tr>
<td>DOT</td>
<td>Directly observed therapy</td>
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<tr>
<td>DR</td>
<td>Drug resistance</td>
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<tr>
<td>DR-TB</td>
<td>Drug-resistant tuberculosis</td>
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<tr>
<td>DST</td>
<td>Drug susceptibility test(ing)</td>
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<td>-----------------------------</td>
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<tr>
<td>E</td>
<td>Ethambutol</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>EPTB</td>
<td>Extrapulmonary tuberculosis</td>
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<tr>
<td>Eto</td>
<td>Ethionamide</td>
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<tr>
<td>FDC</td>
<td>Fixed-dose combination</td>
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<tr>
<td>FNAC</td>
<td>Fine needle aspiration cytology</td>
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<tr>
<td>FQ</td>
<td>Fluoroquinolone</td>
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<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
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<tr>
<td>H</td>
<td>Isoniazid</td>
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<tr>
<td>HCW</td>
<td>Health care worker</td>
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<td>HIV</td>
<td>Human immunodeficiency virus</td>
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<tr>
<td>HPF</td>
<td>High-power field</td>
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<tr>
<td>IC</td>
<td>Infection control</td>
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<tr>
<td>IM</td>
<td>Intramuscular</td>
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<tr>
<td>Imp/Cln</td>
<td>Imipenem/cilastatin</td>
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<tr>
<td>IPT</td>
<td>Isoniazid preventive therapy</td>
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<td>IRIS</td>
<td>Immune reconstitution inflammatory syndrome</td>
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<tr>
<td>IUATLD</td>
<td>International Union against Tuberculosis and Lung Disease</td>
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<tr>
<td>Km</td>
<td>Kanamycin</td>
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<td>LFT</td>
<td>Liver function test</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>Lfx</td>
<td>Levofloxacin</td>
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<td>LPA</td>
<td>Line probe assay</td>
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<td>Lzd</td>
<td>Linezolid</td>
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<tr>
<td>MDR</td>
<td>Multidrug resistance</td>
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<tr>
<td>MDR-TB</td>
<td>Multidrug-resistant tuberculosis</td>
</tr>
<tr>
<td>Mfx</td>
<td>Moxifloxacin</td>
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<tr>
<td>MGIT</td>
<td>Mycobacteria growth indicator tube</td>
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<tr>
<td>MODS</td>
<td>Microscopic observation of drug susceptibility</td>
</tr>
<tr>
<td>Mpm</td>
<td>Meropenem</td>
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<tr>
<td>NNRTI</td>
<td>Non-nucleoside reverse transcriptase inhibitor</td>
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<tr>
<td>NRTI</td>
<td>Nucleoside reverse transcriptase inhibitor</td>
</tr>
<tr>
<td>NTM</td>
<td>Non tuberculous mycobacteria</td>
</tr>
<tr>
<td>Ofx</td>
<td>Ofloxacin</td>
</tr>
<tr>
<td>PAS</td>
<td>Para-aminosalicylic acid</td>
</tr>
<tr>
<td>PCP</td>
<td>Pneumocystosis</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PI</td>
<td>Protease inhibitor</td>
</tr>
<tr>
<td>PO</td>
<td>Orally (per os)</td>
</tr>
<tr>
<td>Pto</td>
<td>Prothionamide</td>
</tr>
<tr>
<td>R</td>
<td>Rifampicin</td>
</tr>
<tr>
<td>Rfb</td>
<td>Rifabutin</td>
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</table>
Chapter 1: Introduction and epidemiology

1.1 Characteristics of *Mycobacterium tuberculosis* bacillus

1.2 Transmission

1.3 Evolution of tuberculosis infection and disease in humans

1.4 Prognosis

1.5 Factors modifying tuberculosis epidemiology

1.6 Epidemiological indicators

1.7 Global burden of tuberculosis
1.1 Characteristics of Mycobacterium tuberculosis bacillus

*Mycobacterium tuberculosis*, along with *M. bovis, M. africanum, M. microti* and others, make up the *Mycobacterium tuberculosis* complex, a group of bacteria that cause clinical tuberculosis (TB) in humans. Most TB cases are caused by *M. tuberculosis*. Cases due to other species are far less prevalent.

*M. tuberculosis* is a small, rod-shaped, strictly aerobic, acid-fast bacillus. Like other mycobacteria, it is slow growing, resulting in more gradual development of disease when compared with other bacterial infections.

**Notas**

(a) Acid-fast bacilli are bacilli, which once stained, resist discoloration by acid and alcohol.

1.2 Transmission

*M. tuberculosis* is transmitted from human-to-human and spread is mainly airborne. The source of infection is usually a patient with pulmonary or laryngeal TB. During coughing, speaking, or sneezing, the patient produces tiny infectious droplets. These particles, called droplet nuclei, are about 1 to 5 microns in diameter. Depending on the environment, they can remain suspended in the air for several hours.

Transmission may occur when these infectious droplets are inhaled. UV light (sunshine or artificial sources) and ventilation reduce the probability of transmission (Chapter 14).
Other modes of transmission are far less common. Inoculation of cutaneous or mucous membranes rarely occurs, although such cases have been observed in laboratory personnel. Congenital infection (by transplacental transmission or via aspiration or swallowing of infected amniotic fluid at birth) has been reported, but is very rare. Transmission through breast milk does not occur.

The infectiousness of a patient is associated with the quantity of bacilli contained in their sputum. Patients with smear-positive sputum on microscopy are by far the most infectious. Those with smear-negative/culture-positive results are less infectious, but still contribute to TB transmission due to more frequent delays in diagnosis.

Patients infected with *M. tuberculosis*, but who have not developed active TB (latent tuberculosis infection), are not infectious. Patients with extrapulmonary TB (EPTB) are only infectious in exceptional circumstances.

Children are generally much less infectious than adults. This may be due to weaker cough mechanics, less sputum production and lower bacillary load.

Not everyone who is exposed to an infectious TB patient becomes infected with *M. tuberculosis*. The probability that TB will be transmitted depends on several factors:

**Infectiousness of the source** (the most important factor)
- Bacteriological status: smear-positive patients are the most infectious.
- Virulence of the bacilli: some strains are highly transmissible (and/or more likely to cause active TB).

**Environment where the exposure occurred**
- Outdoor environments or those with good ventilation and sunlight are less likely to lead to transmission. Small rooms or rooms with no ventilation are conditions most likely to lead to transmission.
- The proximity of the person to the patient is also important (e.g. the risk is higher if the person sleeps next to the patient than if they sleep 20 metres away from the patient).

**Duration of exposure**
People in close and prolonged contact with TB patients are at highest risk of becoming infected with *M. tuberculosis*. They may be family members, roommates, friends, co-workers or other people who spend several hours a day with the infectious patient.

The best way to stop transmission is to start effective TB treatment as soon as possible. It is estimated that a person with untreated smear-positive TB transmits the bacillus to 10 to 20 people a year (with variations according to living conditions and environment).

1.3 Evolution of tuberculosis infection and disease in humans
When a person inhales infectious droplets containing *M. tuberculosis*, most of the larger droplets become lodged in the upper respiratory tract (nose and throat) where infection is unlikely to develop. However, smaller droplet nuclei may reach the small air sacs of the lung (the alveoli) where infection can occur.

### 1.3.1 Primary infection and latent tuberculosis infection

After transmission, *M. tuberculosis* multiplies slowly, in most cases in the terminal alveoli of the lungs (primary focus) and in the lymph nodes of corresponding drainage areas: this is the primary infection. The primary focus and related hilar lymphadenopathy form the primary complex.

In one to two months, due to the action of lymphocytes and macrophages (cellular immunity), the primary focus is contained and encapsulated, with a central zone of parenchymal necrosis (caseous lesions). It is not usually detectable on chest x-ray, unless it calcifies or grows substantially. Primary infection is usually asymptomatic. In most cases (90 to 95% of non-HIV infected patients), the pulmonary lesions gradually heal.

During the primary infection, specific immunity develops and a positive skin reaction to tuberculin is observed[^1]. This immune response may persist without clinical signs of TB. The patient is infected by *M. tuberculosis*, but does not develop the disease. This is referred to as latent tuberculosis infection (LTBI).

In 5 to 10% of infected people, primary infection and/or LTBI progresses to active TB over their lifetime. For HIV co-infected patients, this risk is much higher.

### 1.3.2 Active tuberculosis

Before immunity is established, bacilli from the primary infectious focus or from a near-by lymph node can be transported and disseminated throughout the body via the lymph system or the bloodstream. Secondary foci can develop this way, particularly in the lungs, lymph nodes, serous membranes, meninges, bones and kidneys. As soon as an immune response is mounted, most of these foci resolve spontaneously. However, some bacilli may remain dormant in the secondary foci for months and sometimes years.

Different factors can reduce the immune response (e.g. HIV infection) and lead to reactivation of the bacilli and their multiplication in one or more of these foci. This reactivation or progression of the primary or secondary foci results in active TB[^2].

An active TB lesion contains actively, slowly or sporadically multiplying bacilli as well as dormant bacilli. While active TB may occur months or years following primary infection, half of TB cases appear in the year following infection.

### 1.3.3 Risk factors for developing active tuberculosis

Certain factors increase the risk of developing active TB within the first two years of being infected. These factors include any factor that results in a weakened immune system, damaged lungs and the intensity and duration of exposure.
Host immune response factors:
- HIV infection
- Children under 5 years[3][4]
- Malnutrition
- Persons over 60 years
- Diabetes mellitus
- Other risk factors: prolonged corticosteroid therapy (g. prednisolone) and other immunosuppressive therapies, severe kidney disease, alcoholism, substance abuse, certain types of cancer (e.g. leukaemia, Hodgkin’s lymphoma, cancer of the head and neck); pregnancy

Conditions that damage the lung:
- Tobacco smoking
- Silicosis
- Chronic obstructive pulmonary disease (COPD)

Intensity of exposure (high number of inhaled bacilli):
- Highly infectious source
- Poorly ventilated environment
- Proximity with infectious source, including residents and employees of institutions such as prisons, boarding schools and residential care facilities
- Long duration of exposure

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1.4 Prognosis

Without treatment, TB is a severe and potentially fatal disease. After 5 years without treatment, the outcome of smear-positive pulmonary TB (PTB) in non-HIV-infected patients is as follows[1] :

- 50 to 60% die (case fatality ratio (CFR) for untreated TB);
- 20 to 25% are cured (spontaneous cure);
- 20 to 25% continue to have symptoms.

In non-HIV infected patients, the CFR is estimated at 3% [2]. Untreated TB in HIV-infected patients (not on effective antiretroviral therapy) is almost always fatal. Even on antiretroviral therapy, the CFR is higher than in non-HIV infected patients[3][4].

Risk factors for poor outcomes of TB treatment (death and relapse) include co-morbidities (e.g. HIV infection, diabetes, COPD), cavities on chest x-ray, high bacillary load and resistance to TB drugs.

Referencias


1.5 Factors modifying tuberculosis epidemiology
Five major factors influence TB epidemiology: (1) socioeconomic conditions, (2) TB treatment, (3) HIV infection, (4) diabetes and (5) BCG vaccination.

### 1.5.1 Socioeconomic conditions

The principal factors leading to a reduction in TB cases are improved social and housing conditions. Most cases occur in low-income countries. In industrialised countries, TB generally affects the most disadvantaged social groups.

### 1.5.2 Tuberculosis treatment

Diagnosing and initiating effective treatment in a patient early during their TB disease before they can infect multiple people is considered the most effective preventive measure against TB. Once an effective TB treatment is started, there is a rapid reduction in transmission[^1][^2].

Since the introduction of TB treatment, the risk of TB infection decreased by approximately 10% per year in industrialised countries[^3]. This trend was observed in countries with a BCG vaccination programme as well as in those without one. Detection programmes, diagnosis and treatment of TB contributed to this reduction in the risk of TB infection.

### 1.5.3 HIV infection

Immunodeficiency induced by HIV infection is a major risk factor for progression to active TB and has a considerable impact on the epidemiology of TB. While the lifetime risk of developing active TB in the general population is 5 to 10% after infection with *M. tuberculosis*, this risk is approximately 10% per year in patients co-infected with HIV and *M. tuberculosis*. Approximately 8% of incident TB cases in the world are among HIV-infected patients (highest in the WHO African Region, more than 50% in parts of southern Africa[^4]).

### 1.5.4 Diabetes

The risk of TB among people with diabetes is higher than among those without diabetes. It is estimated that diabetes contributes to 15% of TB cases worldwide[^5]. Diabetes is also associated with poor absorption of TB drugs and therefore higher rates of drug resistant tuberculosis (DR-TB).

### 1.5.5 BCG vaccination

**Effectiveness of BCG at the individual level**

BCG vaccination, if given at birth, is highly effective against the severe forms of TB (miliary and meningitis) in children[^6].

**Epidemiological impact of vaccination**

Despite some protection from the BCG vaccination, the impact of BCG vaccination on TB transmission and the TB epidemic is considered negligible[^7].
1.5.6 Other factors

Other modifying factors include infection control measures (Chapter 14) and treatment of LTBI (Chapter 16). The degree to which in a given context the TB epidemiology is affected by these measures is not known.

Referencias


1.6 Epidemiological indicators

When a National TB Programme (NTP) functions well, indicators can be obtained from the local authorities and NTP. The WHO tuberculosis country profiles also provide an estimation of TB indicators by individual country.

Box 1.1 - Most common indicators
Annual incidence rate of TB cases

*Numerator:* number of new TB cases (all forms) that occur in a population over one year  
*Denominator:* population at the start of the year

Annual incidence rate of smear-positive PTB cases

*Numerator:* number of new smear-positive PTB cases that occur in a population over one year  
*Denominator:* population at the start of the year

Prevalence of smear-positive PTB cases over a given period of time, usually one year

*Numerator:* number of smear-positive PTB cases  
*Denominator:* population at the start of the period of time

Proportion of multidrug- and rifampicin-resistant TB cases among TB cases over a given period of time

*Numerator:* number of multidrug- and rifampicin-resistant TB cases  
*Denominators:*  
- Total number of TB cases  
- Number of new TB cases  
- Number of previously treated TB cases

Proportion of extensively drug-resistant TB cases among TB cases over a given period of time

*Numerator:* number of extensively drug-resistant cases  
*Denominators:* as for multidrug- and rifampicin-resistant TB cases

Proportion of HIV-infected patients among new TB cases over a given period of time

*Numerator:* number of HIV-infected patients  
*Denominator:* number of new TB cases

(a) The rate is expressed as the number of new TB cases (or new smear-positive PTB cases) per 100,000 population.  
(b) Prevalence is expressed as the number of smear-positive PTB cases per 100,000 population. It includes new and pre-existing cases. Prevalence represents approximately double the incidence rate.  
(c) Proportion is expressed in %.
1.7 Global burden of tuberculosis

1.7.1 Latent tuberculosis infection

The global prevalence of LTBI is unknown due to difficulties in diagnosis. However, WHO estimates that one-quarter of the world population has LTBI[1].

1.7.2 Active tuberculosis

Globally, active TB remains a leading cause of death from infectious disease.

WHO estimates that each year there are approximately 10 million incident cases of TB and 1.5 million deaths due to TB, including 1.3 million among HIV-negative individuals and 214,000 among HIV-infected individuals[2].

Children under 15 years account for 11% of all estimated TB cases[2]. However, TB cases in children are frequently undiagnosed and unreported.

While the absolute number of global TB cases is stable, there are large individual country and regional differences in incidence and prevalence.

Most TB cases are in Southeast Asia (43%), Africa (25%) and the Western Pacific (18%), with lower percentages in the Eastern Mediterranean, the Americas and Europe[2].

1.7.3 Drug-resistant tuberculosis

Drug-resistant TB (DR-TB) is a growing worldwide problem, and no region is spared.

WHO estimates that annually worldwide there are[3]:

• More than one million rifampicin-susceptible and isoniazid-resistant TB (Hr-TB) cases (11% of all incident TB cases).
• 3.3% of new cases and 18% of previously treated cases, with multidrug-resistant TB (MDR-TB)a and rifampicin-resistant TB (RR-TB)b representing 465,000 cases and 182,000 deaths.

In Eastern Europe and Central Asia, TB incidence is lower than in Southeast Asia and Africa, but up to 30% of new and 65% of retreatment cases exhibit rifampicin-resistance.

In China and India, there is a low proportion of rifampicin-resistant cases among all TB cases. However, because of their large populations, these two countries represent 41% of global MDR/RR-TB cases.

Resources for detecting drug resistance are limited in many parts of Africa. However, available data suggest that the MDR-TB burden is significant, especially in the south.

The prevalence of extensively drug-resistant TB (XDR-TB)c, according to the new WHO definition, is currently unknown.
Chapter 2: Clinical presentation

2.1 Pulmonary tuberculosis

2.2 Extrapulmonary tuberculosis

2.3 Disseminated or miliary tuberculosis

2.4 Clinical presentation in HIV-infected patients

2.5 Summary of clinical presentations of tuberculosis

Update: January 2022

2.1 Pulmonary tuberculosis

Prolonged cough (more than 2 weeks), with or without sputum production, is a common symptom in patients with pulmonary tuberculosis (PTB).
Other frequent, less specific, signs and symptoms include weight loss, anorexia, fatigue, haemoptysis (blood in sputum), shortness of breath, chest pain, moderate fever and night sweats.

Signs and symptoms may vary between individuals and generally evolve in a chronic, insidious manner. History-taking is therefore of the utmost importance.

Advanced forms and complications are common:
- Respiratory insufficiency due to extensive lesions and destroyed lungs;
- Massive haemoptysis due to large cavities with hyper-vascularisation and erosion of vessels;
- Pneumothorax due to the rupture of a cavity in the pleural space.

In endemic areas, the diagnosis of PTB should be considered in any patient consulting for respiratory symptoms lasting more than 2 weeks.

Table 2.1 provides a differential diagnosis of PTB for non-HIV infected patients.

**Table 2.1 - Differential diagnosis for PTB (non-HIV infected patients)**
<table>
<thead>
<tr>
<th>Diseases</th>
<th>Remarks</th>
</tr>
</thead>
</table>
| **Bacterial pneumonia**        | • Usually more acute and shorter in duration; high fever often present.  
• Response to antibiotics with no anti-TB activity suggests bacterial pneumonia.  
• Lobar consolidation is typical of bacterial pneumonia; however, CXR alone cannot differentiate PTB from bacterial pneumonia. |
| **Pulmonary abscess**          | • May arise from aspiration in individuals with impaired consciousness (coma, intoxication with alcohol/drugs, etc.).  
• Foul-smelling, purulent sputum.  
• Cavities typically have a thick wall and air fluid levels. |
| **Bronchiectasis**             | • Frequent complication of successive, poorly-treated bronchopulmonary infections in tropical regions.  
• Characterised by chronic or repeated episodes of productive cough.  
• Haemoptysis, usually mild, can be present. |
| **Lung cancer**                | • History of smoking or environmental exposure (working in a mine, etc.).  
• Haemoptysis in 20 to 50% of patients. |
| **Paragonimiasis** (lung flukes) | • To be ruled out in presumed PTB cases in endemic areas (certain areas of Southeast Asia, West Africa and Latin America). |
| **Pulmonary echinococcosis** (hydatid disease) | • In Latin America, the Middle East, some Sub-Saharan African countries and China.  
• Lung involvement may cause chronic cough, with or without haemoptysis.  
• Cysts can mimic TB cavities. |
| **Pneumocystosis**             | • Common in patients with advanced HIV disease and patients receiving long-term, even low dose, corticosteroid therapy. |
| **Less common diseases**        | • Silicosis, sarcoidosis, melioidosis.  
• Cryptococcosis, aspergillosis, histoplasmosis. |

For differential diagnosis in HIV-infected patients see [Section 2.4](#).

### 2.2 Extrapulmonary tuberculosis
Starting from a pulmonary localisation (primary infection), *M. tuberculosis* can spread to other organs during a silent phase, usually soon after primary infection (Chapter 1). Active TB can develop in many other parts of the body, particularly in lymph nodes, meninges, bones and joints, kidneys, genital organs and the abdominal cavity.

Extrapulmonary tuberculosis (EPTB) can develop at any age. Due to relative immunodeficiency, young children, HIV-infected and malnourished patients are more at risk of developing EPTB.

Approximately 15% of global TB cases are classified as EPTB, although this figure varies according the local epidemiology.[1]

A patient with EPTB may also have pulmonary involvement, which should be searched for whenever EPTB is diagnosed or suspected.

Table 2.3 at the end of this chapter summarises the characteristics of EPTB.

### 2.2.1 Lymph node tuberculosis

Lymph node TB is common, particularly in certain areas of Africa and Asia, and especially in children and HIV-infected patients.

The presentation of lymph node TB is a non-inflammatory adenopathy. Nodes are cold and painless, multiple (usually bilateral) or single, evolving in a chronic mode towards softening and fistulisation. Cervical localisation is most frequent. Axillary and mediastinal localisations are also common. Other sites may be involved.

Diagnosis may be clinical, but whenever possible, fine needle aspiration should be performed (Chapter 3 and Appendix 7).

Adenopathy usually disappears within 3 months of treatment initiation. Paradoxical reactions may occur at the beginning of treatment (appearance of abscesses, fistulas or other lymph nodes), but a change in the treatment is not required.

Differential diagnoses include malignancies (lymphoma, leukaemia, ear/nose/throat tumours, Kaposi sarcoma) and other infections (bacterial, viral, non-tuberculosis mycobacteria, toxoplasmosis, HIV infection, syphilis, African trypanosomiasis).

### 2.2.2 Tuberculous meningitis

TB meningitis is a serious form of TB that affects the meninges. It is most common in children under 2 years and in HIV-infected patients. It is a medical emergency. Any delay in diagnosis or treatment will result in irreversible neurological sequelae or death.[2]

TB meningitis typically has a subacute insidious course over days or weeks. Symptoms include headaches, irritability, fever, vomiting and altered mental status, which worsen if treatment is delayed. The meningeal syndrome (stiff neck, hypotonia in infants, photophobia and headache) is present in most cases. Third cranial nerve palsy (oculomotor paralysis) may occur.

Diagnosis is assisted by examination of cerebrospinal fluid (Chapter 3).

The main differential diagnoses are other forms of meningitis.
2.2.3 Tuberculosis of bones and joints

Up to 40% of patients with TB of bones and joints have concurrent PTB\[3\].

**Spinal TB (spondylodiscitis or Pott's disease)**
TB can affect vertebrae and intervertebral disks, causing destruction and deformation of the spine. The thoracic spine is the most frequently affected. Localised back pain may precede by several months the appearance of the first radiological anomalies (destruction of an inter-vertebral disk). A spinal prominence (gibbus) due to destruction and deformity of the vertebral bodies may be felt. Paravertebral cold abscesses and/or neurological complications can develop. A missed diagnosis of thoracic or cervical spinal TB can result in paralysis.

**Arthritis**
TB most frequently causes a chronic mono-arthritis, starting insidiously, with little or no pain and accompanied by joint destruction. The joints most often affected are the hips, knees, elbows and wrists.

**Osteitis**
Osteitis is the least common presentation of TB of the bones. It may be a primary osteitis or an osteitis secondary to TB arthritis. Typically, long bones are affected. Cold abscesses may occasionally occur. Like arthritis, it is distinguished from common bacterial infections by the presence of mild symptoms, despite bone and joint destruction.

The diagnosis is based on the patient’s history, clinical examination and radiography, as biopsy and culture are difficult to perform in many settings. A history of prolonged and insidious osteitis or arthritis associated with a deterioration of the general physical condition favours TB aetiology, as opposed to bacterial osteomyelitis or brucellosis. The patient may have a history of non-response to antibiotics.

2.2.4 Urogenital tuberculosis

Renal involvement is frequent and may be asymptomatic for a long period, with a slow development of signs and symptoms: painful urination (dysuria), urinary urgency and frequency (pollakiuria), including during the night (nocturia); back/abdominal pain; tenderness/swelling of the testes or epididymitis or haematuria. General physical condition is generally preserved. Diagnosis is suspected in the presence of pyuria (white blood cells in the urine) and micro- or macroscopic haematuria, which does not respond to antibiotics. Examination of the urine helps with diagnosis (Chapter 3).

In men, genital localisation is secondary to renal involvement. Signs are most often epididymitis with scrotal pain.
In women, genital tract infection can also occur by a hematogenous path. Signs are non-specific: pelvic pain, leucorrhoea and abnormal vaginal bleeding. Infertility is often the reason leading women to seek medical attention.

Extension may be found in the peritoneum, with resulting ascites.

2.2.5 Abdominal tuberculosis

Abdominal TB commonly presents as ascites resulting from the peritoneal localisation of the infection. Abdominal mass (often in the right lower quadrant), pain and diarrhoea may be present. The frequency of chronic ascites in tropical regions, with its many different causes, makes this relatively uncommon form of TB difficult to diagnose\(^4\).

Diagnosis is assisted by examination of the ascitic fluid via paracentesis (Chapter 3). Constitutional symptoms (fever, night sweats, malaise and weight loss) may be present. Accumulation of ascites may mask weight loss.

2.2.6 Tuberculous pleural effusion

Tuberculous pleural effusion is one of the most common forms of EPTB. It is often asymptomatic, especially if less than 300 ml. Shortness of breath and chest pain (often unilateral) occur when the effusion is large. Sputum production and cough are present in the case of concurrent PTB, which is common.

Constitutional symptoms such as fever, night sweats, malaise and weight loss may also be present. Effusion can progress to tuberculous empyema, characterised by purulent fluid containing large numbers of bacilli. Tuberculous empyema is often associated with thickened, scarred and calcified pleura.

Diagnosis is assisted by examination of the pleural fluid via paracentesis and chest x-ray (CXR). See Chapter 3.

2.2.7 Tuberculous pericardial effusion

Clinical signs of a tuberculous pericardial effusion include chest pain, shortness of breath, oedema of the lower limbs and sometimes ascites.

Clinical examination may show pericardial friction rub, raised jugular pressure and tachycardia.

CXR and ultrasound are key elements for diagnosis (Chapter 3).

Pericardiocentesis may be necessary in the event of acute heart failure with haemodynamic compromise. It must be performed by experienced personnel in well-equipped hospitals, and when possible, under direct visualisation with ultrasound.

2.2.8 Cutaneous tuberculosis

The clinical presentation of cutaneous TB is chronic, painless, non-pathognomonic lesions, ranging from small papula and erythema to large tuberculomas.

The diagnosis is based on culture from a biopsy.
2.3 Disseminated or miliary tuberculosis

Miliary TB is a generalised massive infection characterised by hematogenous diffusion of *M. tuberculosis* throughout the body. It is a medical emergency.

The disease may manifest as a miliary pattern, or very small nodular elements ('millet seeds') in the lungs.

The classic acute form is mostly found in children, young adults and HIV-infected patients. The presentation can be either abrupt or insidious, with progressive deterioration in the patient’s physical condition. The clinical picture is often completed within one to two weeks and is characterised by a profoundly altered physical condition, marked wasting, headache and constant high fever. Discrete dyspnoea and coughing suggest a pulmonary focus; however, lungs can often be clear on auscultation. A moderate hepatosplenomegaly is occasionally found. Certain forms of miliary TB evolve in a subacute manner over several months.

Given this non-specific clinical picture, typhoid fever and septicaemia should be considered in the differential diagnosis.

Diagnosis of miliary TB is confirmed by CXR (Chapter 3).

When feasible, fundoscopy may reveal choroidal tubercles.

Sputum smear examination is usually negative.

When there is no possibility of obtaining CXR, the lack of response to antibiotics is an argument in favour of miliary TB.

The tuberculin skin test is more likely to be falsely negative than in any other form of TB.

In children, the risk of meningitis (20-40%)\(^1\) is high. Lumbar puncture should be routinely performed if miliary TB is suspected.

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**Referencias**


2.4 Clinical presentation in HIV-infected patients

Among HIV-infected patients, TB is the most common opportunistic infection and the leading cause of morbidity and mortality\[1\]. According to the WHO clinical staging system for HIV/AIDS, patients with PTB are in clinical stage 3 and patients with EPTB in clinical stage 4\[2\].

In the early stages of HIV infection, when the immune system is functioning relatively normally, the clinical signs of TB are similar to those in seronegative individuals.

As the immune system deteriorates in later stages of the disease, smear-negative PTB, disseminated TB and EPTB become more common. These cases are more difficult to diagnose, and have a higher fatality rate than smear-positive PTB cases. Patients may have difficulty expectorating, so more advanced sputum collection techniques may be necessary (Chapter 3 and Appendix 3).

Algorithms presented in Chapter 4 use clinical criteria combined with laboratory and other investigations to help diagnose TB in HIV-infected individuals.

Table 2.2 provides a differential diagnosis of PTB in HIV-infected patients.

**Table 2.2** - Differential diagnosis for PTB in HIV-infected patients

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   https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6850233/
The most common EPTB in HIV-infected patients are miliary TB, TB meningitis and diffuse lymphadenopathy in children, and lymph node TB, pleural effusion, pericarditis, TB meningitis and miliary TB in adults.

Immune reconstitution inflammatory syndrome (IRIS) is a clinical presentation of TB in patients starting antiretroviral therapy. See Chapter 12 for clinical presentation and management of IRIS.

### Referencias


2.5 Summary of clinical presentations of tuberculosis

Table 2.3 - Clinical presentations and considerations for HIV-infected patients
<table>
<thead>
<tr>
<th>Sites</th>
<th>Clinical presentations</th>
<th>Considerations for HIV patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary TB</strong></td>
<td>• Prolonged cough (&gt; 2 weeks), with or without sputum production.</td>
<td>• Fever and weight loss are more common and pronounced.</td>
</tr>
<tr>
<td></td>
<td>• Weight loss, anorexia, fatigue, shortness of breath, chest pain, moderate fever, night sweats, haemoptysis.</td>
<td>• Cough and haemoptysis may be less common (less inflammation and cavity formation).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• See algorithms, Chapter 4.</td>
</tr>
<tr>
<td><strong>Disseminated miliary TB</strong></td>
<td>• Non-specific symptoms: high fever, headache, weight loss.</td>
<td>• May be confused with severe wasting in advanced HIV disease.</td>
</tr>
<tr>
<td></td>
<td>• Deterioration over days or weeks.</td>
<td>• M. tuberculosis sometimes isolated from blood cultures.</td>
</tr>
<tr>
<td></td>
<td>• Simultaneous involvement of multiple organs.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• High risk of meningitis in children.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Miliary findings CXR.</td>
<td></td>
</tr>
<tr>
<td><strong>Lymph nodes TB</strong></td>
<td>• Most often in cervical region.</td>
<td>• HIV infection can cause persistent generalised lymphadenopathy (PGL). PGL lymph nodes are painless, and symmetrical. Posterior cervical or epitrochlear nodes are often involved.</td>
</tr>
<tr>
<td></td>
<td>• Non-inflammatory, painless node &gt; 2 cm, chronic (&gt; 4 weeks); fistulisation possible.</td>
<td>• Other common causes of lymphadenopathy include lymphoma, carcinomatous metastases, Kaposi sarcoma.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TB meningitis</strong></td>
<td>• Subacute, insidious.</td>
<td>• Rule out cryptococcal meningitis: perform antigen test on serum and CSF.</td>
</tr>
<tr>
<td></td>
<td>• Headaches, irritability, fever, altered mental status.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Meningeal syndrome usually present.</td>
<td></td>
</tr>
<tr>
<td><strong>Bone and joint TB</strong></td>
<td>• Monoarthritis with joint destruction and little or no pain.</td>
<td>• Multifocal disease more common.</td>
</tr>
<tr>
<td></td>
<td>• Deformity of the spine (Pott’s disease).</td>
<td></td>
</tr>
</tbody>
</table>
TB is considered as non-severe if the following criteria are met:

- negative smear microscopy, and
- uncomplicated PTB with a small infiltrate confined to one lobe and no cavities, or
- uncomplicated extra-thoracic lymph node TB, or
- uncomplicated intrathoracic lymph-node TB.

### Chapter 3: Diagnostic investigations

#### 3.1 Sputum smear microscopy

#### 3.2 Culture

#### 3.3 Phenotypic drug susceptibility tests (DST)

#### 3.4 Molecular techniques

#### 3.5 Summary of bacteriological examinations

#### 3.6 Indications for DST

#### 3.7 Radiology

#### 3.8 Tuberculin skin test (TST)

#### 3.9 Interferon gamma release assays (IGRAs)
3.1 Sputum smear microscopy

Sputum smear microscopy allows a rapid and reliable identification of patients with pulmonary tuberculosis (PTB) where there are more than 5000 bacilli/ml of sputum. If the sputum has less than 5000 bacilli/ml, smear microscopy is highly unlikely to diagnose PTB, thus has an overall low sensitivity for PTB [1][2][3].

Another shortcoming of smear microscopy is its non-specificity, such that *M. tuberculosis* appears the same as non tuberculous mycobacteria (NTM). However, in areas of high TB prevalence, positive smears have a very high probability of being *M. tuberculosis*.

The reliability of sputum microscopy depends on the quality of sputum collection. Sputum produced on early morning often shows a higher concentration of *M. tuberculosis*. Importantly, the reliability of sputum microscopy depends on the proper preparation and interpretation of slides. Thus, laboratory technicians must be properly trained and quality control checks must be regularly carried out in a supervising laboratory.

It is recommended that all patients suspected of PTB should submit at least two sputum specimens. Studies have shown that, when collection and examination techniques are correctly conducted, about 80% of sputum smear-positive patients are found during the first sputum examination and over 15% more during the second. Successive, repeated examinations yield fewer positives [4].

Usually, a first sample is collected at the time of the consultation when the patient is identified as a suspected TB case. A second sample is collected in the early morning the day after the initial consultation (and the patient brings the sample to the health facility if it is collected at home).

In order to limit the number of visits to the health facility, “frontloaded microscopy” (also referred to as 'same day' or 'spot-spot' microscopy) can be performed. Two sputum specimens are collected one hour apart. This strategy has shown similar results to the standard strategy over two days (spot-morning-spot) in terms of diagnostic yield [5].

See Appendix 3 for sputum specimen collection, storage and shipment.

The staining methods uses a technique where the mycobacteria retain a primary stain after exposure to decolourising acid-alcohol, hence the term “acid-fast bacilli” (AFB). The two most common methods of staining, which determine the acid-fast nature of the mycobacteria, are Ziehl-Neelsen staining and auramine staining (Appendix 4) [8].
Auramine staining has the advantage of permitting a more rapid slide reading. It is recommended in laboratories with a high workload defined as ≥ 20 slides per reader per day. It requires trained, experienced technicians and a fluorescent microscope. LED (light-emitting-diodes) modules that can be adapted to ordinary microscopes or new LED microscopes are simpler, cheaper and safer alternatives to traditional mercury vapor lamp microscopes and do not require dark room.

Concentration techniques increase the sensitivity of sputum smear microscopy and fluorescence and have also been shown to increase the detection up to 20% in some settings with high HIV prevalence[7].

Referencias


3.2 Culture

Culture allows diagnostic confirmation of TB and is more sensitive than microscopy, 10-100 bacilli/ml are required to obtain a positive result[1]. Only specialized laboratories with regular quality assurance procedures in place can be relied upon for culture.
After decontamination of the sputum specimen to eliminate other organisms, the sample is centrifuged. The sediment is cultured in a special medium, in an incubator at 37°C. For specimen storage and shipment, see Appendix 3.

*M. tuberculosis* is a slow-growing pathogen thus, culture results are obtained after several days. The turn around time (TAT) for these techniques is summarized in Section 3.5, Table 3.1.

Culture should play a bigger role in diagnosis and patient follow-up due to the limited value of direct microscopy for:

– Confirmation of failures;
– Diagnosis of EPTB;
– Confirmation of smear negative TB when the diagnosis is in doubt;
– Distinction between *M. tuberculosis* complex and NTM;
– Monitoring treatment and outcome evaluation for patients on second-line anti-TB drugs.

Once there is growth on either a solid or liquid media, the organism must be identified. There are a number of ways to identify *M. tuberculosis*. The tests can be phenotypic (the most common being the niacin test) or genotypic (which use DNA analysis, Section 3.4). Given the complexities associated with phenotypic identification, genetic tests are preferred. The drawback is their cost. Nonetheless, laboratories performing cultures, at a minimum, should be able to conduct identification tests for *M. tuberculosis* that follow international guidelines.

**Referencias**


### 3.3 Phenotypic drug susceptibility tests (DST)

Phenotypic DST determines if a strain is resistant to an anti-TB drug by evaluating the growth (or metabolic activity) in the presence of the drug[1]. The laboratory performing phenotypic DST should be specialised in mycobacterial cultures, reliable and subject to external quality assessment, often by a supranational laboratory or national reference laboratory.

The turn around time (TAT) for these techniques is summarized in Section 3.5, Table 3.1.
The reliability of DST varies from one drug to another. For Group 1 anti-TB drugs, DST is very reliable for rifampicin and isoniazid but less so for pyrazinamide and much less for ethambutol. DST for aminoglycosides, polypeptides and fluoroquinolones have been tested in different laboratories and shown to have relatively good reliability and reproducibility. DST to other second-line drugs (paraaminosalicylic acid, ethionamide and cycloserine) is much less reliable and reproducible.

Referencias


3.4 Molecular techniques

Molecular (or genotypic) tests can be used to diagnose TB through the amplification of nucleic acids (DNA or RNA). They are also used to detect drug resistance through identifying genetic mutations (drug-resistant alleles) in the bacterium responsible (genotypic DST). Different assays and platforms have been developed.

3.4.1 Automated real time PCR (Xpert MTB/RIF)

This test can diagnose TB and resistance to rifampicin. In contrast to other techniques (in vitro culture, DST and conventional molecular techniques) the Xpert MTB/RIF can be used in peripheral laboratories and does not require sophisticated equipment or highly-skilled personnel.

The test is based on real-time PCR, targeting specific nucleic acid sequences in the M. tuberculosis complex genome, while also simultaneously providing information about the most common mutations related to rifampicin resistance.

It is a highly automated test (only 3 manual steps required), which is run in a closed system with one cartridge per sample. Thus, it is less prone to contamination than other PCR-based tests. Each instrument can process 4 samples at one time, with a processing time of just under 2 hours. Higher capacity machines are available. See Appendix 3 for more information on Xpert MTB/RIF instruments.

The performances of this test are almost similar to that of the culture. Published results have shown that for PTB detection, the assay has sensitivities of 98% for smear-positive, culture-positive samples, and 72% for smear-negative, culture-positive samples (sensitivity can reach 90% if the test is repeated 3 times).
The test Xpert MTB/RIF also has good sensitivity (80%) and excellent specificity (> 98%) when performed on cerebrospinal fluid, lymph node material and gastric fluid. Because of its excellent performance, its quick turn around time and its ease of use, this test should be used as an initial diagnostic test in HIV-infected patients and when multidrug-resistant TB (MDR-TB) or TB meningitis are suspected, in both adults and children.

It can also be used for diagnosis of lymph node TB. As the sensitivity of the Xpert test in pleural fluid is low, its use is not recommended.

The sensitivity for the detection of rifampicin resistance compared with conventional DST on culture is 97.6%. The test has a high negative predictive value, therefore, non rifampicin resistant results can be considered to be true susceptible.

In populations where the prevalence of MDR-TB is below 10%, the positive predictive value is below 85% (Appendix 3). Therefore when a Xpert with RIF positive results is found, the test should be immediately repeated in order to rule out possible labelling or clerical errors. If the second Xpert MTB/RIF test does not show rifampicin resistance, the patient can be considered has having a susceptible TB. If the result of the second Xpert MTB/RIF test also shows rifampicin resistance, it should be confirmed by a phenotypic DST or a different genotypic DST method.

Xpert MTB/RIF does not eliminate the need for conventional microscopy, culture and DST, which are required to monitor treatment progress and to detect resistance to drugs other than rifampicin.

### 3.4.2 Line probe assays (LPA)

To date no fully automated LPA exist. These molecular tests can only be performed by specialized laboratories with strict quality assurance procedures in place.

There are a number of different molecular assays available:

- Conventional Nucleic Acid Amplification (NAA) amplifies \textit{M. tuberculosis}-specific nucleic acid sequences with a nucleic acid probe, enabling direct detection of the bacillus. The current NAA tests available show a lower sensitivity than culture and therefore, are not recommended for the diagnosis of TB. They are also too labour-intensive to be implemented for routine diagnosis in most laboratories.

- Two molecular techniques are commercially available:
  - Hain assays: GenoType® MTBDR\textit{plus} assay and GenoType® MTBDR\textit{sl} (Hain Lifescience GmbH, Nehren, Germany). The GenoType® MTBDR\textit{plus} assay has been shown to be good at detecting rifampicin resistance but less so for isoniazid resistance among smearpositive patients (sensitivity and specificity values for rifampicin and isoniazid were 95.3% and 95.5% and, 89.9 and 87.1%, respectively)[8][9]. The GenoType® MTBDR\textit{sl} assay can detect resistance to fluoroquinolones and injectables drugs with a good specificity but a lower specificity (85% for fluoroquinolones and 43 to 84% for injectables)[10].
  - The INNO-LiPA Rif. TB® line probe assay (Innogenetics, Belgium)[11].

The GenoType® MTBDRplus assay can identify mutations on the KatG or on the InhA genes:
- Mutation on KatG gene corresponds to resistance to high-dose isoniazid;
- Mutation on InhA gene corresponds to resistance to both isoniazid and ethionamide, but not necessarily to high-dose isoniazid.

The GenoType®MTBDRsl assay can be used as a triage test on smear-positive patients to guide the initial treatment in extensively drug-resistant TB (XDR-TB) suspects while awaiting confirmatory results from conventional phenotypic testing. However, LPA assays cannot be used as replacement tests for conventional phenotypic second-line anti-TB DST.

These molecular methods have the advantage of giving fast results, within a few hours, for smear-positive patients (referred to as direct testing, because the sputum can be directly tested). For smear negative patients, a primary culture is needed prior to testing (referred to as indirect testing because a culture first has to be grown from the patient’s sputum).

In order to benefit from the short turn around time of these tests, good logistical support is required for sample transportation to the reference laboratory with timely return of results. The main constraints remain the high cost, high infrastructure requirements, high level of technical training and the risk of cross-contamination.

Referencias


3.5 Summary of bacteriological examinations

Table 3.1 - Summary of bacteriological examinations[1][2][3][4][5]
<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity AFB/ml</th>
<th>Median turn-around time</th>
<th>Additional turn-around time with DST</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Smear microscopy</strong></td>
<td>&gt; 5 000</td>
<td>2 hours</td>
<td></td>
</tr>
<tr>
<td>(Light, fluorescent)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Culture solid medium</strong></td>
<td>+/- 100</td>
<td>16 days (smear+)</td>
<td>6 weeks</td>
</tr>
<tr>
<td>LJ standard medium, Middlebrook 7H10 and 7H11</td>
<td></td>
<td>29 days (smear−)</td>
<td></td>
</tr>
<tr>
<td><strong>Culture liquid medium</strong></td>
<td>+/- 10</td>
<td>8 days (smear+)</td>
<td>2 weeks (smear+)</td>
</tr>
<tr>
<td>(BACTEC®, MGIT®)</td>
<td></td>
<td>16 days (smear−)</td>
<td>2 weeks (smear−)</td>
</tr>
<tr>
<td><strong>Culture microcolonies</strong></td>
<td>+/- 10</td>
<td>14 days</td>
<td>0 (H and R)</td>
</tr>
<tr>
<td>(TLA, MODS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LPA</strong></td>
<td></td>
<td>1 day (direct testing)</td>
<td>0 (H and R)</td>
</tr>
<tr>
<td>(Hain®, INNO-LiPA®)</td>
<td>Only on positive smear</td>
<td></td>
<td>21 days (indirect testing)</td>
</tr>
<tr>
<td><strong>Automated real-time PCR</strong></td>
<td>+/-10</td>
<td>2 hours</td>
<td>0 (R only)</td>
</tr>
<tr>
<td>(Xpert MTB/RIF)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Referencias**


3.6 Indications for DST

Ideally, genotypic DST is indicated for all patients at the start of TB treatment, as to ensure that the most appropriate therapy for each individual can be determined.[1]

At the very least, the following patients should have DST performed to isoniazid and rifampicin, or rifampicin alone:
– Previously treated patients;
– Persons who develop active TB after exposure to a patient with documented MDR-TB;
– Patients who remain smear-positive after two months of therapy;
– New patients in countries with high prevalence of MDR-TB.

The following groups are targeted for DST for second-line drugs:
– Patients with a DST showing a resistance to at least rifampicin;
– Patients with a DST showing a resistance to at least isoniazid and another Group 1 drug;
– Patients who remain culture positive on or after Month 4 of an MDR-TB treatment or who reconvert to a positive culture after Month 4;
– Persons who develop active TB after exposure to a patient with documented MDR-TB.

Referencias


3.7 Radiology

3.7.1 X-rays

Chest X-ray is a non-specific investigation for TB. In many national programmes, it is not routinely indicated in sputum smear-positive patients because of limited resources.
Chest X-ray is considered as an additional diagnostic tool given its limitations of nonspecificity. Indeed, several comparative studies have shown that the error rate of under- or over-reading the film by specialists is around 20%. It is often difficult to detect the difference between old healed lesions of fibrosis and active TB. They are rarely conclusive and can only complete the clinical presentation and history to constitute a body of arguments suggestive of TB.

Chest X-ray is however recommended when the smear microscopy results are negative or when TB is suspected in children\(^1\). It is particularly useful where the proportion of bacteriologically unconfirmed TB (i.e. smear microscopy or Xpert MTB/RIF negative) is likely to be high; for example, in populations with a high incidence of HIV.

In HIV co-infection, infiltrates (especially in advanced immunodeficiency) tend to be more diffuse and located in the lower lung zones; the X-ray may even appear normal in 10% of the cases. Cavitary disease is seen less in those infected with HIV, and in one study, only 33% of HIV-infected patients with PTB had cavities on X-ray when compared to 78% of HIV-negative patients with PTB\(^2\).

Chest X-rays are valuable tools for the diagnosis of pleural and pericardial effusions, especially at the early stages of the disease when the clinical signs are minimal. The X-ray showing an enlarged heart is a key element for diagnosis of pericardial TB\(^3\).

Chest X-ray is essential in the diagnosis of miliary TB. It shows small characteristic nodular infiltrations disseminated in both pulmonary fields\(^3\).

Another use of radiography includes examination of the joints and bones when TB is suspected. Radiography, including the use of computerized tomography scans (CT scans), can be useful for Pott’s disease.

### 3.7.2 Ultrasound

Ultrasound is useful in confirming pleural effusions\(^4\).

Ultrasound is extremely useful in pericardial TB as it can document that an effusion is the cause of an enlarged heart seen on chest X-ray.

It is moderately useful in diagnosing abdominal TB, whereby documenting multiple enlarged lymph nodes on an abdominal ultrasound is consistent with TB, however, multiple enlarged lymph nodes can be seen in other diseases, especially in HIV. Bowel wall thickening (ileocaecal region) is also suggestive of abdominal TB.

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**Referencias**


3.8 Tuberculin skin test (TST)

Cutaneous hypersensitivity to tuberculin reflects a delayed hypersensitivity reaction to some *M. tuberculosis* antigens.

A positive reaction signifies that an infection has occurred, but it does not determine if the TB is latent or active. It does not differentiate between infection by *M. tuberculosis* and hypersensitivity due to mycobacterium other than TB.

The TST is done by injecting 5 international units of tuberculin intradermally on the ventral surface (side of arm exposed with palm facing up) of the forearm.

The test is read by a trained health care worker, 48 to 72 hours after the injection. The reaction is the area of induration (swelling that can be felt) around the injection. The diameter of induration is measured with a ruler in millimetres across the forearm. The erythema (redness) around the indurated area is not measured, because the presence of redness does not indicate a reaction.

Tuberculin used for the skin test is also known as purified protein derivative, PPD. The TST is sometimes called PPD test or Mantoux test.

BCG vaccination induces a state of hypersensitivity which can result in a false positive TST, such that the average diameter 1 year after BCG vaccination is 10 mm, with extremes ranging from 4 to 20 mm. A false positive TST due to a vaccine reaction has a tendency to be less reactive with time and disappears 5 to 10 years post-vaccination.

**Positive TST**

A TST is considered as positive if:

- Induration is ≥ 5 mm in HIV infected individuals, immunocompromised patients, including those receiving prednisolone therapy of ≥ 15 mg/day for ≥ 1 month, and malnourished children;
- Induration is ≥ 10 mm in all other adults or children (BCG vaccinated or not).

A reaction that appears several minutes or several hours after injection (occasionally even after 24 hours) but which disappears on the day after its appearance is of no value.

---


In practice, TST has little value as a diagnostic tool when the annual rate of infection and BCG vaccine coverage are high. It can only be used as an element among a body of arguments to establish the diagnosis of active TB, and it is usually only used to help with the diagnosis in children (Chapter 5).

A highly positive (induration diameter > 20 mm) or phlyctenular reaction should be considered as an argument in favour of active TB, but insufficient in itself for deciding on treatment.

**Negative TST**

Negative reactions in patients that previously presented positive reactions signify a loss of hypersensitivity. These are considered false negative reactions and can be observed:

*Temporally:*
- In viral (influenza, measles) or bacterial (whooping cough) infections;
- At the start of the evolution of TB meningitis or miliary TB;
- In patients in poor general condition (e.g. malnutrition);
- During immunosuppressive treatment (e.g. corticosteroids).

*Permanently:*
- With natural extinction of post-vaccination reaction, observed from the fifth year that follows BCG;
- In a person with a weak immune response, such in very elderly persons;
- In persons with diseases that result in anergy: AIDS, haemopathies, sarcoidosis.

Approximately 30% of children with active TB have negative or doubtful TST when diagnosed.

TST has an essential role in identifying candidates for isoniazid prophylaxis therapy, see Chapter 16.

**Referencias**


**3.9 Interferon gamma release assays (IGRAs)**
These in vitro tests of cellular immunity detect interferon. Individuals who were once exposed to M. tuberculosis complex have lymphocytes in their blood that maintain memory for the priming TB antigen. Addition of TB antigen to blood in vitro results in rapid stimulation of memory T lymphocytes and release of interferon gamma, which is a specific marker of activation of the immune response[1][2].

IGRAs have the advantage that there is no cross reactivity with prior BCG vaccination and with most environmental mycobacteria. However, overall, they offer little advantage over conventional skin testing and may be a less sensitive test in HIV co-infected. In addition, IGRAs remain expensive and are not routinely used in resource-constrained settings.

**Referencias**


### 3.10 Biopsies, laboratory tests on body fluids and other biological tests

#### 3.10.1 Biopsies and fine needle aspirate cytology (FNAC)

Biopsies of lymph nodes, bone and pleural lining are often not feasible in resource-constrained settings given the technical skill and laboratory resources required. The cytology of the lymph nodes from FNAC is easier to perform. Specific granulomatous tissue, the presence of giant Langhans’ cells, and/or caseous necrosis strongly correlate with TB. AFBs are not always present. For the procedure for FNAC, see Appendix 4.

**Note:** molecular tests can be used on the specimens obtained from FNAC of lymph nodes.

#### 3.10.2 Laboratory tests on body fluids

The diagnosis of some EPTB localisations can be supported or confirmed by a combination of tests performed in respective body fluids.

**Table 3.2 - Summary of findings suggestive of TB in body fluids**
### 3.10.3 Other biological examinations

<table>
<thead>
<tr>
<th>Fluids</th>
<th>Tests</th>
</tr>
</thead>
</table>
| **Ascitic fluid** | - Typically translucent yellow-coloured liquid.  
- Exudate rich in lymphocytes, usually > 300 white cells/mm³; Rivalta test positive ([Appendix 8](#)).  
- Serum-ascites albumin gradient (SAAG) < 1.1 g/dl is consistent with TB (and many other conditions) while a SAAG > 1.1 g/dl makes peritoneal TB unlikely.\(^1\)  
- Adenosine desaminase can be used as a surrogate marker for TB in peritoneal fluid ([Appendix 6](#)).  
- The search for *M. tuberculosis* by microscopy is most often negative. |
| **Pleural fluid**  | - Typically straw-coloured.  
- Proteins ≥ 30 g/l (Rivalta test, [Appendix 8](#)).  
- Rich in white cells (1,000-2,500/mm³), with predominant lymphocytes  
- Adenosine desaminase can be used as a surrogate marker for TB in pleural fluid ([Appendix 6](#)).  
- Microscopy for *M. tuberculosis* is most often negative.  
- Xpert MTB/RIF in pleural fluid has a moderate sensitivity, and therefore, is not recommended. |
| **Cerebrospinal fluid** | - Clear, hyper-concentrated liquid.  
- Proteins > 0.40 g/l (Pandy test, [Appendix 8](#)).  
- Glucose diminished: < 60 mg/l.  
- CSF glucose/blood glucose < 0.5.  
- Between 100 and 1,000 white blood cells/ml, of which over 80% are lymphocytes.  
- *M. tuberculosis* can be found by CSF direct microscopy in less than 10%.  
- Xpert MTB/RIF has a moderate sensitivity that can be increased following centrifugation. Centrifugation is recommended if facilities for efficient and safe centrifugation exist (high-speed centrifuge and biosafety cabinet).  
- In HIV+ patients, cryptococcal meningitis is a concern. Perform the antigen test with cryptococcal antigen on serum and CSF (CrAgLFA). |
| **Urine**       | - A culture or molecular testing, after centrifugation, are the only measures to confirm diagnosis.  
- The search for *M. tuberculosis* in urinary microscopy is almost always negative.  
- Xpert MTB/RIF has a moderate sensitivity. Priority should be given to patients with CD4 counts < 50 due to demonstrated higher sensitivity in this group\(^2\).  
- The LAM assay is useful in patients with CD4 < 200 ([Section 3.10.3](#)). |
New TB diagnostic tests are in development for point-of-care use. These antigen-detection assays are based on detecting liporabinomannan (LAM): a carbohydrate cell wall antigen that is excreted in the urine of TB patients. The performances of the LAM urine assay for most populations are poor. An exception is the sensitivity of the LAM assay in patients with CD4 counts < 200\(^{[3][4][5]}\). The test may have some utility where advanced HIV-associated immunodeficiency is common.

Sedimentation rate is almost always higher but this examination is very non-specific. A normal sedimentation rate makes TB less likely but still possible.

C-reactive protein is also generally increased but this test also is very non-specific.

There exist commercial rapid blood tests for “serological diagnosis of TB”, but they are so far not very reliable in diagnosing active TB and should not be used.

**Referencias**


**Chapter 4: Diagnostic algorithms for pulmonary tuberculosis (PTB) in adults and adolescents**

4.1 Guiding principles for the use of the algorithms
4.1 Guiding principles for the use of the algorithms

The aim of algorithms is to assist the diagnostic process and minimize incorrect diagnosis. The following algorithms are for adults and adolescents. For diagnostic algorithms for children < 10 years, see Chapter 5.

4.1.1 Clinical assessment[^1]

- An assessment for danger signs is the first part of the clinical assessment. The adult or adolescent is classified as seriously ill if one or more of the following danger signs are present:
  - Respiratory rate $> 30$/minute;
  - Fever $> 39^\circ$C;
  - Pulse rate $> 120$/minute;
  - Unable to walk unaided.

- In cases where there is no bacteriological confirmation of TB, the clinical (and radiological) assessment should determine if the patient needs broad-spectrum antibiotics and/or anti-TB drugs.

- HIV testing should be routinely offered to all individuals suspected of having TB. If testing is refused or unavailable, it might be assumed that a certain patient is likely to be HIV-positive (according to context and/or clinical presentation). In this event, follow the algorithm for HIV-infected patients.

4.1.2 Clinical response

For patients who are treated empirically for bacterial pneumonia or pneumocystosis (PCP), a “non-response to antibiotics” increases the likelihood of TB. The converse is not necessarily true, such that a response to antibiotics does not automatically exclude TB in a person suspected of having TB, particularly if respiratory symptoms persist after treatment. Pneumonia or PCP may occur in patients with underlying TB.

Antibiotic treatment is appropriate for HIV-infected patients with cough because bacterial infections are common both with and without TB. All seriously ill patients being started on anti-TB treatment should also be treated empirically, with broad-spectrum antibiotics for bacterial pneumonia because benefits outweigh the risks[^1].
4.2 Adult and adolescent algorithms

Diagnostic algorithm 1

PTB in HIV-negative patients with low risk of MDR-TB
When the patient’s serological status is unknown, this algorithm should be used in settings with HIV prevalence < 5%.
Patients are considered to be at low risk of multidrug-resistant TB (MDR-TB) if they do not meet one of the following criteria: 1) resident in areas with high MDR-TB prevalence; 2) all retreatment categories; 3) exposure to a known MDR-TB case; 4) patient remaining smear + at 2 months; 5) exposure to institutions with high risk of MDR-TB (e.g. prisons).

danger signs: respiratory rate > 30/min and/or fever > 39°C and/or pulse rate > 120/min and/or unable to walk.

smear microscopy: two sputum examinations performed on the same day.

broad spectrum ATB:
- If no danger signs: amoxicillin for 7 days (NO fluoroquinolones);
- If danger signs: parenteral ATB (e.g. ceftriaxone).

Clinical response to a broad spectrum antibiotic does not rule out TB. Patient should be informed to return for reassessment if symptoms recur.

According to setting:
- Xpert MTB/RIF available: two sputum smear microscopy on the same day and one Xpert MTB/RIF from one of the samples collected for smear microscopy;
- Xpert MTB/RIF not available: two sputum smear microscopy on the same day.

In groups of patients with high level of resistance to isoniazid (> 10%) it is recommended to perform a conventional DST at baseline (and/or a line probe assay) in order to provide adequate treatment.

According to setting:
- In groups of patients with prevalence of MDR-TB < 10%, patients seriously ill should immediately be initiated under empiric MDR-TB treatment. H and R will be included in the regimen until confirmation of MDR-TB by conventional methods. If the patient is stable, the clinician may choose to wait for confirmation before initiating a MDR treatment.
- In groups of patients with prevalence of MDR-TB ≥ 10%, patients should be initiated under empiric MDR-TB treatment. Consider adding H in settings where mono-resistance to R is not uncommon.

Clinical signs and chest X-ray (CXR) findings tend to be more typical in those who are HIV-negative having active TB:
When clinical signs AND CXR are strongly suggestive of active TB, treatment should be initiated without waiting for diagnosis confirmation.

### Diagnostic algorithm 2

**PTB in HIV-positive patients**

<table>
<thead>
<tr>
<th>Clinical signs</th>
<th><strong>TB</strong></th>
<th><strong>Bacterial pneumonia</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical signs</strong></td>
<td>Weight loss, productive cough, purulent sputum, haemoptysis, pleuritic chest pain</td>
<td>• Acute onset</td>
</tr>
<tr>
<td><strong>CXR</strong></td>
<td>• Infiltrates, nodules with or without cavitation in the upper lobes and in the superior segments of the lower lobes.</td>
<td>• Fever</td>
</tr>
<tr>
<td></td>
<td>• Pleural effusions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Adenopathy in the mediastinum or hila (rare in TB in adults and adolescents)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Miliary disease</td>
<td>• Lobar consolidation</td>
</tr>
</tbody>
</table>
When the patient’s serological status is unknown, this algorithm should be used in settings with HIV prevalence > 5%.
b. TB suspect is defined as: cough for more than 2 weeks or any cough with at least one of the following signs: loss of weight, night sweats, fever, and suspicion based on clinical judgment.

c. Danger signs: respiratory rate > 30/min and/or fever > 39°C and/or pulse rate > 120/min and/or unable to walk.

d. According to setting:
   • Xpert MTB/RIF available: two sputum smear microscopy on the same day AND one Xpert MTB/RIF from one of the samples collected for smear microscopy;
   • Xpert MTB/RIF not available: two sputum smear microscopy on the same day.

e. In patients groups with high level of resistance to isoniazid (> 10%) it is recommended to perform a conventional DST at baseline (and/or a line probe assay) in order to provide adequate treatment.

f. When possible a culture should be performed. A positive culture result at any point in time in the algorithm should lead to a full TB treatment.

g. TB treatment should be started when clinical signs AND chest X-ray (CXR) are suggestive of TB (Note k).

h. Broad spectrum ATB/PCP:
   • If no danger signs: amoxicillin for 7 days (or recommended oral agent for community-acquired pneumonia in the area). Do NOT use fluoroquinolones;
   • If danger signs: parenteral ATB (e.g. ceftriaxone) AND high dose cotrimoxazole.

i. If no danger signs: patient should be re-assessed after 7 days.
   If danger signs: patient should be assessed daily and if no response, TB treatment should be considered after 3 to 5 days.
   Clinical response to broad-spectrum ATB does not rule out TB. Patient should be informed to return for reassessment if symptoms recur.

j. Differential diagnosis of a coughing HIV-infected adult/adolescent: bacterial (including atypical) pneumonia, PCP, fungal infection, non-tuberculous mycobacteria, nocardiosis, Kaposi sarcoma and lymphoma.

k. The diagnosis should be based on clinical assessment, CXR and CD4 results, whether cotrimoxazole preventive therapy (CPT) was used, and other treatment already used in the patient. If the index of suspicion for active TB is high, empiric TB treatment should be initiated without waiting for diagnosis confirmation. Other treatments such as broad-spectrum ATB or therapy for PCP may be needed in addition to TB treatment.
In the absence of any improvement of clinical signs (no weight gain, persistent cough, pain, etc.) AND no improvement on CXR after 2 months of a well conducted TB treatment, diagnosis and treatment should be reconsidered. MDR-TB should also be considered.  

In addition to the differential diagnosis in Note k above, DR-TB should be considered.  

Immediately start empiric MDR treatment, even if positive predictive value of Xpert MTB/RIF for R resistance is low (this is done to avoid the rapid and high mortality due to untreated MDR-TB in HIV patients). H and R should be included in the regimen until confirmation of MDR-TB by conventional methods if the patient comes from a group with less than a prevalence of MDR-TB < 10%. In groups of patients with prevalence of MDR-TB ≥ 10%, patients should be initiated under an empiric MDR treatment without H or R, although one can consider adding H in settings where mono-resistance to R is not uncommon.

### Diagnostic algorithm 3 with Xpert MTB/RIF

#### PTB in patients with high risk of MDR-TB

<table>
<thead>
<tr>
<th>Clinical signs</th>
<th>TB</th>
<th>PCP (HIV+)</th>
<th>Bacterial pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Current cough</td>
<td>• Dry cough</td>
<td>• Acute onset</td>
<td></td>
</tr>
<tr>
<td>• Weight loss</td>
<td>• Dyspnoea ++</td>
<td>• High fever</td>
<td></td>
</tr>
<tr>
<td>• Purulent sputum and haemoptysis less likely if HIV-positive with low CD4 count</td>
<td>• Hypoxemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fever</td>
<td>• Not on CPT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Night sweats</td>
<td>• More likely if low CD4 count</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pleuritic chest pain</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CXR</th>
<th>TB</th>
<th>PCP (HIV+)</th>
<th>Bacterial pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Upper lobe infiltrates and cavitation only likely in HIV-positive adults with higher CD4 counts. Any lobe of the lung may be affected</td>
<td>• Bilateral interstitial infiltrate with reticulonodular markings that are more pronounced in the lower lobes</td>
<td>• Lobar consolidation</td>
<td></td>
</tr>
<tr>
<td>• In HIV-positive adults with lower CD4 counts, the following 4 patterns are suggestive of TB:</td>
<td>• Findings lag behind symptoms and may be normal early in the disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. miliary pattern</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. pleural effusion without airspace (with straw-coloured liquid aspirate)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. hilar and mediastinal adenopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. large heart (especially if symmetrical and rounded)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The following patients are considered to be at high risk of MDR-TB: 1) resident in areas with high MDR-TB prevalence; 2) all retreatment categories; 3) exposure to a known MDR-TB case; 4) patient remaining smear-positive at 2 months; 5) exposure to institutions with high risk of MDR-TB (e.g. prisons).

Groups of patients at risk of MDR-TB are also at risk of other types of DR-TB as well. DST to the first-line should be performed in order to provide adequate treatment for possible mono- or poly-drug resistance.

In populations with a prevalence < 10% of MDR-TB, the resistance to R diagnosed by Xpert MTB/RIF must be confirmed by conventional methods. Drug sensitivity testing (DST) to both first-line drugs and secondline TB drugs should be performed if possible.

In groups of patients with prevalence of MDR-TB ≥ 10%, the patient should be initiated using an empiric MDR-TB treatment. Consider adding H in settings where mono-resistance to R is not uncommon.

Baseline sputum smear microscopy result on 1 specimen in order to: 1) allow patient follow-up with microscopy; 2) take immediate decisions related to TB infection control.
Chapter 5: Diagnosis of tuberculosis in children

5.1 Background

Tuberculosis (TB) is a significant cause of morbidity and mortality in children in settings of high TB prevalence. The lack of an accurate diagnostic method has contributed to a gross underestimation of its true burden. In high prevalence settings, children < 15 years old are expected to make up 10 to 20% of all TB cases.\(^1\)

The characteristics of TB disease and approach to diagnosis in children > 10 years old are similar to those for adults. This section focuses on children < 10 years old.

Referencias

5.2 Characteristics of tuberculosis in children

Children have a high risk of TB infection. In endemic areas, children are likely to be exposed to TB in their household or community. A careful contact history is extremely important in children with signs and symptoms suggestive of TB. In children with diagnosed TB, an effort should be made to detect the source case and any other undiagnosed cases in the household. The younger the child, the more likely it is that a contact can be identified. Equally, all TB cases, especially children or adults who are smear-positive, should be asked about close contact with children (Chapter 16).

Children have a high risk of progression to active TB disease and of developing severe forms: 90% of young children, who develop TB, do so within 12 months of infection[1]. Children < 3 years and children with immune suppression (e.g. HIV, malnutrition, post-measles) are particularly vulnerable. TB screening with prompt treatment or prophylaxis is especially critical in these children.

Most cases are pulmonary TB (PTB), but smear positivity is rare because children generally have low bacillary loads. Furthermore, sputum samples can be difficult to obtain from children. As a result, smear-positive TB represents only an estimated 10% of all TB observed in the 0 to 14 age group.

Extrapulmonary TB (EPTB) is common in children. The site of EPTB disease is age related. Miliary and meningeal TB is more frequently seen in young children. TB lymphadenitis and osteoarticular TB are more common in older children.

BCG administered at birth offers partial protection against severe forms in young children. It offers little if any protection against pulmonary TB. A history of BCG vaccination does not exclude the possibility of TB in a child with suggestive signs and symptoms.

Referencias


5.3 Diagnostic approach
For the majority of children, careful history, clinical assessment and follow up alone are sufficient to make a diagnosis of TB, even if confirmation is not possible.

Bacteriology, chest x-ray and tuberculin skin test are useful but not essential in most cases.

A trial of treatment with anti-TB drugs is not recommended as a method to diagnose TB. The decision to treat a child should be carefully considered. Once such a decision is made, the child should be treated with a full course of therapy.

5.4 Key elements of the diagnosis

Recommendations of how to combine the following elements to arrive at a treatment decision are summarized in the diagnostic algorithms (Section 5.6).

5.4.1 Careful history

- Contact with a known or presumed TB case:
  - Timing of the exposure: greater risk if exposure occurred in the past 12 months;
  - Closeness of the contact: greater risk if living in same household or sleeping in the same room;
  - Type of TB of the source case: greater risk if smear-positive or cavities on x-ray; resistance pattern of the source case.
- Symptoms suggestive of TB:
  - Cough persistent for > 2 weeks and not improving;
  - Unexplained fever for > 1 week;
  - Unexplained weight loss or failure to thrive;
  - Unexplained fatigue, lethargy or reduced playfulness.

5.4.2 Clinical examination

- Vital signs: fever and increased respiratory rate may be present.
- Growth: weigh the child and compare with previous records. Weight loss or flattening of the growth curve can signal chronic disease.
- Respiratory examination: abnormal auscultation or percussion may be present. Signs of severe respiratory infection: tachypnoea, cyanosis, hypoxemia ($\text{SpO}_2 < 90\%$), nasal flaring, chest indrawing, grunting and feeding difficulties in infants.
- Physical signs of EPTB (see also Chapter 2):
  - Highly suggestive, e.g.:
    - Angular deformity of the spine;
    - Cervical lymph node with fistula formation.
  - Non specific requiring further investigation, e.g.:
    - Sub-acute meningitis not responding to antibiotic therapy;
    - Distended abdomen with ascites;
    - Lymphadenopathy without fistula formation;
5.4.3 Re-assessment and follow up

The diagnosis is rarely made at the first consultation, as the initial clinical presentation is usually non-specific. Follow up is critical to assess if signs and symptoms persist despite a trial of well-monitored non-TB antibiotic treatment.

Particularly suggestive of TB disease are:
- Persistent pneumonia after appropriate, well-monitored antibiotic treatment;
- Measured or reliably reported fever of > 38 °C for > 1 week, after common causes such as malaria or pneumonia have been excluded;
- No weight gain despite appropriate nutritional support;
- Persistent or worsening fatigue.

5.4.4 HIV testing

HIV testing should be routinely offered to children with presumed or diagnosed TB.

5.4.5 Diagnostic investigations

The following investigations should be performed in children suspected of TB whenever possible. The unavailability of a test due to resource limitations should not delay the diagnosis of TB.

**Tuberculin skin test (TST)**
- A positive test can support a diagnosis of TB in a symptomatic child;
- A negative TST does not exclude TB;
- Causes of false positive: BCG, atypical mycobacteria (NTM);
- Causes of false negative: HIV infection, malnutrition.

**Chest x-ray**

Chest x-ray can be helpful for the diagnosis of intrathoracic TB\(^1\). Hilar lymphadenopathy is the most common finding. However, obtaining quality films in children and accurately interpreting them may be difficult. This limits their utility in many settings.

**Bacteriology**

Try to confirm TB, although treatment should not be delayed if clinically indicated.

For EPTB, obtain specimens from the suspected sites for microscopy and, when possible, for culture, cytology or histopathological examination and molecular methods (e.g. Xpert MTB/RIF).
Bacterial yields are higher in older children, and in children of all ages with severe disease. Two sputum specimens should be obtained: an on-the-spot specimen (at first evaluation), and an early morning specimen. Alternatively, two specimens collected one hour apart are an acceptable option (see Appendix 3).

Xpert MTB/RIF is the initial test of choice in screening for multidrug-resistant TB (MDR-TB). When Xpert MTB/RIF is not available, conventional drug susceptibility test (DST) can be done. DST indications are the same as for adults.

**Referencias**


### 5.5 Collecting sputum specimens in children

Given the importance of trying to obtain confirmation of disease in areas of high drug-resistant TB prevalence or in contact cases of MDR-TB, optimizing the collection of appropriate specimens is critical.

Children < 6 years old, and some as old as 10 years old, may be unable or unwilling to spontaneously expectorate. Explanation and encouragement are important. Chest clapping is a simple, yet, often effective measure to help expectoration.

If these measures fail, sputum specimen can be obtained by sputum induction or gastric aspiration (Appendix 3). Given the distress caused to the child and the generally low yield on smear microscopy, these procedures should only be done if culture or Xpert MTB/RIF is available.

### 5.6 Paediatric diagnostic algorithms

**Paediatric diagnostic algorithm 1**

**Contact of a TB case**
Contact: child living in the same household or in close and regular contact with any known or suspected TB case in the last 12 months.

b. Malnutrition or growth curve flattening.

c. Clinical assessment (including growth assessment), bacteriological tests, HIV testing (in high HIV prevalence areas), and when relevant and available: X-ray (CXR), investigations for EPTB, TST.

d. Examples of “obvious TB” may include cases of Pott's disease, TB meningitis, lymph node TB with fistula formation, smear or Xpert MTB/RIF positive or highly suggestive chest X-ray (e.g. hilar lymphadenopathy, upper lobe infiltrates, miliary picture).

e. Broad spectrum ATB:
   - If no danger signs: amoxicillin PO for 7 days;
   - If danger signs: parenteral ATB (e.g. ceftriaxone).

f. Clinical response to a broad-spectrum antibiotic does not rule out TB. Carer should be informed to consult if symptoms re-occur.
Paediatric diagnostic algorithm 2

Symptomatic child
Paediatric diagnostic algorithm 2: Symptomatic child

Day 1
- Clinical assessment and other investigations
- Antibiotics, nutritional support or other treatment according to clinical findings

- Clinical assessment and other investigations after 1 week
  - Is the child still symptomatic?
    - NO
    - Day 7
      - Is the child HIV exposed or infected or is a contact of a TB case?
        - YES
          - Antibiotics, nutritional support or other treatment according to clinical findings for one week
        - NO
          - Clinical assessment:
            - Poor weight gain
            - Persistent cough
            - Persistent fever
            - Fatigue or lethargy
            - CXR suggestive of TB

- Day 7-12
  - None present
    - TB unlikely
  - One present
    - Start TB treatment
  - ≥ 2 present
    - Start TB treatment

TB treatment in particular if child is HIV+ or < 3 years or presents severe malnutrition, or TST+.

---

a. Malnutrition or growth curve flattening.
b. Temperature > 38°C.

c. Clinical assessment (including growth assessment), bacteriological tests, HIV testing (in high HIV prevalence areas), and when relevant and available: X-ray (CXR), investigations for EPTB, TST.

d. Smear microscopy positive or Xpert MTB/RIF positive, CXR showing suggestive lesions (e.g. hilar lymphadenopathy, upper lobe infiltrates, miliary picture), gibbus.

e. Broad spectrum antibiotics:
   - If no signs of severity:
     - first-line: amoxicillin PO for 7 days (NO fluoroquinolones). Advise carer to return with the child if no improvement after 48 hours of antibiotics;
     - if a second course of antibiotic if needed: azithromycin PO for 5 days.
   - If signs of severity: parenteral antibiotics (ceftriaxone ± cloxacillin if S. aureus is suspected).

   In addition: PCP treatment should be given presumptively to all HIV-exposed or HIV-infected children < 1 year of age, and any older child with severe immune suppression and not on CTX prophylaxis. For all other HIV-exposed or HIV-infected children, it should be considered if there is poor response to broad spectrum antibiotics after 48 hours.

f. Clinical response to a broad-spectrum antibiotic does not rule out TB. Carer should be informed to consult if symptoms re-occur.

Chapter 6: Intensive case finding in HIV-infected individuals

6.1 Routine screening

6.2 Purposes of screening

6.1 Routine screening

Intensive case-finding (ICF) should be in place in all projects providing care to HIV-infected patients. Screening can be performed at multiple points in time by different levels of health care workers (e.g. counsellors during HIV testing, health care providers during clinical consultations).

All children and adults should be regularly screened for TB using the following criteria:

Table 6.1 - Screening criteria/symptoms in children and adults[1]
6.2 Purposes of screening

6.2.1 Early detection and treatment of active TB

Children and adults found to have one or more of the above symptoms/criteria during screening may have active TB, and they should be evaluated with an appropriate TB diagnostic algorithm in order to rapidly diagnose those who do have TB (see Diagnostic algorithms, Chapter 4 and Chapter 5).

6.2.2 Identification of patients eligible for isoniazid preventive therapy (IPT)

The significant proportion of asymptomatic active TB described in patients eligible for ART (15 to 20%)\(^{[1][2]}\) leads to use this screening method with caution. It should only be used for ruling out TB in patients not yet eligible for antiretroviral therapy (CD4 greater than 350 and no WHO stage 3 or 4 illnesses) or after three months of treatment in patients started under antiretroviral therapy in order to allow for possible unmasking of TB.

For IPT, see Chapter 16.

References

Chapter 7: Case definitions for registration

7.1 Definition of a tuberculosis case

7.2 History of prior anti-TB treatment

7.3 Anatomical site of the disease

7.4 Bacteriological status

7.5 HIV status

7.6 Other co-morbidities

7.7 Summary of patient registration

7.1 Definition of a tuberculosis case

A tuberculosis (TB) case is a patient that has been diagnosed as such by a clinician, regardless if the diagnosis has been confirmed bacteriologically or not.

The elements necessary for defining a TB case are: the TB treatment history, the bacteriological status, the anatomical site of the disease and the patient’s HIV status.
Note: any person receiving treatment for TB should be recorded as a TB case.

### 7.2 History of prior anti-TB treatment

Patients who have interrupted or failed a previous anti-TB treatment have a higher risk of developing drug-resistance (DR). Therefore, it is important to question patients about their previous treatment prior to treatment initiation.

Case registration distinguishes between:

- **New patients**: patients who have never been treated for TB or have taken anti-TB drugs for less than 1 month.

- **Previously treated patients**: patients who have received 1 month or more of anti-TB drugs in the past. Previously treated patients are further sub-classified into relapse, failure and return after treatment interruption:
  - **Relapse**: patients who were cured or completed treatment on their last TB treatment;
  - **Failure**: patients who have failed their most recent treatment (see Chapter 17 for outcome definitions for failure);
  - **Treatment interruption**: patients who interrupted (see Chapter 17 for outcome definition of treatment interruption) their last treatment should be classified as “Return after treatment interruption”.

- **Others**: patients who cannot be included in one of the above categories (e.g. patients who have previously been treated via an erratic or unknown TB regimen).

### Referencias


### 7.3 Anatomical site of the disease
Pulmonary TB (PTB)

Refers to a case of TB presenting with involvement of the lung parenchyma.

Notes:
- Miliary TB is also classified as PTB because there are lesions in the lungs.
- Any patient presenting with PTB and an EPTB form at the same time is classified as a PTB case for recording purposes.

Extrapulmonary TB (EPTB)

Refers to a case of TB involving organs other than the lungs. Diagnosis is based on clinical signs corresponding to extrapulmonary active TB and a decision by a clinician to treat with a full course of anti-TB drugs.

Notes:
- Sputum smear microscopy should always be done, and if possible culture and/or molecular test.
- Patients presenting with tuberculous pleural effusion, or mediastinal lymphadenopathy without evidence of parenchymal localization are classified in this category.

Notas

(a) If possible, obtain histological or bacteriological evidence (microscopy, culture or molecular test).

7.4 Bacteriological status

Bacteriological status refers to the detection of M. tuberculosis by smear, culture or molecular methods. The bacteriological status can be further sub-classified on the basis of drug sensitive and drug resistant cases.

7.4.1 Detection of M. tuberculosis

Every TB case should be classified into one of two categories:
- **Confirmed TB case**: a case with a positive bacteriological result (microscopy, culture or molecular method).
- **Non-confirmed TB case**: a case where investigations are negative (microscopy, culture or molecular method) and for whom a clinician prescribes anti-TB treatment.

Confirmed TB cases are further sub-classified as:
1. smear positive/negative/not done
2. culture positive/negative/not done
3. molecular test positive/negative/not done
7.4.2 Strain sensitivity/resistance

When possible, culture and DST should be done to determine if the strain presents resistance to some drugs:

- **Susceptible TB**: the strain is not resistant to any first-line anti-TB drugs.
- **Drug-resistant TB**:
  - **Monodrug-resistant TB**: resistance to one first-line anti-TB drug only;
  - **Polydrug-resistant TB** (PDR-TB): resistance to more than one first-line anti-TB drug, other than isoniazid and rifampicin;
  - **Multidrug-resistant TB** (MDR-TB): resistance to at least isoniazid and rifampicin;
  - **Extensively drug-resistant TB** (XDR-TB): MDR-TB resistant to at least one fluoroquinolone and at least one second-line injectable drug (Km, Amk, Cm).

Patients with DR-TB should be classified in the following manner:

- **Confirmed isoniazid resistance and rifampicin susceptible**: resistance to isoniazid but not rifampicin. Resistance to first and second-line anti-TB drugs may be present.
- **Confirmed rifampicin resistant TB** (RR-TB): resistance to rifampicin confirmed by phenotypic drug susceptibility test or line probe assay or Xpert MTB/RIF (isoniazid susceptible or unknown).
- **Confirmed MDR-TB**: resistance to isoniazid and rifampicin, with or without resistance to first and second-line anti-TB drugs.
- **Confirmed XDR-TB**: resistance to isoniazid and rifampicin, and to at least one fluoroquinolone, and one second-line injectable drug (Km, Amk, Cm).
- **Unconfirmed DR-TB**: patients treated as DR-TB but without DST results (e.g. children who are contacts of a known case, patients with clinical failure and for whom no DST was available for some reason).

7.5 HIV status

Determining and recording the patient’s HIV status is critical for treatment decisions, as well as for assessing programme performances. The TB treatment card and TB register, which should be treated as confidential documents, should include: dates and results of HIV tests, starting date of cotrimoxazole and antiretroviral therapy.

7.6 Other co-morbidities

Any other significant diseases, such as diabetes, hepatitis B or C, cancer and malnutrition, should be noted at registration.
7.7 Summary of patient registration

Table 7.1 summarizes the elements necessary for defining a TB case.

Table 7.1 - Patient registration by outcome of most recent TB treatment

<table>
<thead>
<tr>
<th>Registration groups based on treatment history</th>
<th>Further classification</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Relapse</strong></td>
<td>1. PTB or EPTB? If EPTB, indicate site.</td>
</tr>
<tr>
<td><strong>Failure</strong></td>
<td>2. Bacteriologically confirmed or non-confirmed TB case?</td>
</tr>
<tr>
<td><strong>Treatment interruption</strong></td>
<td>3. Sub-category of bacteriological status:</td>
</tr>
<tr>
<td></td>
<td>▪ Smear positive/negative/not done</td>
</tr>
<tr>
<td></td>
<td>▪ Culture positive/negative/not done</td>
</tr>
<tr>
<td></td>
<td>▪ Molecular test positive/negative/not done</td>
</tr>
<tr>
<td><strong>Previously treated</strong></td>
<td>4. If previously treated:</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>▪ Document last regimen received</td>
</tr>
<tr>
<td></td>
<td>▪ History of second-line drug use</td>
</tr>
<tr>
<td></td>
<td>5. DST pattern: susceptible to H and R, confirmed H resistance and R susceptible, RR-TB, MDR-TB or XDR-TB</td>
</tr>
<tr>
<td></td>
<td>6. HIV status (negative/positive/not done)</td>
</tr>
<tr>
<td></td>
<td>7. Other co-morbidities?</td>
</tr>
</tbody>
</table>

Referencias


Chapter 8: Anti-TB drugs and treatment regimens
8.1 Introduction

A combination of several antibacterial drugs is necessary for treating the disease and avoiding the emergence of resistance. Treatment regimens define the specific drug combinations used and the intended length of treatment.

Anti-TB drugs are classified into 5 groups based on efficacy, experience of use and drug class. Not all drugs in the same group have the same efficacy, mechanisms of action, adverse effect profile or safety. Each drug has a specific action on one or more bacillary populations but none on dormant bacilli.

Treatment regimens are expressed in a standardised and abbreviated manner.

8.1.1 Standard code for TB treatment regimens

Anti-TB drugs

Table 8.1 - Drug groups and abbreviations (adapted from the WHO[1])
<table>
<thead>
<tr>
<th>Group name</th>
<th>Anti-TB drug</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GROUP 1</strong></td>
<td>Isoniazid</td>
<td>H</td>
</tr>
<tr>
<td>First-line oral agents</td>
<td>Rifampicin</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>Pyrazinamide</td>
<td>Z</td>
</tr>
<tr>
<td></td>
<td>Ethambutol</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Rifabutin</td>
<td>Rfb</td>
</tr>
<tr>
<td><strong>GROUP 2</strong></td>
<td>Streptomycin</td>
<td>S</td>
</tr>
<tr>
<td>Injectable agents</td>
<td>Amikacin</td>
<td>Amk</td>
</tr>
<tr>
<td></td>
<td>Kanamycin</td>
<td>Km</td>
</tr>
<tr>
<td></td>
<td>Capreomycin</td>
<td>Cm</td>
</tr>
<tr>
<td><strong>GROUP 3</strong></td>
<td>Moxifloxacin</td>
<td>Mfx</td>
</tr>
<tr>
<td>Fluoroquinolones (FQs)</td>
<td>Levofloxacin</td>
<td>Lfx</td>
</tr>
<tr>
<td></td>
<td>Ofloxacin</td>
<td>Ofx</td>
</tr>
<tr>
<td><strong>GROUP 4</strong></td>
<td>Ethionamide</td>
<td>Eto</td>
</tr>
<tr>
<td>Oral bacteriostatic second-line anti-TB drugs</td>
<td>Prothionamide</td>
<td>Pto</td>
</tr>
<tr>
<td></td>
<td>Cycloserine</td>
<td>Cs</td>
</tr>
<tr>
<td></td>
<td>Para-aminosalicylic acid</td>
<td>PAS</td>
</tr>
<tr>
<td><strong>GROUP 5</strong></td>
<td>Bedaquiline</td>
<td>Bdq</td>
</tr>
<tr>
<td>Drugs with limited data on efficacy and/or</td>
<td>Linezolid</td>
<td>Lzd</td>
</tr>
<tr>
<td>long-term safety in the treatment of DR-TB</td>
<td>Clofazimine</td>
<td>Cfz</td>
</tr>
<tr>
<td></td>
<td>Amoxicillin/clavulanic acid</td>
<td>Amx/Clv</td>
</tr>
<tr>
<td></td>
<td>Isoniazid high dose</td>
<td>High dose H</td>
</tr>
<tr>
<td></td>
<td>Thioacetazone</td>
<td>Thz</td>
</tr>
<tr>
<td></td>
<td>Imipenem/cilastatin</td>
<td>Ipm/Cln</td>
</tr>
<tr>
<td></td>
<td>Meropenem</td>
<td>Mpm</td>
</tr>
</tbody>
</table>

**Notes:**
- The traditional “first-line anti-TB drugs”: H, R, Z, E and streptomycin (S) are now referred to as Group 1 drugs, with the exception of S, which is included in Group 2. Groups 2 (except S) to 5 are usually reserved for drug-resistant (DR) TB and are referred as “second-line anti-TB drugs”.
- In these guidelines, clarithromycin (Clr) is not included in the Group 5 drugs until further data on its efficacy is available.

**Treatment regimens**
TB regimens are abbreviated according to the following system:
– Drugs are listed using their abbreviations.
– Treatment is divided into two phases, initial (or intensive) phase and continuation phase. These two phases are divided by a slash.
– The number before each phase represents the duration of that phase in months.
– A number in subscript (e.g. 3) after a letter means that intermittent dosing is used (H3R3 means isoniazid and rifampicin are given 3 times weekly).
– No number in subscript means that medications must be taken every day.
– When drugs are placed in brackets, it means that fixed-dose combinations (FDC) are used.
– When drugs are not placed in brackets, individual drugs are used.
– Second line drugs are separated by a hyphen.

Examples:
– 2 (HRZE)/4 (HR): the patient receives a FDC containing four drugs (isoniazid, rifampicin, pyrazinamide, ethambutol) daily for two months, then a FDC containing two drugs (isoniazid, rifampicin) daily for four months.
– 8 Km-Lfx-Eto-Cs-Z/14 Lfx-Eto-Cs-Z: the patient receives a combination of five individual drugs daily for eight months, then a combination of four individual drugs daily for fourteen months. The injectable drug is mentioned first, the fluoroquinolone second, Group 1 drug(s) are mentioned last.

8.1.2 Treatment approaches

Standardized treatment or regimen

All patients in a defined group receive the same regimen. Different groups might receive a different regimen.

For example:
– All patients with a strain susceptible to first-line drugs receive the same standard treatment for 6 months, or for 12 months, depending on the site involved.
– Patients who failed to respond to the first-line drugs may start an empiric standardized regimen for multiresistant TB (MDR-TB), based on drug resistance data of first- and second-line anti-TB drugs from representative patient populations, until the full drug susceptibility testing (DST) returns and the patient’s regimen is individualized.

Individualized treatment or regimen

Each regimen is designed based on the patient’s previous history of TB treatment and individual DST results.

DR-TB programmes often use a combination of the standardized and individualized approaches. However, in situations where DST is unavailable or limited to only one or two first-line drugs, programmes will most commonly use a purely standardized approach.
8.2 Antituberculosis drug formulations

8.2.1 Fixed-dose combinations (FDCs)

FDC formulations incorporate several (2, 3 or 4) individual drugs in the same tablet. FDCs are recommended as they have many advantages in improving adherence, removing the risk of patients taking only part of the prescribed medications, reducing the risk of failure and development of resistance. Quality assured FDC formations only exist for Group 1 drugs, and their composition is provided in Table 8.2

Table 8.2 - Quality-assured FDC formulations

Notas

(a) An active TB lesion contains distinct *M. tuberculosis* populations: actively multiplying bacilli in open cavities (responsible for transmission); slowly multiplying bacilli in acidic inflammatory tissue; sporadically multiplying bacilli in tissues and dormant bacilli in solid lesions.

Referencias

8.2.2 Single drug formulations

Quality assured FDCs do not exist for drugs in Groups 2 to 5. Therefore, the treatment of MDR-TB is provided by using a combination of individual drugs.

8.2.3 Paediatric formulations

<table>
<thead>
<tr>
<th>FDC tablets</th>
<th>Formulations available for daily treatment[1]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment in adults:</strong></td>
<td></td>
</tr>
<tr>
<td>4 drug FDC</td>
<td>E275 mg/H75 mg/Z400 mg/R150 mg</td>
</tr>
<tr>
<td>3 drug FDC</td>
<td>E275 mg/H75 mg/R150 mg</td>
</tr>
<tr>
<td>3 drug FDC</td>
<td>H75 mg/Z400 mg/R150 mg</td>
</tr>
<tr>
<td>2 drug FDC</td>
<td>H75 mg/R150 mg</td>
</tr>
<tr>
<td><strong>Treatment in children:</strong></td>
<td></td>
</tr>
<tr>
<td>3 drug FDC</td>
<td>H50 mg/Z150 mg/R75 mg</td>
</tr>
<tr>
<td>3 drug FDC(a)</td>
<td>H30 mg/Z150 mg/R60 mg</td>
</tr>
<tr>
<td>2 drug FDC</td>
<td>H50 mg/R75 mg</td>
</tr>
<tr>
<td>2 drug FDC(a)</td>
<td>H30 mg/R60 mg</td>
</tr>
<tr>
<td>2 drug FDC(a)</td>
<td>H60 mg/R60 mg</td>
</tr>
</tbody>
</table>

(a) These formulations must be phased out if new paediatric FDCs are available that correspond to the WHO recommended doses for children.
Paediatric formulations are not available for all medicines, and the dosing thereof can be problematic. For some drugs, the only option is to manipulate the commercial formulations available for adults by doing the following:

- Splitting of tablets: if available use tablets with a score line. However not all tablets are meant to be split, as this can affect the bioavailability and the efficacy of the drug (e.g. ingredients protected from stomach acidity by an enteric coating).
- Crushing of tablets and opening of capsules: a fraction of the powder is estimated to deliver the required dose. The remaining powder should be discarded right after the administration. These powders can be mixed with food or liquid vehicles like juice, etc. Such manipulations should be done immediately before administrating the medicine. There is little information on the impact of mixing drugs with food or liquids. In some cases, interactions might occur that may change the bioavailability.
- An alternative to the manipulation of adult dosages are extemporaneous formulations. However, this can only be considered when qualified staffs are available to ensure the preparation of these formulations following good compounding procedures.

Referencias


8.3 Quality-assured anti-TB drugs

Using sub-standard anti-TB drugs can be disastrous both to the individual and the community. This includes treatment failure resulting in death or resistance and transmission of resistant strains to other individuals. Only quality-assured drugs must be used.

There are several internationally recognized mechanisms that evaluate the quality of TB drugs. These mechanisms are: the WHO pre-qualification programme\(^a\), approval by Stringent Regulatory Authorities\(^b\) or evaluation and temporary approval by the Expert Review Panel of Global Fund/Global Drug Facility\(^c\).

Notas

(a) WHO Prequalification Scheme: http://apps.who.int/prequal/
8.4 Dosing of anti-TB drugs

For the daily dose of anti-TB drugs to be administered:
- See Appendix 8 for FDC tablets to be administered (number of tablets/day) based on the weight of the patient.
- See Appendix 10 for individual drugs.

8.5 Cross resistance

There is well-known cross-resistance between some of the antibacterial drugs used in treatment of TB. Resistance mutations 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 other families. For example, among aminoglycosides, resistance to kanamycin is associated with near complete cross-resistance to amikacin. In contrast, cross-resistance between kanamycin and streptomycin is generally low. Moreover, TB isolates that are resistant to kanamycin at high doses may be resistant to capreomycin (a polypeptide).

Table 8.3 - Summary on cross-resistance between anti-TB agents[1]
<table>
<thead>
<tr>
<th>Drugs class</th>
<th>Cross-resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rifamycins</strong></td>
<td>R and Rfb have high levels of cross-resistance.</td>
</tr>
<tr>
<td><strong>Isoniazid</strong></td>
<td>Eto/Pto can have cross-resistance to H if the inhA mutation is present.</td>
</tr>
<tr>
<td><strong>Aminoglycosides</strong> and polypeptides</td>
<td>Amk and Km have very high cross-resistance. Km (or Amk) and Cm have low to moderate cross-resistance. S has low cross resistance with Amk and Km.</td>
</tr>
<tr>
<td><strong>Fluoroquinolones</strong></td>
<td>FQs are believed to have variable cross-resistance between each other. Some <em>in vitro</em> data show that strains can be susceptible to some later-generation FQs when resistant to earlier-generation FQs (Ofx). In these cases, it is unknown if the later-generation FQs remain clinically effective.</td>
</tr>
<tr>
<td><strong>Thioamides</strong></td>
<td>Eto and Pto have 100% cross-resistance.</td>
</tr>
</tbody>
</table>

**Referencias**


**Chapter 9: Treatment of drug-susceptible tuberculosis**

9.1 Standard first-line treatment regimens

9.2 Special situations

9.3 Adjunctive corticosteroid therapy

9.4 Follow-up for patients treated with first-line regimens

9.5 Management of adverse effects in patients on first-line regimens
9.1 Standard first-line treatment regimens

Standard first-line regimens are used for patients with presumed drug-susceptible tuberculosis (TB), documented drug-susceptible TB or while waiting for drug susceptibility testing (DST) results when drug-resistant (DR) TB is unknown but considered a low probability.

9.1.1 New patient regimens

New patients are defined as those who have no history of anti-TB treatment or who have received less than one month of anti-TB drugs. New patients may have smear positive or smear negative pulmonary TB (PTB) or extrapulmonary TB (EPTB).

Pulmonary TB and extrapulmonary TB

(once TB meningitis and osteoarticular/spinal TB)[1][2]

2 (HRZE)/4 (HR)

The treatment lasts 6 months with an intensive phase of 2 months with 4 anti-TB drugs and a continuation phase of 4 months with 2 anti-TB drugs.

In lymph node TB, adenopathies usually disappear in less than 3 months after treatment initiation. Paradoxical reactions may be observed at the beginning of treatment (appearance of abscesses, fistulas or other lymph nodes) and should not lead to a change in treatment. Non-steroidal anti-inflammatory drugs can be used in patients that experience paradoxical reactions.

This regimen should NOT be used:
- In patients who develop active TB after close contact with a known DR-TB case: Obtain DST and while waiting for results, start a regimen based on the DST of the presumed source case (Chapter 10).
- In areas with high prevalence of resistance to isoniazid: In these areas, all patients should get a DST at the start of treatment. The regimen 2 (HRZE)/4 (HR)E can be used[1] in places where DST is not available or while waiting for DST result. This recommendation is based only on expert opinion. As a result, many patients will receive ethambutol unnecessarily if the DST is not available, but this could prevent rifampicin resistance in theory.
Notes:
– An 8-month regimen 2 (HRZE)/6 (HE) or 2 S(HRZ)/6 (HE) is still used by some countries however, it has been demonstrated that it gives more frequent relapses and failures than the 6-month regimen. It should be replaced by the above 6-month regimen.
– Three times a week regimens are not recommended as a routine practice. However, for patients who are: (1) under strict directly observed therapy and (2) not HIV-infected, three times a week regimen for the continuation phase can be considered. Three times weekly administration during the intensive phase should not be done in any situation.

TB meningitis and osteoarticular/spinal TB

2 (HRZE)/10 (HR)

TB meningitis
Treatment of TB meningitis lasts 12 months. Although 6 months are probably sufficient in most cases, treatment lasts longer because of the uncertain cerebrospinal fluid penetration of some anti-TB drugs. It is also recommended that all patients with TB meningitis receive a course of corticosteroids (Section 9.3).

Osteoarticular TB and spinal TB (Pott's disease)
Although there is limited evidence to the benefit of extending the treatment, treating for 12 months with 2 (HRZE)/10 (HR) is recommended mainly because it is difficult to assess the response to the treatment. Pott’s disease is a severe form of TB that should be treated as a priority because of the risk of neurological sequelae due to the chronic compression of the spinal nerve. In the absence of significant deformity and neurological deficit, most cases of spinal TB can be successfully treated with rest, back support bracing and anti-TB drugs. Surgery should be considered for patients with neurological deficit, an unstable spine lesion, and/or when they are not responding to therapy.

9.1.2 Previously treated patient regimens

Previously treated patients are defined as those who have received one month or more of anti-TB drugs in the past. It is critical in these patients to detect drug resistance, especially multidrug-resistant TB (MDR-TB) so that an effective drug regimen can be used. First-line drug regimens are not effective against MDR strains and their use can result in mortality and morbidity, amplification of resistance and spread of MDR-TB.

Strategy in previously treated patients:

Drug-resistance should be determined in all previously treated patients at or before the start of treatment. Xpert MTB/RIF is the preferred screening method for MDR-TB because of its sensitivity and quick turnaround time. The following are strategies depending on the availability of DST:
1 - Xpert MTB/RIF is available[4]: Xpert MTB/RIF indicating rifampicin resistance in previously treated patients should lead to an empiric MDR regimen (see Adult and adolescent diagnostic algorithm 3, Chapter 4). Previously treated patients with an Xpert MTB/RIF test indicating no rifampicin resistance should have DST to first-line drugs and be started on a first-line retreatment regimen².

2 - Only conventional DST is available: Patients whose treatment has failed⁵ or other patients with a high likelihood of MDR-TB (close contacts) should be started on an empiric MDR regimen while waiting for DST results. Relapse patients or patients returning after interruption may receive a retreatment regimen with first-line drugs⁶ while waiting DST⁸. When DST result becomes available, the regimen should be adjusted. If the clinical condition does not improve or deteriorates on the retreatment regimen with first-line drugs⁸ while waiting DST results, change to an empiric MDR regimen.

3 - DST is not available: Strategies without DST for previously treated patients are not recommended. Some programmes may have no choice but to care for patients under these circumstances. In this case, it is advised for TB patients whose previous treatment has failed⁵ or other patients with a high likelihood of MDR-TB (close contacts) to be started on an empiric MDR regimen. Patients with low to moderate risk of having MDR-TB (relapse or returning after interruption) may receive a retreatment regimen with first-line drugs: 2 (HRZE)⁹ /1 (HRZE)/5 (HR)E. If no response is seen, the patient should be switched to an empiric MDR regimen. The MDR regimen should be continued throughout the course of treatment.

Empiric MDR regimens are described in Chapter 10.

Notas
(a) Most national TB programmes use 2 S(HRZE)/1 (HRZE)/5 (HR)E while waiting DST. These guidelines suggest using HRZE until DST returns, as the benefits of streptomycin are minimal and the daily injections discomforting.

(b) For PTB, failure should be confirmed with either: a positive culture OR a positive smear and the presence of clinical deterioration. This indicates that the patient is a true failure and not a case of being smear-positive with dead bacilli.

(c) MDR-TB rates of failures should be documented in all programmes to determine if their rates of MDR-TB are high enough to warrant empiric MDR-TB treatment while waiting DST.

(d) Most national TB programmes use 2 S(HRZE)/1 (HRZE)/5 (HR)E. These guidelines suggest using HRZE as the benefits of streptomycin are minimal and the daily injections discomforting.

Referencias

9.2 Special situations

See references[1][2]

9.2.1 Women

Pregnant women

All first-line oral drugs can be administered.

Streptomycin is contra-indicated (ototoxic to the fetus).

Rifampicin can increase the metabolism of vitamin K, resulting in clotting disorders. Prophylactic administration of vitamin K to the mother and the neonate is recommended when the mother has received rifampicin during pregnancy:

- For the mother:
  - **phytomenadione** (vitamin K) PO: 10 mg/day for the 15 days prior to expected date of delivery
  - Even with this maternal prevention, the infant still needs prophylactic IM vitamin K to prevent haemorrhagic disease of the newborn.
- For the newborn infant:
  - **phytomenadione** (vitamin K) IM: 1 mg as a single dose, the day of birth

All pregnant women should also receive preventive treatment for isoniazid-related peripheral neuropathy (**pyridoxine** PO: 10 mg/day along with their anti-TB drugs).

Breast-feeding women

Breast-feeding women should routinely receive preventive treatment for isoniazid-related peripheral neuropathy (**pyridoxine** PO: 10 mg/day along with their anti-TB drugs). In addition, the breast-fed infant should receive **pyridoxine** PO: 5 mg/day.

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Women under contraception

Rifampicin and rifabutin interact with hormonal contraceptives and decreases their efficacy. Patients may choose between: use of medroxyprogesterone IM or barrier methods (diaphragm, condom, UID), or as a last resort, an oral contraceptive containing a high dose of estrogen (50 microgrammes/tab), throughout the course of treatment.

9.2.2 Children

Children should be treated with 2 (HRZE)/4 (HR)\[^3\], except for TB meningitis and osteoarticular TB where the treatment is 2 (HRZE)/10 (HR).

Ethambutol is considered safe regardless of child’s age, in particular regarding ocular toxicity\[^4\], provided it is correctly dosed at 20 mg/kg/day. It is routinely used in drug-susceptible TB in children.

Streptomycin should be avoided in children because irreversible auditory nerve damage may occur and the injections are painful. Thus, the retreatment regimen is not recommended in children.

Children with TB are often malnourished. Therapeutic feeding should be initiated in children with severe malnutrition. Children not severely malnourished should receive nutritional supplementation with a standard food package or ready-to-use food for at least the first two months of treatment wherever possible.

Referencias


9.3 Adjunctive corticosteroid therapy
Corticosteroids are indicated for:
- Meningitis of all stages of severity;
- Effusions: pleural effusion with severe respiratory difficulties; pericardial effusion;
- Compressions: laryngitis with obstruction of upper airways; urinary tract TB (in order to prevent ureteric stenosis); lymph node hypertrophy with bronchial or arterial compression;
- Severe hypersensitivity to TB drugs (although effectiveness has not been demonstrated);
- Life-threatening paradoxical reactions (immune reconstitution inflammatory syndrome) at the beginning of antiretroviral therapy or TB treatment (Chapter 12, Section 12.7)\(^a\).

The suggested treatment is **prednisolone** PO (or prednisone) for 6 to 12 weeks according to the severity of symptoms and clinical response:
- Children: 2 mg/kg once daily in the morning, up to 4 mg/kg once daily in severely ill children (max. 60 mg once daily)
- Adults: 40 to 60 mg once daily in the morning

The dose should be tapered off in the last 2 weeks. For adults, decrease the dose by 5-10 mg every 2 to 3 days. Stopping the corticosteroids abruptly may result in adrenal crisis.

### Notas

(a) Though corticosteroids are immunosuppressive, they may still be used safely in many HIV patients, depending on the immune status and concurrent infections. Never start corticosteroid treatment before anti-TB therapy.

### 9.4 Follow-up for patients treated with first-line regimens

Patients should be followed for the entire duration of treatment. Follow-up includes, in particular, assessing the treatment results, adjusting the treatment if necessary, and detecting and managing adverse effects and adherence problems.

#### 9.4.1 Clinical visits

Frequency of visits will depend on the patient’s clinical condition and evolution. On average, for an outpatient who is not having any particular problem, the recommendation is weekly visits during the first month, a visit every other week during the second month and once a month thereafter.

The patient should be weighed at each visit and the doses should be adjusted, if necessary.

The occurrence of adverse effects should be asked at each visit.
Visits should coincide with bacteriological testing, when done. In EPTB, the clinical evolution is essential to assess the treatment response. The resolution of the symptoms and weight gain are important elements for monitoring response to treatment.

9.4.2 Bacteriological examinations

For EPTB, sputum smears are only performed if the patient develops pulmonary signs.

Patients with PTB should have their sputum examined as follows:

Smears at the end of intensive phase

All PTB (smear-positive and smear-negative) should have sputum smear performed at the end of Month 2 (new patients) or end of Month 3 (retreatment patients).

If the smear is negative, start the continuation phase.

If the smear is positive:

<table>
<thead>
<tr>
<th>Xpert available</th>
<th>Evaluate for resistance to rifampicin:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xpert RIF−</td>
<td>start continuation phase with first-line anti-TB drugs for one month then repeat smear.</td>
</tr>
<tr>
<td>Xpert RIF+</td>
<td>switch to empiric MDR regimen (Chapter 10), perform culture and DST and adapt treatment accordingly.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Xpert not available</th>
<th>Initially smear-positive patients:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Start continuation phase, repeat smear one month later. In most patients, sputum will test negative a month later (patients who started out with high bacillary loads may still have dead bacilli in their sputum at the end of the intensive phase but this is less likely a month later).</td>
</tr>
<tr>
<td></td>
<td>A patient with positive smear at Month 3 (new patients) and Month 4 (retreatment patients) should have a culture and DST performed. If clinically deteriorating, consider switching to empiric MDR treatment while waiting for DST.</td>
</tr>
<tr>
<td></td>
<td>If the results show a DR-TB, adapt treatment accordingly.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Initially smear-negative patients:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspect a treatment failure; perform culture and DST. If clinically deteriorating, consider switching to empiric MDR treatment while waiting for DST.</td>
</tr>
<tr>
<td>If the results show a DR-TB, adapt treatment accordingly.</td>
</tr>
</tbody>
</table>

Smears in middle of continuation phase
If smear is negative at the end of Month 4 (new patients) or at the end of Month 5 (retreatment patients), continue treatment until the end.

A positive smear at the end of Month 4 (end of Month 5 for retreatment patients) meets the standard definition of “treatment failure”.

Be careful when defining failure on the basis of microscopy alone; a positive smear might be due to the presence of dead bacilli, especially in patients who started out with a high bacillary load.

Always try to confirm the failure:
– By rapid culture;
– By clinical evaluation of the patient (if culture is not available, clinical evaluation can be sufficient).

If the culture is negative, and clinical evolution is good: a positive smear alone at Month 4 or Month 5 may not automatically indicate treatment failure. If the patient is considered highly likely not to be a failure despite the positive smear, then continue the present treatment and monitor every two weeks with clinical visits, smears and cultures, until it is determined with certainty the patient has been cured.

Xpert MTB/RIF (or other molecular methods) should not be used to monitor therapy. However it can be useful to show that a positive smear during the follow-up has rifampicin resistance, making it likely that the current therapy is not working.

End of treatment sputum examination

The sputum smear performed at the end of Month 6 (new patients) or Month 8 (retreatment patients) helps establish the final outcome of the treatment. Outcome definitions are discussed in Chapter 17.

9.4.3 Patient information and adherence interviews

The clinician who makes the diagnosis and prescribes treatment should inform the patient about his disease and its treatment. Nevertheless, this initial interview alone is not sufficient to ensure that all the information has been given and taken in.

Interviews are recommended:
– At the start of treatment: two interviews devoted to informing the patient (one for informing him/her, the second for making sure the information has been absorbed);
– At the end of the intensive phase: an interview to explain the treatment changes that accompany the change in treatment phase;
– Throughout the treatment at all consultations: an interview to help assess and encourage adherence should be performed.

See Chapter 13 for more information on adherence and patient’s support.

When there are a large number of patients, interviews devoted to treatment adherence with specially trained personnel may be justified.

9.4.4 Follow-up schedules[1]
New patients on 6 month first-line regimen

<table>
<thead>
<tr>
<th>Month</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical visits&lt;sup&gt;(a)&lt;/sup&gt;</td>
<td>* * *</td>
<td>* *</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Bacteriological monitoring&lt;sup&gt;(b)&lt;/sup&gt;</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Adherence</td>
<td>* * *</td>
<td>* *</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

(a) If the patient’s clinical condition is not improving or deteriorating, a DST or a molecular test for resistance should be performed.

(b) Bacteriological monitoring is not needed for EPTB, except if lung involvement is suspected.

(c) Smear-positivity or culture-positivity at Month 4 or later is defined as “treatment failure” and necessitates re-registration as “previously treated patient” and a change of treatment as described in Section 9.1.2.

(d) It is not necessary to perform smear microscopy after Month 2 if patient was not bacteriologically confirmed at the start of treatment, smear was negative at Month 2, and patient is clinically improving.

Patients on retreatment 8 month first-line regimen

<table>
<thead>
<tr>
<th>Month</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical visits&lt;sup&gt;(e)&lt;/sup&gt;</td>
<td>* * *</td>
<td>* *</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Bacteriological monitoring&lt;sup&gt;(f)&lt;/sup&gt;</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Adherence</td>
<td>* * *</td>
<td>* *</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

(e) If the patient’s clinical condition is not improving or deteriorating at any time a DST or a molecular test for resistance should be performed.

(f) Bacteriological monitoring is not needed for EPTB, except if lung involvement is suspected.

(g) If a positive smear microscopy is found at Month 3, a DST or a molecular test should be performed.

(h) Smear- or culture-positivity at Month 5 or later is defined as treatment failure and necessitates reregistration and a change of treatment as described in Section 9.1.2.

Referencias

9.5 Management of adverse effects in patients on first-line regimens

9.5.1 Symptom-based approach to managing adverse effects

The drugs used to treat TB may cause adverse reactions. Managing drug reactions rapidly and aggressively is an important means to increase tolerance. Generally with minor adverse effects, drugs need not be stopped and encouragement to the patient and use of ancillary medicines is all that is necessary. With major adverse effects, the drugs often have to be stopped and modified regimen continued.

Table 9.1 - Main adverse effects and probably responsible drugs
Generally it is not necessary to monitor renal or liver function, or blood counts unless there are clinical reasons to do so (e.g. a history of liver disease).

For more information, see individual drug sheets in Appendix 10.

### 9.5.2 Cutaneous or generalized hypersensitivity

Hypersensitivity reactions usually appear early during treatment, often in the first month, but rarely during the first week. The drug the most likely to provoke these reactions is streptomycin however, other drugs can be involved. Consider also other causes of skin rash (e.g. scabies).

Hypersensitivity reactions show up in the form of itching and skin rashes. General signs, such as fever, dizziness, vomiting and headache, may occur.
Severe — even lethal — exfoliative dermatitis may occur very occasionally (Stevens-Johnson’s syndrome), particularly if administration of the drug continues after signs of hypersensitivity appear.

In the event of simple itching: symptomatic treatment (e.g. antihistaminics), without interrupting or modifying treatment.

In the event of skin rash with or without itching:
1 - Stop anti-TB drugs; give symptomatic treatment (no corticosteroids except in emergencies) and wait for disappearance of symptoms.
2 - Identify the drug that caused the reaction in order to re-start treatment as rapidly as possible. Use trial doses as in the table below. Test first the drugs least likely to have caused the reaction: start with isoniazid over 3 days then add rifampicin over 3 days, etc.

For patients on re-treatment regimen including streptomycin: if isoniazid, rifampicin, pyrazinamide and ethambutol have been all re-introduced without recurrence of rash, streptomycin should be discontinued without testing.

**Table 9.2 - Re-challenge of first-line anti-TB oral drugs and streptomycin (adapted from the WHO[1])**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Likelihood</th>
<th>Trial doses</th>
<th>From Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day 1</td>
<td>Day 2</td>
</tr>
<tr>
<td>H</td>
<td>least likely</td>
<td>50 mg</td>
<td>Full dose</td>
</tr>
<tr>
<td>R</td>
<td></td>
<td>75 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>Z</td>
<td></td>
<td>250 mg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td>100 mg</td>
<td>500 mg</td>
</tr>
<tr>
<td>S</td>
<td>most likely</td>
<td>125 mg</td>
<td>500 mg</td>
</tr>
</tbody>
</table>

*Note: if the initial reaction to treatment was severe, a weaker trial dose should be used (approximately 1/10th of the dose indicated for Day 1).*

### 9.5.3 Hepatotoxicity

All anti-TB drugs may cause hepatotoxicity. Pyrazinamide is the most hepatotoxic and isoniazid the second but to a much lesser extent. Some combinations, such as rifampicinpyrazinamide potentiate the hepatotoxic effect of each drug.

Clinical aspects resemble that of viral hepatitis: anorexia, nausea, vomiting, jaundice, etc.
If available, laboratory examination of liver injury is useful in diagnosing and following liver toxicity. Serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are elevated in liver toxicity.

AST or ALT or serum bilirubin > 3 times upper limit of normal with symptoms or > 5 times normal limit in the absence of symptoms are considered elevated. An AST or ALT or serum bilirubin < 5 times normal limit defines mild toxicity; 5 to 10 times normal limit defines moderate toxicity and > than 10 times normal limit defines severe toxicity.

When such symptoms occur or if liver enzymes are moderately or severely elevated, all anti-TB drugs should be stopped while waiting for resolution of signs. Treatment with the same drugs may, most of the time, be resumed without incident. The objective is to resume treatment either with the initial regimen or with another, and as rapidly as possible.

When the clinical status of the patient does not allow interruption of TB treatment, the least toxic drugs, streptomycin and ethambutol, can be used while waiting for clinical resolution of the hepatitis.

If symptoms reappear, it might be wise to reintroduce the drugs one by one and stopping the last drug re-introduced if symptoms recur or liver tests become abnormal. Some authors recommend starting with rifampicin (and ethambutol) and reintroduce isoniazid 3 to 7 days later. If rifampicin, ethambutol and isoniazid have been introduced and the biochemical abnormalities have not recurred, do not introduce pyrazinamide as it is most likely the causative agent.

The alternative regimen depends on the drug causing the toxic hepatitis, these regimens are similar to those recommended in case of resistance to the given drug.

- Pyrazinamide is involved: 2 S(HR)/7 (HR) or 2 (HR)E/7 (HR)
- Isoniazid is involved: 9 RZE
- Rifampicin is involved: 3 S-Lfx-HZE/12 Lfx-HZE or 3 Km-Lfx-HZE/12 Lfx-HZE
- Pyrazinamide and rifampicin are involved: 3 S-Lfx-HE/12 Lfx-HE or 3 Km-Lfx-HE/12 Lfx-HE

In the rare event of rifampicin and isoniazid are involved the treatment regimen is as an MDR regimen.

### 9.5.4 Isoniazid-associated neuropathy

Peripheral neuropathy refers to damage to the nerves located outside of the central nervous system. This usually occurs more commonly in pregnant and breastfeeding women and patients with HIV infection, alcohol dependency, malnutrition, diabetes, chronic liver disease, and renal impairment. These patients should receive preventive treatment with pyridoxine PO (5 to 10 mg/day in children; 10 mg/day in adults) along with their anti-TB drugs. Other guidelines recommend 25 mg/day but there is some evidence that this dose may overcome the antibiotic action of isoniazid. If only 25 mg tablets are available give 3 times weekly or cut in half and give daily.

If peripheral neuropathy develops, administer pyridoxine PO:
- Children less than 12 years: 20 to 40 mg/day in 2 divided doses
- Children over 12 years: 60 to 100 mg/day in 2 divided doses
- Adults: 100 to 200 mg daily
9.6 Management of treatment interruption in patients on first-line regimens

The approach depends on initial bacteriological status, the moment when the patient returns, and the length of previous treatment. The questions of whether or not a patient still presents an active form of the disease, and whether or not he has developed a resistance should always be determined. Treatment interruption can be for any reason.

Every effort should be made to re-start or complete TB treatment in patients who experience treatment interruption.

The approach is, in theory, standardised as described in Table 9.3 and Table 9.4. However, it is often complex and should be based on rigorous study of the patient’s history, meticulous clinical examination, and bacteriological examination results. A chest X-ray might be useful, especially if previous ones are available for comparison.

A patient who interrupted his treatment is more at risk of interrupting again. The patient should be followed even more closely and re-motivated with the greatest attention: retreatment regimen may be the last chance of cure, and adapted strategies should be considered to support patient’s adherence (Chapter 13).

9.6.1 New patients on first-line regimens

Table 9.3 - Management of new patients who interrupted treatment
<table>
<thead>
<tr>
<th>Length of treatment</th>
<th>Length of interruption</th>
<th>Sputum result at return</th>
<th>Treatment outcome</th>
<th>Classification at return</th>
<th>Treatment action and registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 month</td>
<td>&lt; 2 weeks</td>
<td>Not needed</td>
<td>–</td>
<td>–</td>
<td>Continue treatment at the point it was stopped.</td>
</tr>
<tr>
<td></td>
<td>2-7 weeks</td>
<td>Not needed</td>
<td>–</td>
<td>–</td>
<td>Re-start treatment.</td>
</tr>
<tr>
<td></td>
<td>≥ 8 weeks</td>
<td>Smear+ Smear−</td>
<td>Interruption</td>
<td>New</td>
<td>Re-start treatment, perform DST (^{(a)}).</td>
</tr>
<tr>
<td>1-2 months</td>
<td>&lt; 2 weeks</td>
<td>Not needed</td>
<td>–</td>
<td>–</td>
<td>Continue treatment at the point it was stopped.</td>
</tr>
<tr>
<td></td>
<td>2-7 weeks</td>
<td>Smear+</td>
<td>–</td>
<td>–</td>
<td>Re-start treatment, perform DST (^{(a)}).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Smear−</td>
<td>–</td>
<td>–</td>
<td>Continue treatment at the point it was stopped.</td>
</tr>
<tr>
<td></td>
<td>≥ 8 weeks</td>
<td>Smear+ Smear−</td>
<td>Interruption</td>
<td>TAI (^{(b)}) TAI (^{(b)})</td>
<td>Start retreatment, perform DST (^{(a)}) and give a new number to the patient.</td>
</tr>
<tr>
<td>≥ 2 months</td>
<td>&lt; 2 weeks</td>
<td>Not needed</td>
<td>–</td>
<td>–</td>
<td>Continue treatment at the point it was stopped.</td>
</tr>
<tr>
<td></td>
<td>2-7 weeks</td>
<td>Smear+</td>
<td>Cancel previous registration Others</td>
<td>Start retreatment, perform DST (^{(a)}), register as “Others”.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Smear−</td>
<td>–</td>
<td>–</td>
<td>Continue treatment at the point it was stopped.</td>
</tr>
<tr>
<td></td>
<td>≥ 8 weeks(^{(e)})</td>
<td>Smear+ Smear−</td>
<td>Interruption</td>
<td>TAI (^{(b)}) TAI (^{(b)})</td>
<td>Start retreatment, perform DST (^{(a)}) and give the patient a new number.</td>
</tr>
</tbody>
</table>
9.6.2 Retreatment patients on first-line regimens

Table 9.4 - Management of retreatment patients who interrupted treatment

<table>
<thead>
<tr>
<th>Length of treatment</th>
<th>Length of interruption</th>
<th>Sputum result at return</th>
<th>Treatment outcome</th>
<th>Classification at return</th>
<th>Treatment action and registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 month</td>
<td>&lt; 2 weeks</td>
<td>Not needed</td>
<td>–</td>
<td>–</td>
<td>Continue retreatment at the point it was stopped.</td>
</tr>
<tr>
<td></td>
<td>2-7 weeks</td>
<td>Not needed</td>
<td>–</td>
<td>–</td>
<td>Re-start retreatment.</td>
</tr>
<tr>
<td></td>
<td>≥ 8 weeks</td>
<td>Smear+ Smear–</td>
<td>Interruption</td>
<td>Same as previous registration</td>
<td>Re-start retreatment and give the patient a new number.</td>
</tr>
<tr>
<td>&gt; 1 month</td>
<td>&lt; 2 weeks</td>
<td>Not needed</td>
<td>–</td>
<td>–</td>
<td>Continue retreatment at the point it was stopped.</td>
</tr>
<tr>
<td></td>
<td>2-7 weeks</td>
<td>Smear+</td>
<td>–</td>
<td>–</td>
<td>Re-start retreatment, ask for DST (d).</td>
</tr>
<tr>
<td></td>
<td>≥ 8 weeks</td>
<td>Smear–</td>
<td>–</td>
<td>–</td>
<td>Continue retreatment at the point it was stopped, ask for DST (d).</td>
</tr>
<tr>
<td></td>
<td>Smear+ Smear–</td>
<td>Interruption</td>
<td>TAI (e)</td>
<td>TAI (f)</td>
<td>Re-start retreatment, give a new number to the patient, ask for DST (d).</td>
</tr>
</tbody>
</table>

(d) Xpert MTB/RIF and conventional DST if available.
(e) TAI = Treatment after interruption.
Chapter 10: Treatment of multidrug-resistant TB (MDR-TB)

10.1 Design of therapeutic regimens in MDR-TB

10.2 Selection of anti-TB drugs in MDR-TB regimens

10.3 Building a treatment regimen for MDR-TB

10.4 Duration of MDR-TB regimens

10.5 Follow-up for patients treated for MDR-TB

10.6 Management of adverse effects in patients on second-line regimens

10.7 Surgery as an adjunctive treatment measure

10.8 Management of patients whose treatment failed and palliative care

10.9 Special situations

10.10 Treatment of extensively drug-resistant TB (XDR-TB)

10.1 Design of therapeutic regimens in MDR-TB

The following are the basic principles involved in MDR-TB regimen design[1] :

- The intensive phase includes at least four core Group 2 to 4 anti-TB drugs likely to be effective, including an injectable agent – plus pyrazinamide (Z).

- In the case of unclear evidence about the effectiveness of a certain drug, it can be part of the regimen but it should not be counted as one of the four core second-line anti-TB drugs.

- An anti-TB drug is considered “likely to be effective” when:
1 - The drug has not been used in a regimen that failed for the individual patient;
2 - Drug susceptibility testing (DST) performed on the patient’s strain indicates that the strain is susceptible. Only DST for isoniazid, rifampicin, Group 2 and 3 drugs is considered reliable;
3 - No known resistance to drugs with high cross-resistance;
4 - No known close contacts with a patient infected with a strain resistant to the drug;
5 - In the absence of DST or for drugs in which individual DST is not reliable, a drug resistance survey demonstrates that resistance to the drug is rare in patients with similar TB history.

- It is not always possible that all five criteria can be ascertained and clinical judgment is often necessary on whether to count a drug as “likely effective”.

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

- The most effective regimens for MDR-TB include at least a fluoroquinolone (preferably a third-generation), an injectable agent, ethionamide (or prothionamide), either cycloserine or para-aminosalicylic acid, and pyrazinamide.

- There are conditions when more than five drugs may be started, as is the case if the susceptibility pattern is unknown or the effectiveness is questionable for a drug(s).

- A drug should not be used when patient is known to have a major contraindication of usage (e.g. known major drug-drug interactions, history of allergic reaction, pregnancy).

- Each dose is given under directly observed therapy (DOT) throughout the treatment. A treatment card is marked for each observed dose. DOT can be performed either facility-based or home-based (often referred to as community-based). See Chapter 13.

- Treatment is given six or seven days a week. Six days a week is chosen for those patients managed in outpatient settings where DOT cannot be done everyday.

Referencias

10.2 Selection of anti-TB drugs in MDR-TB regimens

See reference[1]

**Group 1 (Oral first-line agents)**

Pyrazinamide is routinely added to MDR regimens if susceptibility (by DST) is documented or if DST is unknown. If well tolerated it is used for the entire treatment, although patients doing well and with minimal lung disease can have it stopped with the injectable agent and continue with at least three likely effective drugs.

Ethambutol is not routinely added to MDR regimens, however it can be added if the criteria of it being a likely effective drug are met.

For patients with strains resistant to low concentrations of isoniazid, but susceptible to higher concentrations, the use of high-dose isoniazid may have some benefit (see Group 5).

The newer rifamycins, such as rifabutin have very high cross-resistance to rifampicin and are not used in MDR regimens.

**Group 2 (Injectable agents)**

All patients should receive a Group 2 injectable agent if susceptibility is documented or the drug is considered likely to be effective.

Kanamycin or amikacin are the first choice injectable agent. Both are low cost, and have been used extensively for the treatment of MDR-TB. They are considered to be very similar and have a high frequency of cross-resistance.

Given the high rates of resistance to streptomycin in patients with MDR-TB, streptomycin is not used in MDR-TB treatment regimens.

If the strain is susceptible to capreomycin or if resistance is rare in the patient population and if aminoglycosides are contra-indicated or poorly tolerated or ineffective on the patient’s strain, capreomycin should be used. Capreomycin should also be used while waiting for the DST results in places where resistance to kanamycin and amikacin is common.

**Group 3 (Fluoroquinolones)**
The most potent available fluoroquinolones in descending order based on \textit{in vitro} activity and animal studies are: moxifloxacin > levofloxacin > ofloxacin\cite{2}\cite{3}.

This guide recommends not using ofloxacin (second-generation fluoroquinolone) as it has inferior performance against TB compared to the other Group 3 fluoroquinolones. In addition, resistance may develop more easily to the fluoroquinolone group when ofloxacin is used in a multidrug regimen. Ciprofloxacin (second-generation fluoroquinolone) is not included in Group 3 and should never be used to treat drug-susceptible or DR-TB because of its low efficacy against TB bacilli\cite{4}.

Third-generation fluoroquinolones (moxifloxacin and levofloxacin) may have some efficacy against ofloxacin-resistant strains\cite{5}.

Mostly based on cost and availability, levofloxacin is often the fluoroquinolone used in most MDR-TB regimens, whereas moxifloxacin is reserved for cases of high resistance (resistance to ofloxacin, injectable agents, or other second-line anti-TB drugs).

In case of resistance to fluoroquinolones, the use of bedaquiline should be considered (see below).

\textbf{Group 4 (Oral bacteriostatic second-line anti-TB drugs)}

Ethionamide and prothionamide are considered the most potent Group 4 drugs\cite{6}. However it should be noted that these drugs do have some cross-resistance with isoniazid. Ethionamide and prothionamide can be included in the regimen if \textit{inhA} gene is detected but should not be counted as a likely effective drug.

Cycloserine and/or para-aminosalicylic acid should be included in MDR-TB regimens. Both share no cross-resistance to other anti-TB drugs. Since the combination of ethionamide or prothionamide and para-aminosalicylic acid often causes a high incidence of gastrointestinal disturbances and hypothyroidism, these agents are usually used together only when three Group 4 agents are needed.

The drugs in Group 4 may be started at a low dose and escalated over 1 to 2 weeks to improve tolerance.

\textbf{Group 5 (Drugs with limited data on efficacy and/or long-term safety)}

Group 5 drugs are recommended in cases where adequate regimens are impossible to design with the drugs from Groups 1 to 4.

Compared to other drugs in this group bedaquiline is the only one with proven efficacy against TB. While there is no clear evidence for the hierarchy of use of Group 5 drugs, these guidelines propose that the three most attractive agents from this group in order of preference are: bedaquiline, linezolid, clofazimine.
**Bedaquiline[^7][^8][^9]**: Bedaquiline is a diarylquinoline with bactericidal anti-mycobacterial activity. This new drug was registered by the US FDA in December 2012[^b] for MDR-TB patients with no other therapeutic options. It is recommended in case of resistance to fluoroquinolones or when it is not possible to have four effective anti-TB drugs from Group 2 to 4 in the regimen. The dosage in adult is 400 mg once daily for 2 weeks followed by 200 mg 3 times per week for 22 weeks. The drug is not yet recommended for children or pregnant women. The main adverse effects are nausea, arthralgia, headache and QT prolongation. QT prolongation can result in cardiac arrhythmia and sudden death. Baseline and regular electrocardiogram (ECG) monitoring should be performed. QT prolongation is more pronounced when combined with clofazimine. Combination with other QT prolonging drugs (moxifloxacin, ondansetron, etc.) should be avoided or closely monitored. Bedaquiline must not be combined with rifamycins and some antiretrovirals (see Chapter 12). Bedaquiline is not registered in most high burden countries and only available through compassionate use (see also Appendix 11).

For situations that require the use of Group 5 drugs other than bedaquiline (or when bedaquiline is not available), use at least two other drugs from Group 5 given the limited knowledge of their efficacy.

**Linezolid**: Linezolid has good activity *in vitro* and in animal studies. There are also a number of reports and case series in MDR-TB and XDR-TB[^10][^11][^12][^13][^14][^15][^16][^17] and a recent study showing efficacy in XDR-TB[^18]. It has numerous severe adverse effects including myelo-supression and irreversible peripheral neuropathy. It is presently very expensive.

**Clofazimine**: There is a moderate amount of experience with clofazimine in MDR-TB treatment but no clear *in vivo* data on efficacy against TB. It is usually added to regimens for XDR-TB.

**Amoxicillin/clavulanic acid**: Generally the B-lactam antibiotics are not regarded as very useful drugs in TB. However, the addition of the B-lactamase inhibitor makes them active *in vitro* against TB. There is one *in vivo* study that showed good early bactericidal activity. While amoxicillin/clavulanic acid is probably a relatively weak anti-TB drug, it is often included because it is available, inexpensive and causes only minor adverse effects.

**High-dose isoniazid**: High-dose isoniazid (16-20 mg/kg/day) can be used as a Group 5 drug in the presence of resistance to low concentrations of isoniazid[^19] (> 1% of bacilli resistant to 0.2 mcg/ml but susceptible to 1 mcg/ml of isoniazid). Isoniazid is not recommended for high-dose resistance (>1% of bacilli resistant to 1 mcg/ml of isoniazid)[^20] or in presence of katG gene mutation (see LPA, Chapter 3, Section 3.4.2).

**Notes:**
- **Gatifloxacin** (Group 3): Although gatifloxacin is similar to moxifloxacin in efficacy against TB, it is associated with serious hypo/hyperglycaemia, and new onset diabetes. Thus, its use is not recommended.
- **Terizidone** (Group 4): It is unknown whether this drug is equally efficacious as cycloserine, therefore these guidelines recommends the use of cycloserine over terizidone.
- **Imipenem/cilastatin and meropenem** (Group 5): These beta-lactam/carbapenems are only given intravenously. Given the cost and difficulty of the twice-daily intravenous administration, it is not
commonly used in resource-constrained settings. Meropenem is preferred in children as there is more experience with its use. Meropenem can be combined with oral doses of clavulanate. These drugs are commonly used for a duration of two months past conversion.

- **Clarithromycin** (Group 5): This drug is included in various TB manuals yet evidence to support its efficacy in MDR-TB is minimal. It may have a synergistic effect on first-line anti-TB drugs with enhanced intracellular effectiveness against the TB bacilli. However, until more information on effectiveness in TB and MDR-TB, its use is not recommended.

- **Thioacetazone** (Group 5): While thioacetazone is known to be active against TB bacilli, it is placed in Group 5 because its role in DR-TB treatment is not well established. Thioacetazone has cross-resistance with some of the other anti-TB agents (Chapter 8, Section 8.5) and overall is a weakly bacteriostatic drug. It is contraindicated in HIV-infected individuals due to a risk of serious adverse reactions (Stevens-Johnson syndrome and death). Persons of Asian descent also have a higher incidence of Stevens-Johnson syndrome. For these reasons, thioacetazone is rarely added as a Group 5 drug. Until there is more information in its role in MDR-TB therapy, its use is not recommended.

**Notas**

(a) Bedaquiline is relatively well tolerated. Data and experience on its use is very limited. In a blinded randomized placebo-control study there were an increase number of deaths in the study arm that received bedaquiline. While none of the deaths were considered directly related to the drug, the possibility that the use of the drug carries an increase risk of death cannot be ruled out. The risks and benefits of receiving this drug should be fully explained to the patient.

(b) [http://www.accessdata.fda.gov/drugsatfdadocs/label/2012/204384s000lbl.pdf](http://www.accessdata.fda.gov/drugsatfdadocs/label/2012/204384s000lbl.pdf)

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10.3 Building a treatment regimen for MDR-TB

Adapted from Drug-resistant tuberculosis: a survival guide for clinicians. San Francisco, Francis J. Curry National Tuberculosis Center and California Department of Health Services, 2004.

Individual regimens are designed based on DST of the infecting strain, history of TB treatment, and contact history. Figure 10.1 describes the steps to build a regimen for MDR-TB treatment.

Figure 10.1 - Building a regimen for MDR-TB
Box 10.1 - Examples of how to initiate and design MDR-TB regimens
Example 1 - patient doing poorly on first-line treatment

A patient receiving first-line treatment for new patients (2 HRZE/4 HR) continues to be smear positive at Month 3 with symptoms including weight loss, fever, shortness of breath and cough. The patient feels the shortness of breath is getting severe and he spends more than 50% of the day in bed. No DST was performed at the start of treatment. Xpert MTB/RIF performed at Month 3 shows MTB+ and rifampicin resistance. What should be done?

Answer: A positive Xpert MTB/RIF at Month 3 in a patient doing poorly on a first-line regimen that shows R resistance is highly likely to be a true positive. This patient should be placed on MDR-TB therapy. A confirmatory DST with conventional methods to at least H and R and if possible to injectable agents and fluoroquinolones should be performed.

If a rapid molecular test was not available, this patient should be placed on an MDR-TB regimen while waiting conventional DST results.

- If there is low second-line drug resistance in patient’s strains with MDR-TB in the area then a common regimen is: Km-Lfx-Eto (or Pto)-Cs-ZE.
- If there is moderate to high second-line drug resistance in MDR-TB strains in the area or if the level of resistance to second-line drugs is not known: Cm-Mfx-Eto (or Pto)-Cs-PASZE. Once DST becomes available the regimen can be adjusted. In this case, the infecting strain was determined to be resistant to H-R-S and susceptible to Km-Cm-Ofx-E; resistance to Z was unknown. Given the DST results, it is recommended to continue with Km-Lfx-Eto (or Pto)-Cs-ZE and drop the PAS if it was used in the initial regimen.

Example 2 - Xpert RIF positive in a patient with low probability of MDR-TB

A HIV-negative smear-negative TB suspect is referred to Xpert MTB/RIF to establish the diagnosis of TB. The result of the Xpert is MTB+ and rifampicin resistance. The patient has never been diagnosed with TB. The MDR-TB prevalence for new patients in the area is 1%. The patient only complains of a mild cough for 3 weeks and X-ray shows minimal lesions. What should be done?

Answer: The RIF resistance positive predictive value (PPV) for the Xpert MTB/RIF in the setting of 1% rifampicin resistance prevalence is 32% (Appendix 3). Because of the relatively low PPV of the Xpert MTB/RIF under these circumstances and the fact that patient is HIV-negative and not seriously ill, he can be placed on a first-line drug regimen while waiting confirmation DST. If possible, DST confirmation should be done through a rapid phenotypic method or using LPA on culture (indirect method). If the patient deteriorates clinically at any time while waiting confirmation DST, an empirical MDR-TB regimen should be started. When the DST returns, the regimen should be adjusted if the resistance to rifampicin is confirmed.
An alternative shorter 9 month standard regimen (4 Km-Gfx-Pto-Cfz-high dose H-ZE/5 Gfx- Cfz-ZE) has shown good effectiveness in a study in Bangladesh\textsuperscript{[1]}. Adaptations are made in some countries in Western Africa\textsuperscript{[2]} with moxifloxacin replacing gatifloxacin and extension of the regimen to 12 months. At present, this regimen is still considered experimental\textsuperscript{[3]}.

Given the limited evidence supporting this regimen these guidelines recommend the following:

- Obtain country-level and institutional ethical approval before implementation.
- Implement it under operational research conditions following good practices.
- Consider this regimen on a case-by-case basis for programmes with proper follow-up and outcome documentation in unstable settings where a 2 year-treatment is not an option.
- Perform DST to the fluoroquinolones in a liquid medium and do not use in any patient with documented fluoroquinolone resistance (the third-generation fluoroquinolones are the backbone of the regimen and the regimen does not perform well against strains resistant to fluoroquinolones).
- Use only in HIV-negative patients until more information is published on the regimen and its use in HIV-positive patients.
- Do not use in areas with a high prevalence of resistance to second-line anti-TB drugs until more information is published.

\textbf{Referencias}


\textbf{Notas}


\textbf{10.4 Duration of MDR-TB regimens}
10.4.1 Intensive phase

Duration of intensive phase is guided by culture. The injectable agent should be continued for at least 8 months\textsuperscript{[1]} and at least 4 months after the patient becomes culture negative – which ever is longer. The use of an individualized approach which reviews the cultures, smears, X-rays and the patient’s clinical status may also aid in deciding whether or not to continue an injectable agent longer than the above recommendation, particularly in the case of patients for whom the susceptibility pattern is unknown, effectiveness is questionable for an agent(s) or extensive or bilateral pulmonary disease is present.

A change to intermittent therapy with the injectable agent (3 times weekly) is done when signs of toxicity are noticed. Three times a week therapy is recommended in patients after 6 months of an injectable agent and who have had culture conversion, as toxicity becomes a greater risk to patients with longer periods of the injectable agent.

10.4.2 Length of treatment

The duration of treatment is guided by culture. It is recommended continuing therapy for a minimum of 20 months\textsuperscript{[1]} and at least 18 months after the patient becomes culture negative.

Extension of therapy to 24 months may be indicated in chronic cases with extensive pulmonary damage.

Referencias


10.5 Follow-up for patients treated for MDR-TB

Table 10.1 - Routine patient monitoring
### Evaluation

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Frequency</th>
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| **Assessment by a clinician**     | *During intensive phase:* every day during the first weeks if hospitalized and at least every week if treated as outpatient, until the treatment is well tolerated. Once stable, the patient is seen once or twice monthly.  
**During continuation phase:** monthly assessment unless there is a medical necessity to see the patient more often.  
The DOT supporter sees the patient daily and signals any concerns to the clinician. |
| Treatment adherence and tolerance | Daily at every DOT encounters by the DOT supporter.                                                                                                                                               |
| Sputum smear and cultures         | Monthly until the end of treatment.  
*Note:* programmes with very limited culture capacity may consider doing smears monthly but cultures every other month for the continuation phase. |
| Weight                            | At baseline and then monthly.                                                                                                                                                                      |
| DST                               | At baseline and for any positive culture during treatment.                                                                                                                                       |
| Chest X-rays                      | At baseline and then every three to six months.                                                                                                                                                   |
| Serum creatinine                  | At baseline, then twice a month for the first two months, then monthly while receiving an injectable agent. Every one to three weeks in HIV-infected patients, diabetics throughout the course of the injectable agent. |
| Serum potassium (K+)              | Every six months if receiving Eto/Pto and/or PAS (every three months in HIV positive patients) and whenever signs/symptoms of hypothyroidism are present.  
TSH is sufficient for screening for hypothyroidism and it is not necessary to measure hormone thyroid levels. |
| Thyroid stimulating hormone (TSH) | At baseline then monthly during the intensive phase. Every 3 months thereafter.  
Monthly monitoring for HIV-infected.  
In patients with viral hepatitis: once weekly for the first month, then every one to four weeks.  
Monthly for patients taking Bdq. |
| Liver serum enzymes               | Monthly for patients taking Bdq.                                                                                                                                                                 |
| Bilirubine                        | Monthly for patients taking Bdq.                                                                                                                                                                  |
10.6 Management of adverse effects in patients on second-line regimens

Treating rapidly and aggressively adverse reactions is an important means to increase tolerance and is critical to improve outcomes.

All patients should be informed that they are likely to experience adverse effects. Adverse effects appear most commonly at the start of therapy, especially during the first few weeks of treatment where the patient can feel quite lousy – with nausea and vomiting being the most common adverse effect. Patients should be informed that many of the common minor adverse effects will improve with time and medical treatment.
Patients are monitored for general toxicities and drug-specific toxicity at every DOT encounter. They should be educated that if serious adverse effects appear (e.g. hearing loss, dizziness, ringing in the ears, jaundice, edema, decreased urine output, skin rash or burning in the legs), they must inform the health care worker immediately.

It is often difficult to ascertain whether a given adverse effect is due to a single drug or is the result of several drugs given simultaneously. If after management of adverse effects the patient remains intolerably symptomatic, a dose reduction or elimination of one of the drugs may be necessary. Permanent dose reduction or definitive elimination of a drug should be considered only after all other possibilities have been exhausted i.e., in cases of significant organ dysfunction or intractable intolerance. Ideally, any drug eliminated from a treatment regimen should be replaced with an equally effective drug, as to not compromise the overall effectiveness of the regimen.

Dose reduction can be done in a systematic manner by starting with the most likely offending drug for one week to see whether the symptoms diminish or disappear. If symptoms persist, the drug is returned to its original dose and the same process repeated for the other drugs, until all potentially responsible drugs have been tested. Systematic dose reduction of multiple drugs simultaneously would be the next option.

Whenever reducing or holding a drug to determine the cause of an adverse effect, tell the patient that this is a test to determine which drug is involved and that the drug dose will be increased back to therapeutic dose in a manner that will be better tolerated. Returning back to therapeutic doses gradually (over one to two weeks) while implementing strategies to decrease a specific adverse effect can often allow the patient to better tolerate it.

Treatment supporters and nurses working with TB programmes should report an adverse event to the physician at the earliest appropriate time. Only the managing physician should do dose changes or eliminate a specific anti-TB drug.

Often, if an adverse effect cannot be completely eliminated, patients may be asked to tolerate symptoms until they subside. Often reassurance and emotional support can result in the avoidance of adding yet another medication to the high burden of medications the patient is already receiving.

For specific management of common adverse effects, see Appendix 17.

Ancillary medicines (anti-emetics, potassium replacement, thyroid hormone, medicines for psychiatric conditions, etc.) should be provided free of charge to the patient.

10.7 Surgery as an adjunctive treatment measure
Surgery can be considered only in optimal surgical facilities with trained thoracic surgeons. Specialized surgical facilities should include stringent infection control measures since infectious substances and aerosols are generated in large quantities during surgery, during mechanical ventilation and post-operative pulmonary hygiene manoeuvres.

General indications for surgery for programmes with limited access to surgery include patients with resistance to a large number of drugs and localized pulmonary disease. Computerized tomography, pulmonary function testing, and quantitative lung perfusion/ventilation are recommended as part of the preoperative work-up.

The most common operative procedure in patients with MDR-TB is resection of part or all of a lung. Large case series analysis suggest surgical resection can be effective and safe under appropriate surgical conditions\(^1\)[\(^2\)\]. It is considered an adjunct to chemotherapy and appears to be beneficial for patients when skilled thoracic surgeons and excellent postoperative care are available\(^3\). It is not indicated in patients with extensive bilateral disease.

Resection surgery should be timed so as to offer the patient the best possible chances of cure with the least morbidity. Thus, the timing of surgery may be earlier in the course of the disease when the patient’s risk of morbidity and mortality are lower, for example, when the disease is still localized to one lung or one lobe. Furthermore, bacilli excretion during treatment has a “window” when the bacilli load decreases under pressure of anti-TB drugs and it can be registered by decreasing or even disappearing of mycobacteria in smear and/or culture. This “window” is the best time for surgery. It is critical to operate before the mycobacterial count begins to rise. The best time for surgery is usually considered to be between two and six months after initiation of treatment\(^3\)[\(^4\)[\(^5\)]. Surgery should not be considered a last resort.

Even with successful resection, an additional 12 to 24 months of chemotherapy should be given.

**Referencias**


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10.8 Management of patients whose treatment failed and palliative care

When it has been determined a patient is failing therapy for DR-TB, the first priority is to design a new regimen using the principles described in Sections 10.1 to Section 10.3. The new regimen should contain at least two new effective drugs.

The employment of newly developed TB drugs available for compassionate use (Appendix 11) is encouraged. For some of these drugs (delamanid), approval is expect in 2013.

When no therapeutic option or new regimen is possible, the patient can be continued on an anti-TB regimen that is reasonably tolerated (and if the patient desires) or the regimen can be completely stopped. The decision to stop therapy should be made after careful evaluation and consultation with the patient, the family and the MDR-TB treatment team.

Palliative/supportive care should be continued. Supportive measures for minimizing suffering due to the disease or the therapy should be implemented according to the patient needs. Supportive measures may include:

- Relief of respiratory symptoms: oxygen should be used to alleviate shortness of breath; corticosteroids (prednisolone) are beneficial in severe respiratory insufficiency; codeine helps control cough.
- Identification, assessment and treatment of pain: according to the standard recommendations (non opioids/mild opioids/strong opioids adapted to the level of pain).
- All necessary ancillary medications needed should be used.
- Patients with poor nutritional status should receive nutritional support.
- In debilitated patients, important measures for making patients comfortable and preventing complications must be taken. Regular scheduled movement of the bedridden patients prevents bedsores. Bathing and oral care assistance keeps patients clean and comfortable, while preventing skin infections.
- Disorders such as anxiety or depression due to prolonged sickness, separation from family, difficult living conditions, etc. should be addressed when present. The patient as well as the family may need support.
- Potential social problems should also be addressed. When necessary, hospice-like care should be offered to families who want to keep the patient at home. Inpatient end-of-life care should be available to those for whom home care is not available.
Note: the above palliative/supportive measures should be implemented to all DR-TB patients if indicated whether or not they are failing treatment. Some measures may even need to be continued after a patient’s TB has cured, but the patient still remains with significant respiratory damage.

10.9 Special situations

10.9.1 Pregnant women

Pregnant women should be carefully evaluated, such that the risks and benefits of treatment considered according to gestational age and severity of disease.

- The primary goal is culture conversion to protect the health of the mother and child, both before and after birth.
- If the patient is very stable with minimum disease, treatment may be delayed and started in the second trimester with 3 or 4 drugs known to be safe in pregnancy and active on the infecting strain. In most cases of moderate to severe disease the treatment should be started right away with the risks and benefits explained to the mother.
- Aminoglycosides are contraindicated. If an injectable agent is required, capreomycin is the only option as there are case reports of safe use in pregnancy.
- Ethionamide and prothiomanide should be avoided due to data suggesting teratogenicity in animals.
- Fluoroquinololones are considered acceptable to use despite limited data.
- Moxifloxacin, para-aminosalicylic acid, cycloserine and amoxicillin/clavulanic acid is an appropriate initial regimen with a consideration of capreomycin in cases of advanced disease (extensive parenchymal damage or life-threatening condition).
- If some drugs were withheld because of the pregnancy, they can be added back postpartum if needed to make a more complete regimen.

The child should receive BCG at birth.

10.9.2 Breastfeeding women

Most anti-TB drugs will be found in the breast milk in concentrations that would equal only a small fraction of the therapeutic dose used in an infant. Effects on infants of such exposure during the full course of DR-TB treatment have not been established. Therefore, when resources and training are available, it is recommended to provide infant formula as an alternative to breastfeeding. If infant formula is used, the infant formula, clean water, fuel for boiling water and the apparatus (stove, heating pans and bottles) must be provided to the mother, as well as training on how to prepare and use the infant formula. If infant formula cannot be provided regularly and used safely, the child should be breastfed and the risks/benefits explained to the mother.

Treatment administered timely and properly is the best way to prevent transmission of tubercle bacilli to the breastfed infant.
If a mother is smear-positive and there is a possibility the mother is failing treatment, the care of the infant should be entrusted to family members until she becomes smear-negative, if feasible. Otherwise, nursing mothers with DR-TB should not be separated from their infants.

10.9.3 Women of child-bearing age

A pregnancy test should be performed before starting anti-TB therapy (to be repeated if indicated). Women of child-bearing age should be provided contraception in addition to MDR-TB treatment. Patients should be advised to take their oral contraceptives at times well away from when they may experience vomiting caused by the anti-TB drugs. Patients who vomit within the first two hours of taking the contraceptive tablet should use a barrier method of contraception for the duration of symptoms and for seven days after recovery.

Note: for patients with mono- and poly-drug resistant TB susceptible to rifampicin (Chapter 11), rifampicin interacts with hormonal contraceptives and decreases their efficacy. Patients may choose between these options, throughout the course of anti-TB treatment: medroxyprogesterone IM or barrier methods (diaphragm, condom, UID) or, as a last resort, oral contraceptive containing a high dose of estrogen (50 micrograms/tablet).

10.9.4 Children

Children with DR-TB generally have primary resistance transmitted from an adult contact with DR-TB. Culture and DST, if available, should be used to guide therapy. In other cases, the child should be treated empirically, guided by the DST pattern of the index case. However, every effort should be made to obtain a sample from the child for culture and DST.

Given the severity of DR-TB, there are no drugs that are absolutely contraindicated in children.

Children generally tolerate well second-line anti-TB drugs.

The administration of second-line drugs can be problematic due to the lack of commercially available paediatric formulations.

10.9.5 Extrapulmonary drug-resistant TB

Regimen construction and duration for extrapulmonary DR-TB is the same as for pulmonary DR-TB. If a patient with DR-TB has symptoms suggestive of central nervous system involvement, the regimen should include drugs with good cerebrospinal fluid (CSF) penetration:\[1\] [2]:

- Ethionamide or prothionamide and cycloserine have good penetration into the CSF.
- Kanamycin, amikacin, and capreomycin do so only in the presence of meningeal inflammation.
- Para-aminosalicylic acid and ethambutol have little or no penetration.
- Fluoroquinolones have variable CSF penetration, with better penetration seen in the higher generations.
10.9.6 Renal insufficiency

Renal insufficiency may be due an injectable anti-TB drug or other aetiologies including longstanding TB infection.

In patients with renal insufficiency, the creatinine clearance should be calculated. If less < 30 ml/min, anti-TB drugs should be adjusted. The formula to estimate the creatinine clearance, and the dose of anti-TB drugs in renal insufficiency are presented in Appendix 12.

Referencias


10.10 Treatment of extensively drug-resistant TB (XDR-TB)

XDR-TB is much more difficult to treat than other MDR-TB and extremely difficult to treat in HIV-infected patients\(^1\)\(^2\) \textsuperscript{[1][2]} . While reports of HIV-infected patients being promptly diagnosed with XDR-TB and placed on adequate regimen are non-existent to date, a few reports of cohorts of HIV-negative patients have been shown to have cure rates that exceed 50\%\(^1\)\(^3\) \textsuperscript{[1][3]} .

There is very limited data on different clinical approaches to XDR-TB. Management of a patient with documented, or almost certain, XDR-TB should be as follows\(^4\)\(^5\) :  

1 - Consider a longer duration of use for the injectable agent (12 months or possibly the whole treatment). If the patient’s strain is resistant to all injectable agents, use one the patient has never used before\(^6\) .

2 - Use a third-generation fluoroquinolone such as moxifloxacin. The potential benefit of moxifloxacin should be weighed against the increased risk of QT prolongation when combined with bedaquiline.

3 - Use all Group 4 agents that have not been used extensively in a previous regimen or any that are likely to be effective.
4 - Use two or more agents from Group 5. Add bedaquiline. Consider high-dose H if low-level resistance is documented or no katG mutation is detected.

5 - Use any likely effective Group 1 drugs.

6 - Consider adjuvant surgery if there is localized disease.

7 - Consider compassionate use of new agents (Appendix 11).

Extension of therapy to 24 months is the suggested minimum length of treatment for XDR-TB.

**Box 10.2 - A case of XDR-TB and example regimen**

**Example:**

A patient is receiving Km-Ofx-Eto-Cs-Z and remains smear-positive and culture-positive after 8 months of treatment. In addition the patient is not improving clinically. The DST performed on a sputum collected 2 months ago reveals resistance to H, R, Z, E, S, Km, Cm and Ofx. This patient has XDR-TB.

The regimen should be designed based on the principles described in Section 10.1. Bdq should be considered. A higher generation FQ may have some effect.

The recommended regimen to be considered in this patient would be:

Lfx-Cs-PAS-Bdq-Lzd-plus two Group 5 drugs (Cfz-Amx/Clv).

- Lfx causes less QT prolongation than Mfx.
- Cfz has an additive effect to the QT prolongation when used with Bdq.
- ECG monitoring is required.
- The risk of sudden death versus the benefits of Bdq should be fully explained to the patient.
- Consider also compassionate use of new anti-TB agents under development.

**Notas**

(a) While the reproducibility and reliability of DST to injectables is good, there is little data on clinical relevance of the test. Options with XDR-TB are very limited and some strains may be affected in vivo by an injectable agent even though they are testing resistant in vitro.

**Referencias**


11.1 Treatment schemes

11.1.1 Choice of the treatment scheme

Mono- and poly-drug resistant tuberculosis (PDR-TB) management is based on the PDR treatment schemes presented in Table 11.1.

Table 11.1 - Resistance pattern and recommended treatment schemes
Sus. = susceptible; Res. = resistant.
The treatment schemes of mono/PDR-TB are based on the assumption that a full baseline drug susceptibility testing (DST) is performed before or at the start of treatment with first line anti-TB drugs.

There is little published evidence to determine the best treatment for mono/PDR-TB. The treatment schemes are therefore based on the principles of TB treatment and expert opinion.[1][2][3]

At least 3, ideally 4, likely effective drugs are included in the regimen. DST results at baseline and previous treatment history are used to choose the appropriate scheme.

The use of Xpert MTB/RIF can greatly aid in getting patients on the proper regimens when isoniazid resistance is present and amplification of resistance to rifampicin is a possibility.

<table>
<thead>
<tr>
<th>Resistance category</th>
<th>H</th>
<th>R</th>
<th>E</th>
<th>S</th>
<th>Treatment scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-resistance</td>
<td>Res.</td>
<td>Sus.</td>
<td>Sus.</td>
<td>Sus.</td>
<td>PDR Scheme A&lt;sup&gt;(a)&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Res.</td>
<td>Sus.</td>
<td>Sus.</td>
<td>Res.</td>
<td>PDR Scheme A&lt;sup&gt;(a)&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Res.</td>
<td>Sus.</td>
<td>Res.</td>
<td>Sus.</td>
<td>PDR Scheme B</td>
</tr>
<tr>
<td></td>
<td>Res.</td>
<td>Sus.</td>
<td>Res.</td>
<td>Res.</td>
<td>PDR Scheme B</td>
</tr>
<tr>
<td>R-resistance</td>
<td>Sus.</td>
<td>Res.</td>
<td>Sus.</td>
<td>Sus.</td>
<td>PDR Scheme C</td>
</tr>
<tr>
<td></td>
<td>Sus.</td>
<td>Res.</td>
<td>Sus.</td>
<td>Res.</td>
<td>PDR Scheme C</td>
</tr>
<tr>
<td></td>
<td>Sus.</td>
<td>Res.</td>
<td>Res.</td>
<td>Sus.</td>
<td>PDR Scheme C</td>
</tr>
</tbody>
</table>

<sup>(a)</sup> Except previously treated patients, for whom PDR Scheme B + ethambutol is preferred.
Perform second-line DST if patients come from a region of high second-line resistance and if there is a history of second-line anti-TB drug use. Resistance to second-line anti-TB drugs will impact the choice of regimen.

### 11.1.2 PDR Scheme A for cases with H or HS resistance

For new patients, the treatment regimen is 9 RZE. However, the combination HRZE can be used if more convenient since it can be given as fixed-dose combination.

At Month 2, perform smear, Xpert MTB/RIF, and culture:

<table>
<thead>
<tr>
<th>Xpert available</th>
<th>Xpert RIF+: switch to empiric MDR regimen while waiting for full DST results then, adapt treatment accordingly.</th>
<th>Xpert RIF−: continue PDR Scheme A.</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Xpert not available</th>
<th>Culture+: switch to empiric MDR regimen with the inclusion of R while waiting for full DST results.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• DST is unchanged (H or HS resistance only): stop the MDR regimen, and resume PDR Scheme A;</td>
</tr>
<tr>
<td></td>
<td>• DST has changed: adapt treatment accordingly.</td>
</tr>
<tr>
<td></td>
<td>Culture−: continue PDR Scheme A.</td>
</tr>
</tbody>
</table>

Perform smear and culture every other month. If cultures or smears are positive, switch to MDR regimen while waiting for full DST results then, adapt treatment accordingly.

For previously treated patients, it is safer to use Scheme B plus ethambutol, as DST to this drug should not be relied upon if the patient has already received it.

### 11.1.3 PDR Scheme B for cases with HE or HES resistance

Start patients on 3 Cm (or Km)-Lfx-RZ/7 Lfx-RZ regardless of smear status at the time of diagnosis.

At Month 2, perform smear, Xpert MTB/RIF and culture:
At Month 3, perform smear, Xpert MTB/RIF, and culture. If Xpert shows RIF+ or if the culture is still positive, this regimen is declared “failure”. Switch to MDR treatment.

Even if found susceptible, streptomycin should not be used given the high rates of resistance to this drug in patients with DR-TB and the poor reliability of the DST.

### 11.1.4 PDR Scheme C for cases with R or RS or RE or RES resistance

Start patient on MDR regimen until confirmation that the strain is susceptible to fluoroquinolones and injectable agents.

When DST results confirm resistance to R, RS, RE or RES and susceptibility to H, fluoroquinolones and an injectable agent, there are two options:

1 - Continue the full course of MDR-TB treatment plus isoniazid. This is a reasonable consideration given that DST reliability is not 100%. This is recommended if the suspicion for MDR-TB is high (i.e. a contact of an MDR-TB patient or failure of a first-line regimen).
2 - Start PDR Scheme C: 3 Cm (or Km)-Lfx-HZ (+/-E)/12 Lfx-HZ (+/- E). Ethambutol is added if it is likely to be effective.

Even if found susceptible, streptomycin should not be used given the high rates of resistance to this drug in patients with DR-TB and the poor reliability of the DST.

At Month 2, perform smear and culture:

- **Culture+**: start empiric MDR regimen and repeat DST.
  - DST is unchanged: resume PDR Scheme C;
  - DST has changed: adapt treatment accordingly.
- **Culture−**: complete PDR Scheme C.

At Month 3, perform smear and culture. If the culture is still positive, this regimen is declared “failure.” Switch to MDR treatment.
Note: if the baseline DST is performed by LPA (Hain® test), only DST for R and H are available. In order to avoid possible resistance amplification, the worst scenario should be assumed:

- If only resistance to H is detected, treat with Scheme B, even new patients while waiting for full DST.
- If only resistance to R is detected, treat as MDR-TB as sensitivity of Hain® test for H resistance is low.

Referencias


11.2 Treatment algorithms for PDR-TB

PDR scheme A
PDR SCHEME A  
H (+/- S) resistance

Note: for previously treated patients it is safer to use Scheme B + ethambutol.

Continue the initial regimen (new or previously treated case)

At Month 2: Xpert RIF+ or culture+

Yes

Start empiric MDR-TB treatment while waiting for DST result.

No

Start continuation phase: 7 RZE
Perform smear and culture every other month.

Any smear+/culture+

Yes

Start empiric MDR-TB treatment while waiting for DST result.

No

Cured or treatment completed

- If DST unchanged: complete continuation phase to a total of 7 RZE after culture negative. Perform smear and culture every other month. 
- If DST changed: adapt treatment accordingly.

PDR scheme B
PDR SCHEME B
HE (+/- S) resistance

Start adapted regimen
3 Cm (or Km)-Lfx-RZ

At Month 2:
Xpert RIF+ or culture+

Yes
Start empiric MDR-TB treatment while waiting for DST result.

No
Complete intensive phase

- If DST unchanged: complete continuation phase to a total of 7 Lfx-RZ after culture negativation. Perform smear and culture every other month.
- If DST changed: adapt treatment accordingly.

At Month 3:
Xpert RIF+ or culture+

Yes
Start continuation phase: 7 Lfx-RZ
Perform smear and culture every other month.

No
Any smear+/culture+

Yes
Failure
Resume MDR-TB treatment.

No
Cured or treatment completed

PDR scheme C
Chapter 12: Co-management and treatment of HIV in TB disease

12.1 HIV testing and counselling for patients known or suspected to have TB
12.2 Prophylaxis against opportunistic infections
12.3 Anti-TB regimens in HIV patients
12.1 HIV testing and counselling for patients known or suspected to have TB

HIV testing is recommended for all patients with signs and symptoms of tuberculosis (TB), whether TB is suspected or already confirmed. HIV testing should be offered as part of an “opt out” approach, which means the patients will have to specifically decline the HIV test after receiving the pre-test counselling if they do not want the test performed.

HIV-infected TB patients may have household members who are also living with HIV. Testing for HIV is recommended in immediate family members where horizontal or vertical transmission may have occurred.

12.2 Prophylaxis against opportunistic infections

It is recommended that cotrimoxazole preventive therapy (CPT) be initiated or continued during TB treatment, as it is associated with a reduced risk of death. CPT prevents a number of infections such as pneumocystosis, toxoplasmosis, some diarrhoea and other bacterial infections (respiratory, urinary tract, etc.) and malaria.

If the patient is receiving prophylaxis against other opportunistic infections, the prophylaxis should continue during TB therapy.
12.3 Anti-TB regimens in HIV patients

HIV patients follow the usual first-line or second-line TB regimens. Intermittent regimens should not be used in HIV-positive TB patients.

Case definitions, treatment categories, sputum examination follow-up, and treatment outcomes are equally applicable for HIV-infected TB patients.

12.4 Concomitant treatment TB and HIV

Antiretroviral therapy (ART) dramatically improves survival in HIV-infected patients. In addition, ART reduces TB rates greatly both at individual and population levels.

ART must be initiated in all HIV positive patients with active TB irrespective of the CD4 cell count. Start the anti-TB treatment first, followed by ART as soon as possible and within eight weeks of starting TB treatment[1][2][3].

For the following patients, at high risk of mortality, consider starting ART within the first two weeks:
- Patients with low CD4 count (especially CD4 < 50);
- Young children (especially < 1 year of age);
- Patients with drug-resistant TB (DR-TB).

The first-line ART regimen should contain two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non nucleoside reverse transcriptase inhibitor (NNRTI). The preferred NNRTI in patients starting ART while on TB treatment is efavirenz (EFV), since there is less interaction between EFV and rifamycins compared to other NNRTIs. The preferred NRTI in the first-line ART regimen is tenofovir (TDF), combined with either lamivudine (3TC) or emtricitabine (FTC). If TDF is not available, then zidovudine (AZT) is preferred over stavudine (d4T) due to the long-term adverse effects.

In summary, for adults and adolescents:
- Tenofovir/lamivudine/efavirenz (TDF/3TC/EFV) is the preferred first-line ART regimen because of the once daily dosing and the availability of a fixed-dose combination.
- In the event of severe central nervous system intolerance to EFV:
a) Give triple NRTI ART regimen: zidovudine/lamivudine/abacavir (AZT/3TC/ABC); or
b) Replace rifampicin (R) with rifabutin (Rfb, 300 mg daily) and start nevirapine (NVP) based ART regimen with lead-in dosing of NVP for 2 weeks; or
c) Give NVP based ART regimen tenofovir/lamivudine/nevirapine (TDF/3TC/NVP) but without lead-in dose when used with rifampicin containing first-line TB treatment. In patients with CD4 > 250, close clinical and ALT monitoring at 4, 8 and 12 weeks is recommended.

Referencias


12.5 Drug interactions

12.5.1 Antituberculous and antiretrovirals

Rifamycins and antiretrovirals

Interactions between rifamycins and 2 groups of antiretrovirals (ARVs) — NNRTIs and protease inhibitors (PIs) — must be expected due to liver enzyme induction of the rifamycins. For possible combinations of ARVs and rifamycins, see Table 12.1.

Patients receiving NVP when TB is diagnosed:

- If rifabutin is available, give 2 months of HZE-Rfb followed by 4 months of H-Rfb.
- If rifabutin is not available, replace NVP with EFV 600 mg. When the TB treatment is completed, NVP may be resumeda.
- If rifabutin is not available and EFV is contraindicated, see options in previous section.

Patients receiving protease inhibitors (PI):

- When PIs and rifamycins are given to the same patient, PI serum levels can decrease to sub-therapeutic levels, while the serum levels of rifamycins could rise to toxic levels.
- Rifabutin is a less potent enzyme inducer than rifampicin; rifabutin is the preferred drug in patients using PIs.
• If rifabutin is not available, dosages of lopinavir and ritonavir (LPV/r) must be significantly increased in patients taking both LPV/r and rifampicin (see Table 12.1). Liver enzymes should be monitored.

Table 12.1 Possible combinations of ARVs and rifamycins
<table>
<thead>
<tr>
<th></th>
<th>Rifampicin</th>
<th>Rifabutin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine (NVP)</td>
<td>Do not combine unless Rfb is not available and there are no other options.</td>
<td>Rfb: 300 mg/day NVP: usual dose</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>May be combined. R: usual dose EFV: 600 mg/day</td>
<td></td>
</tr>
<tr>
<td><strong>NRTIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Didanosine (ddI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>May be combined without dose adjustments.</td>
<td></td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine (AZT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir (TDF)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir (IDV)</td>
<td>Do not combine</td>
<td>Rfb: 300 mg/day IDV: 1 g every 8 hours</td>
</tr>
<tr>
<td>Nelfinavir (NFV)</td>
<td>Do not combine</td>
<td>Rfb: 300 mg/day NFV: usual dose</td>
</tr>
<tr>
<td>Lopinavir/ritonavir (LPV/r)</td>
<td>May be combined if Rfb is not available. LPV/r: double dose of LPV/r (800 mg/ 200 mg twice daily) R: usual dosage</td>
<td>Rfb: 150 mg/day [^1]] LPV/r: usual dose</td>
</tr>
<tr>
<td>Atazanavir/ritonavir (ATZ/r)</td>
<td>Do not combine</td>
<td>Rfb: 150 mg/3 times a week [^2]\ ATZ/r: usual dose</td>
</tr>
</tbody>
</table>
Bedaquiline and antiretrovirals

Data from drug-drug interaction studies with bedaquiline and ARVs to date are extremely limited.

- NNRTI: EFV (enzyme inducer) is estimated to decrease bedaquiline concentrations by 50%. Nevirapine does not significantly affect bedaquiline concentrations.
- NRTI are unlikely to affect bedaquiline concentrations.
- PI: ritonavir is an enzyme inhibitor. The use of ritonavir-boosted lopinavir (LPV/r) with bedaquiline may result in a significant accumulation of bedaquiline and its metabolites. This combination is therefore not recommended.

The following ART regimens can therefore be considered in association with bedaquiline:
1) 2 NRTIs + nevirapine: e.g. AZT/3TC or FTC/NVP or TDF-3TC-NVP;
or
2) 3 NRTIs: e.g. AZT/3TC/ABC.

Fluoroquinolones and didanosine

Buffered didanosine contains an aluminium/magnesium-based antacid that, if given with a fluoroquinolone, can result in its decreased absorption. If it is not possible to avoid prescribing these drugs together, didanosine should be given 2 hours apart fluoroquinolone administration. The enteric-coated formulation of didanosine can be given without such precaution.

Other drug-drug interactions can occur between anti-TB drugs and ARVs, further complicating treatment. Most of the drugs used in the treatment of DR-TB have not had drug-drug interaction studies performed with ARVs.

12.5.2 Other interactions

Rifampicin can interact with drugs commonly used in opportunistic infections.

Interaction occurs with fluconazole. Rifampicin may decrease blood levels of fluconazole by as much as 25-50%. The two drugs can be taken 12 hours apart (i.e. rifampicin in the morning, fluconazole in the evening) without dosage adaptation. However, the patient’s clinical condition should be carefully monitored, as the dosage of fluconazole may need to be increased if clinical improvement is suboptimal.

For the treatment oral candidiasis, miconazole mucoadhesive tablets (gum patches) can be used (no interaction with rifampicin).

Notas

(a) If a patient is changed from EFV back to NVP on completion of TB treatment, no lead-in dosing of NVP is necessary.
12.6 Overlapping toxicities with anti-TB drugs and antiretrovirals

The main potential overlapping toxicities between anti-TB drugs and ARVs are:

- Hepatic reactions;
- Cutaneous reactions;
- Neuropathy;
- Nephrotoxicity.

The use of agents with shared adverse effect profiles should be avoided if possible. Often, however, the benefit of using drugs that have overlapping toxicities outweighs the risk. Thus, if two drugs with overlapping toxicities are essential in a regimen, increased monitoring for potential adverse effects is recommended rather than avoidance of a certain combination.

Important points:

- HIV patients are more likely to develop isoniazid-related peripheral neuropathy. Thus, all patients on isoniazid should receive pyridoxine PO (vitamin B₆): 10 mg daily or 25 mg twice a week.
- The use of thioacetazone is contraindicated in HIV patients due to the high frequency of Stevens-Johnson syndrome and corresponding risk of mortality.
- Due to reports of increased renal toxicity during concurrent use of TDF and injectable agents (kanamycin, amikacin, and capreomycin), the use of TDF is not recommended during the intensive (i.e. injectable) phase of DR-TB treatment. If TDF is absolutely necessary, serum creatinine and creatinine clearance, and electrolytes should be monitored frequently.
12.7 Immune reconstitution inflammatory syndrome (IRIS)

Immune reconstitution inflammatory syndrome (IRIS) occurs after initiation of ART, in the presence of a previously unrecognized, often subclinical, opportunistic infection. Patients present with paradoxical worsening of their clinical status as the immune system recovers on ART.

Symptoms vary according to the infection, but can include fever, enlarging lymph nodes, worsening pulmonary infiltrates, respiratory distress, neurologic signs, or exacerbation of inflammatory changes at other sites.

IRIS can occur anytime between 10 and 180 days after ART initiation (usually 2-4 weeks) and is more common with CD4 count < 50. Mild to moderate forms of IRIS are relatively common in TB patients who are started on ART (seen in up to one third of patients in some studies); however, severe IRIS is relatively rare.

IRIS occurs with respect to TB in two circumstances:
1 - Paradoxical TB IRIS: A patient is diagnosed with TB, starts TB treatment, followed by ART after a few weeks, and then develops IRIS.
2 - Unmasking TB IRIS: A patient is screened for TB before initiation of ART and no TB is found. The patient then starts ART, followed by onset of TB symptoms and signs.

It is important to note that IRIS with respect to TB is a diagnosis of exclusion. Patients with advanced HIV infection may show clinical deterioration for a number of other reasons (all of which should be ruled out before giving the diagnosis of IRIS):
- Clinical worsening due to new opportunistic infections;
- Other subclinical infections unmasked following immune reconstitution with ART initiation;
- TB treatment failure due to DR-TB.

The management of IRIS depends on the clinical status of the patient and the site and extent of involvement. Nonsteroidal anti-inflammatory drugs are used in mild to moderate IRIS cases and corticosteroids in severe IRIS cases (Chapter 9, Section 9.3). The use of corticosteroids can be dangerous if IRIS is misdiagnosed and the clinical deterioration is in fact DR-TB or a different opportunistic infection.

Most cases of IRIS can be treated without interruption of ART; in very severe forms of IRIS, ART may need to be suspended.

12.8 HIV-infected children with TB
Most HIV-positive children with TB respond well to the 6-month TB regimen, similar to HIV-uninfected children. If the clinical response is slow, other causes should be considered such as poor adherence to therapy, inadequate drug absorption, DR-TB, and other infections.

The following ARV regimens are preferred in children on TB treatment:
- Child < 3 years old or < 10 kg: AZT preferred or D4T/3TC + ABC;
- Child > 3 years and > 10 kg: AZT preferred or ABC or D4T/3TC + EFV.

TDF is considered safe in children above 3 years of age.

### 12.9 HIV-infected pregnant women with TB

TB in HIV-positive pregnant/postpartum women is associated with significant maternal and infant mortality. ART in pregnant women with TB is summarized below:
- TDF is the preferred NRTI and is safe to use throughout pregnancy.
- Safety of EFV is considered acceptable during pregnancy[^1].

### Referencias

   [http://apps.who.int/iris/bitstream/10665/70920/1/9789241503792_eng.pdf](http://apps.who.int/iris/bitstream/10665/70920/1/9789241503792_eng.pdf)

### 12.10 HIV-infected patients with DR-TB

DR-TB does not appear to be more prevalent in HIV-infected patients compared to HIV-uninfected patients. However, high mortality rates have been reported in patients coinfected with HIV and DR-TB.

Prompt initiation of appropriate DR-TB therapy (and subsequent initiation of ART) can help to reduce mortality.
Chapter 13: Adherence to tuberculosis treatment

13.1 Introduction

Good adherence is when the patient follows the treatment as prescribed. Patient understanding, acceptance and motivation to start and complete TB treatment are essential to maximise chances of cure. Good knowledge of drug dosing, length of treatment, required clinical follow-up and common adverse effects help patients to follow the prescribed therapy.

Failure to take tuberculosis (TB) drugs consistently, or in an inappropriate manner, or stopping the treatment too soon, can lead to treatment failure or relapse. It may also contribute to the development of resistance, which can complicate subsequent treatment, thereby decreasing the chances of a successful outcome.

13.2 Treatment delivery model

13.2.1 Self-administered treatment

Self-administered treatment (SAT) is taken autonomously by the patient without daily supervision. The patient is seen at a health facility at regular intervals (e.g. monthly) to receive drugs, support and treatment education. SMS telephone reminders may be considered to reinforce adherence.

13.2.2 Directly observed therapy
Drugs are sometimes provided daily to the patient and the treatment is taken under direct observation (DOT) by a third party.

DOT may be provided:
- In health facilities (facility-based DOT): in this model, DOT is implemented in a centralised setting and treatment is administered by healthcare workers.
- Outside of health facilities (community or home-based DOT): in this model, DOT is implemented in a decentralised setting and is usually provided by supervised, trained and remunerated treatment supporters.
  
  For the roles and responsibilities of treatment supporters see Appendix 20.
- Remotely (video-observed therapy or VOT): VOT uses secure Internet connections via a smart phone or computer application to remotely supervise patients taking their treatment.

DOT is labour-intensive to implement and can be inconvenient for patients. Community and home-based DOT and VOT require fewer resources (personnel and transport) than facility-based DOT and may be more convenient for patients.

**Box 13.1 – Recommended treatment delivery models**

### Drug-susceptible TB (DS-TB)
- DOT has not been proven to improve treatment outcomes for DS-TB when compared to SAT in controlled trials[1].
- When there is no factor to complicate adherence, and provided the patient receives appropriate support, treatment should be self-administered.
- There are some situations in which DOT may be preferred:
  - Patients with mental health issues or serious socioeconomic problems (e.g. the homeless) and all patients incapable of taking drugs on their own.
  - Prisoners (risk of drugs being sold or stolen).

### Drug-resistant TB (DR-TB)
- Due to the lack of fixed-dose combinations (FDC), length of treatment, adverse effects of TB drugs and lack of therapeutic alternatives if treatment fails, patients usually require reinforced support.
- If DOT is considered useful, home-based DOT[2] or VOT are preferred to facility-based DOT. A combination of approaches may be required for some patients.

### Latent TB infection (LTBI)
- LTBI treatments can be self-administered.
- DOT may be preferred with the 3HP regimen, as it may cause serious hypersensitivity reactions. However, SAT can be considered if the patient well informed and is able to seek rapid medical attention if adverse effects develop.
13.3 Factors that influence adherence

Several factors can influence adherence, including barriers related to the patient, the treatment or the therapeutic environment. While it is not always feasible to address all these factors, at the very least it is possible to control the treatment and therapeutic environment-related factors.

13.3.1 Patient-related factors

A discussion should be held with the patient prior to treatment initiation and then during every contact they have with the healthcare team. The objective is to identify and anticipate barriers to treatment adherence. Barriers may include:

- Socioeconomic factors (work and home responsibilities, treatment-related costs, decreased income, etc.).
- Psychological factors (feelings of shame, fear of stigma or marginalisation, uncertainty about the future, conceptions about the disease and its treatment, etc.).
- Physical or mental disability.
- Lack of knowledge about the disease and treatment.
- Perception of the disease and treatment (a patient might abandon treatment due to improvement or absence of improvement, a negative experience with a previous treatment, etc.).

Solutions depend on the context and the patient's problem, and therefore should be identified on a case-by-case basis.

13.3.2 Treatment-related factors

- Simplicity of treatment improves adherence. The use of FDC simplifies the treatment by reducing the number of tablets. In addition, FDC prevents omission of one or more prescribed TB drugs.
- Adverse effects may lead patients to interrupt their treatment, so these should be detected and managed promptly.

13.3.3 Factors related to the therapeutic environment

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Referencias


13.4 Patient education and support

Patient education and support require the involvement of the entire healthcare team (clinicians, nurses, treatment supporters, social workers, etc.). In large-scale programmes, the healthcare team sometimes includes trained counsellors who provide information and support.

Treatment education and support may be provided through various channels: organising educational sessions during in-facility or home visits, video and telephone contacts.

Patient education and support are required throughout treatment, as adherence may vary over time and patients may experience phases of treatment acceptance and rejection.

Due to the toxicity and long duration of treatment, patients on DR-TB treatment usually require substantial support.

13.4.1 Patient education

Patient education consists of:

- Helping patients to understand the disease and treatment.

• To ensure the widest possible access to treatment, TB diagnosis, monitoring and treatment (including TB drugs and drugs for adverse effects and co-morbidities) should be provided free of charge.

• The relationship between patients and healthcare workers influences if patients have confidence in healthcare workers, they are more likely to follow recommendations and engage with the treatment process. Patients are also more likely to bring questions and concerns to the attention of healthcare workers. The same applies to the relationship with treatment supporters.

• In health facilities, the way in which patients are received is waiting times for diagnosis or follow-up visits should be reasonable.

• Drug supply management must be rigorous. Shortages can lead to treatment interruption and negatively impact adherence (patients waste time in unnecessary travel and lose confidence in the health facility).

• The proximity of drug distribution sites limits the number of patients who abandon due to transportation problems. To anticipate potential problems, give the patients a few extra days of treatment in case they are unable to come to get their drugs on the scheduled.

• For the co-management of TB and HIV infection, patients should receive TB and HIV treatment at the same time and in the same place (“one-stop service”). This reduces the number of visits and decreases waiting times, which results in greater patient satisfaction and improved treatment outcomes. Co-management of other co-morbidities (e.g. diabetes, hypertension) should, when possible, use the same approach.

• Hospitalisation should be limited to patients with clinical conditions requiring hospital level care. If hospitalisation is necessary, accommodation (comfort, food, heating, etc.) should be adequate. The duration of stay should be as short as possible and patients should be discharged as soon as their clinical condition allows.
• Enabling patients to acquire and maintain skills that allow them to manage their treatment and disease in their everyday lives.
• Answering patients' questions throughout the treatment.

For more information see Appendix 21.

13.4.2 Emotional support

Listen to patients and give them encouragement, so that they feel comfortable saying they have forgotten or have made a mistake with their treatment. This is common, and it is important to know so that solutions can be found.

Psychological problems, such as depression and anxiety are frequent, and may have a negative impact on adherence. The healthcare team should be sensitised to their early detection and management.

13.4.3 Social support

Implement social support measures for patients with limited resources. Depending on the situation and specific needs of patients:
• Social workers can help to obtain disability allowances, housing assistance, shelter for the homeless, etc.
• The programme can provide meals or food, vouchers or money for transportation or reimburse the cost, etc.

Chapter 14: Tuberculosis infection control

14.1 Introduction

14.2 Implementation of TB IC strategies

14.3 Administrative controls

14.4 Environmental controls

14.5 Personal protective measures

14.6 Hospital hygiene

14.7 Patients' homes

14.1 Introduction
The largest source of *M. tuberculosis* transmission is the contagious patients with respiratory tuberculosis not yet diagnosed and put on treatment. Therefore, tuberculosis infection control (TB IC) relies, above all, on:

- Early diagnosis (including in clinics and any non-tuberculosis medical wards, whereby active case finding through cough surveillance of all admissions should avoid days or weeks of transmission from unsuspected TB cases);

AND

- Prompt implementation of effective treatment. With effective treatment, contagiousness decreases even after a few days and may be considered nil after 2 to 3 weeks of treatment[^1][[^2][[^3][[^4]]. It is essential the treatment is “effective,” as multidrug-resistant TB (MDR-TB) patients that are placed on first-line anti-TB drugs are likely to remain contagious.

However, in health care facilities where TB patients or persons suspected of having TB congregate, additional measures are needed to reduce the risk of transmission between patients, to health care staff and to vulnerable (particularly immunocompromised) patients/visitors[^5].

TB infection control (IC)^a consists in different strategies for preventing transmission of TB in health care facilities.

**Notas**

(a) This chapter reviews the basic TB IC strategies. More in depth information can be found from the Tuberculosis Coalition for Technical Assistance which has published a framework and developed a website ([http://www.tbcta.org/Library](http://www.tbcta.org/Library)) that provides a comprehensive set of examples.

**Referencias**


   [https://apps.who.int/iris/bitstream/handle/10665/44148/9789241598323_eng.pdf?sequence=1](https://apps.who.int/iris/bitstream/handle/10665/44148/9789241598323_eng.pdf?sequence=1)
14.2 Implementation of TB IC strategies

There is a trio of infection control levels, which include (1) administrative, (2) environmental and (3) personal protective controls\(^1\). The implementation of these measures requires a dedicated staff and an IC plan.

14.2.1 Infection control practitioner

A person should be clearly identified and designated as responsible for TB IC. This person should have the support and authority to conduct, apply and evaluate TB IC policies. This person in some settings is also known as IC officer.

14.2.2 Infection control committee

The IC practitioner would evaluate the need to create an infection control committee (ICC). The ICC might include doctors, nurses, laboratory technicians, logisticians and administration staff (including representation from the maintenance and housekeeping services). According to the context and degree of risk, experts in IC may be needed.

14.2.3 Infection control plan

All facilities should have a detailed written IC plan that is at least annually updated and distributed to healthcare staff.

A simplified version of the plan must be accessible to all healthcare workers including staff not directly involved in TB patients’ management, such as cleaners, kitchen staff, etc.

The first step in developing an IC plan is assessing the health care facility’s risk for TB transmission\(^2\). This should be performed by the IC practitioner. The plan must be specific to each facility. An example of risk assessment tool is given in Appendix 16.

The IC plan should include the different types of measures—administrative, environmental and personal. Information on specific precautions and procedures for high-risk areas should be detailed.

It is recommended to draw a floor plan of the facility with the different areas, including the patient flow and identifying areas of high risk.

Listed below from highest to lowest level of risk:
14.3 Administrative controls

The administrative controls aim at preventing the exposure to infectious droplet nuclei.

14.3.1 Patients triage

Upon entry into the health facility, a member of the medical staff should identify patients with a cough as soon as possible. Patients with a cough over two weeks should be sent to a separate waiting room if possible.

Referencias

   https://apps.who.int/iris/bitstream/handle/10665/44148/9789241598323_eng.pdf?sequence=1

2. *Implementing the WHO policy on TB infection control*. Tuberculosis Coalition for Technical Assistance.  
All patients with cough (including patients with less than two weeks of cough) should receive tissues or face masks, and they should be requested to cover their mouth and nose when they cough.

14.3.2 Patient, visitors and attendants' flow

Inside the TB department, circulation of patients and attendants is controlled:

- Encourage patients/attendants to spend as much time as possible outdoors if weather permits or in areas that are open on three or four sides.
- Have visible signage on entry doors to TB wards that forbid visitors to enter.
- Limit visitation duration, particularly for contagious patients.
- Encourage visits outside the building, especially for contagious patients.
- Have visiting areas well identified with signage.
- Before any visit, the nurse should provide information on transmission risk, including the usage of respirators if carers need to go in high risk areas, such as smear-positive, drug-resistant TB (DR-TB), re-treatment smear-positive inpatient units and areas or clinics were diagnosis of TB is being undertaken.
- Avoid that known or suspect TB patients go through areas where they may infect other patients, and vice versa, that patients without TB go through areas where they are unnecessarily exposed to the bacillus.

14.3.3 Segregation of hospitalized patients

Patients should preferably be treated in ambulatory care. Hospitalisation should be limited and reserved for clinically unwell patients.

TB wards must be separated from the others wards in the health structure compound.

Ideally, within the TB department, patients should be placed in single rooms. If this is not possible, cohort isolation must be implemented and different sections should be labelled according to the degree of contagiousness (smear/culture status) and risk of resistance.

The following is one scheme of separation. It does involve the use of some single isolation rooms (all TB inpatient facilities should have some isolation rooms. If none exist, a very high priority is to add some).

- Smear-positive patients with proven or suspected DR-TB, including chronic cases and retreatment cases that are likely to have MDR-TB. MDR-TB cases should have single isolation rooms (place in 2 to 4 person rooms with other MDR-TB patients if there are no single rooms and try to match DST patterns). It is particularly important not to mix MDRTB patients with extensively drug-resistant TB (XDR-TB) patients.
- Smear-positive patients with fully susceptible TB.
- Smear-negative patients (or patients who have converted), with proven or suspected DRTB (once patients are on effective treatment, they rapidly become non-contagious).
- Less or non-contagious TB: patients with smear-negative pulmonary TB (PTB), EPTB, patients having converted their sputum/culture and most children.
- Patients who are undergoing diagnosis as suspected cases: when possible do not hospitalize patients for diagnosis. If hospitalization is necessary, these patients need isolation rooms. Never
If women and men are to be separated, this scheme requires at least 8 different wards and enough single rooms for suspect cases and MDR-TB patients.

### 14.3.4 TB IC training

All healthcare personnel should receive initial training on TB transmission, information on high-risk areas in the facility and on protective measures. Continuing education should be offered annually.

The training should also include how staff can teach patients, visitors and attendants about the risk of TB transmission and how to avoid it (cough etiquette, use of masks and respirators).

### 14.4 Environmental controls

The environmental measures aim at reducing the concentration of infectious droplet nuclei in the air.

#### 14.4.1 Ventilation

Ventilation (replacement of inside air with outside air) is the most effective means for reducing the concentration of *M. tuberculosis* in the air, and as a result, the risk of transmission.

The WHO recommends that in areas where TB transmission might occur, a minimum ventilation rate of 12 air changes per hour (ACH) should be achieved. See Appendix 17 for recommendations on ACH measurement.

Effective ventilation can be obtained by natural (assisted or not) or mechanical means.

**Natural ventilation**

Natural ventilation, especially cross-ventilation (windows/doors in opposite sides of the room), has the best cost-effective ratio. It should be done with the windows and outside doors open (as much as weather conditions permit). Inside doors should be closed so that the flow of air is directed outside and not toward the corridors. Create shady spaces so that patients, attendants and visitors can stay outside during the day. Wind-driven roof turbines (whirly birds) or chimneys can also be used to improve natural ventilation, in that they can keep the principle of directing room air towards the exterior. In addition, fans can be used when the natural ventilation flow rate is too low (assisted natural ventilation).

**Mechanical ventilation**

When natural ventilation cannot reach adequate rates, centralised mechanical ventilation should be considered in some settings, such as within cold climates. Centralised mechanical ventilation relies on the use of mechanical equipment to maintain an air pressure difference between two areas in order to draw air into a room and vent it to the outside. It requires continuous and meticulous maintenance, which renders it costly and difficult to implement and operate.
Advantages and disadvantages of each ventilation technique are presented in Appendix 18.

14.4.2 Architectural considerations

Airborne infection control should be always considered during the planning/construction stages of new health facilities and those being modified. It is important to achieve the following:

- Building layout and design with maximised natural ventilation (assisted or not) and sunlight. Waiting areas should be open on three sides. Design of TB wards should avoid internal hallways with doors from the rooms and wards opening into them. Instead, doors should open to outside hallways that are open to air (this may not be feasible in cold climates).
- Specific areas (open air, sputum collection booth, etc.) should be reserved for procedures with a high risk of *M. tuberculosis* transmission (e.g. sputum collection, sputum induction, etc.).
- Allow patient flow that reduces exposure of patients at risk to patients that are infectious (e.g. separate waiting rooms for different cohorts, one patient per room in a hospital). If designing a new TB ward, incorporate plenty of single rooms or at least small rooms with 2 to 4 beds for easier separation of the different cohorts of patients. General hospitals should also have isolation rooms available for TB suspects and contagious patients.

Rehabilitation of existing structures in order to maximise natural ventilation could be a viable economical option instead of building expensive systems, like centralised mechanical ventilation.

14.4.3 Ultra-violet germicidal irradiation

Ultra-violet germicidal irradiation (UVGI) lamps may be used when adequate ventilation cannot be achieved in high-risk areas. When properly installed, designed, maintained and operated, an UVGI system, in addition to 6-12 ACH ventilation, could be the equivalent of 10-25 ACH\(^2\) . For technical information on upper room UVGI, see Appendix 19.

- Main requirements and constraints in UV lamps usage include:
  - Expertise in installation and testing;
  - Rigorous monitoring and maintenance;
  - Electricity, relative humidity less than 70%, good air mixing.
- Potential hazards include: Transient eye and skin injuries from overexposure, mercury poisoning (broken or mishandled lamp).

14.4.4 Areas requiring specific measures

Sputum collection areas
These areas must be settled, wherever possible, outside in open air where bacilli will naturally be dispersed by wind rather than in a closed room where the concentration of bacilli will be high. In cold regions, sputum collection should be performed in very well ventilated indoor rooms (at least 20 ACH) or in well ventilated rooms (at least 12 ACH) equipped with a UVGI system. Another option for sputum collection areas in cold climate regions is to assign a specific room of small size (1 m²) with one single glass door opening outside. Keep the door largely open for 5 minutes between each patient. The small volume of air in this room facilitates rapid ventilation.

**Laboratory**

All laboratories should undergo a risk assessment, and IC measures should be adapted accordingly. In any case, limit the access to all TB laboratories. The use of ventilated workstation ([Appendix 7](#)) is strongly recommended for smear preparation (microscopy and test Xpert). In laboratories where culture are carried out, biological safety cabinets type II must be used. Laboratories must have easy to clean working surfaces (avoid wood) to allow proper disinfection. They should also have large windows to let in sunlight and allow natural ventilation if the laboratory has no mechanical ventilation. Water-filters should be used to avoid contamination by saprophyte mycobacteria that are sometimes present in the water.

**Notas**

(a) UVGI inactivate bacilli. Natural light dries the droplet but does not inactivate bacilli.

**Referencias**


**14.5 Personal protective measures**

Personal protective measures aim at minimising the risk of bacillus transmission by providing barriers to inhaling or exhaling infectious droplet nuclei.
14.5.1 Respirators (or high-filtration masks or anti-inhalation masks)

A respirator is personal protective equipment that prevents inhalation of infectious droplet nuclei by the person who wears it.

Exposed staff

Staff must wear a respirator, regardless if they are the caregiver or not. Respirators should be worn:
- When in contact with contagious patients (suspect or confirmed TB case);
- When collecting sputum samples;
- When collecting and disposing of sputum containers;
- In areas where droplet nuclei could be present (i.e. a room that has been occupied by a TB case, prior to the time required for air cleaning).

Using respirators needs proper training, fit testing and continuous supervision. This also applies to home-based DOT supervisors.

Visitors/attendants

Visitors and attendants must wear a respirator when entering a contagious TB patient’s room.

For more information on respirators, see Appendix 27.

14.5.2 Face or surgical masks

Face masks are medical devices that prevent patients from spreading infectious droplets when talking, coughing or sneezing. They should be worn by contagious patients (suspect or confirmed) when they leave their rooms to go to another department or any other enclosed area. They should not be worn when the patient is alone in his/her room and outdoors.

For more information on surgical masks, see Appendix 28.

Using a mask in public areas could be stigmatizing. Patients can use a cloth scarf to achieve the same purpose.

14.6 Hospital hygiene

14.6.1 Hygiene and disinfection

Sputum containers

Patients with pulmonary TB produce sputum that may contain tubercle bacilli.
- In the wards, patients’ sputum containers should be large (about 200-ml), non-sterile, and sealable. They are to be replaced daily and cannot be re-used.
Environmental cleaning

Sterilization or the use of disinfecting chemicals in a TB patient’s room is not necessary. Ordinary cleaning of rooms and objects (linens, dishes, etc.) used by TB patients is sufficient. After the patient is discharged, air the empty room well according to the calculated ACH.

Reusable medical items

Standard operating procedures for reprocessing items should be followed. There are no specific measures for TB services.

Standard precautions

Standard precautions (hand hygiene, gowns, etc.) apply in TB wards, as they do in any other hospital department.

14.6.2 Waste management

Standard operating procedures for handling and the disposal of healthcare waste (including soft, sharp, etc.) should be followed. There are no specific measures for TB services.

Note: used sputum containers should be collected in a leak proof trash bag and incinerated without filling the containers with chlorine solution before incineration (this can produce toxic gases).

14.7 Patients’ homes

In settings where DR-TB (and HIV) is highly prevalent, systematic TB IC evaluations on patients’ homes are recommended.

TB IC at patients’ homes follows the same principles and measures as in healthcare facilities. Administrative, environmental and personal measures should be followed at least until patient’s smear is negative, ideally until culture conversion.

Administrative measures

• Assess the risk of TB transmission: gather information on the number of people that live in the house, number of rooms, etc.
• Screen contacts for TB.
• Children under 5 should spend as little time as possible in the same spaces as culture-positive patient (although the risk to the child is greatly reduced once a patient starts an effective regimen).
The mother should use a surgical mask while taking care of the child until she becomes smear-negative.

- Offer education on TB transmission, airborne precautions (cough etiquette, masks), clinical symptoms and waste management of sputum containers or tissues (do not empty the container; throw it in the latrines or enclose it hermetically in plastic bags and discard in the normal waste).

**Environmental measures**

- Ideally, the patient should sleep in a separated room, with door closed off to the rest of the house.
- Common spaces should be well ventilated (often done by keeping windows open at all times).
- The patient should be encouraged to spend time outside in a shaded area if weather permits.

**Personal protective measures**

- If smear-positive or not responding to the regimen, the patient should wear surgical masks when in contact with persons in areas poorly ventilated. Once smear-negative, the patient can be considered non-infectious and no longer needs to wear masks.
- Any person attending to the patient in enclosed spaces should wear a respirator. A fit test should be performed, and the person should be educated on the proper use of respirators. Once the patient is smear-negative, respirators are no longer necessary.

# Chapter 15: Follow-up of staff exposed to tuberculosis

**15.1 Initial assessment**

**15.2 BCG vaccination**

**15.3 Follow-up**

**Note:** this chapter only provides general recommendations, which should be adapted to the regulations and context of each country.

## 15.1 Initial assessment

New staff entering a TB facility and who will be in contact with potentially contagious patients and/or clinical laboratory specimens must undergo baseline assessment:
In addition, the following information should be provided:

- \textit{M. tuberculosis} occupational transmission;
- TB infection control measures and good practices for preventing transmission;
- Higher risk of active TB in immunocompromised (mainly HIV-infected, diabetics, pregnant women);
- Suggestive symptoms of TB.

Immunocompromised health staff should not work in settings where the risk of exposure to the bacillus is high (Chapter 14).

Pregnant women should not work in TB facilities, or at least should not be exposed to potentially contagious patients.

\section*{15.2 BCG vaccination}

Recommendations vary between countries, with some countries requiring health staff to be BCG vaccinated if never vaccinated and TST negative. There is limited evidence regarding the benefits of BCG vaccination in adults\textsuperscript{[1]} who have previously not had BCG vaccination.

Despite the limited evidence of efficacy, it is generally recommended to vaccinate healthcare personnel with negative TST, particularly in situations with a significant exposure to MDR-TB\textsuperscript{[1]} (facilities treating MDR-TB, prisons or within regions with high prevalence of MDR-TB).

BCG vaccine should only be administered if:

- The person is HIV negative;
- The person is not pregnant\textsuperscript{a};
- The person has previously never had BCG vaccination;
- The person has previously never had active TB;
- The person is TST negative.

Inform the person vaccinated that BCG does not confer complete protection and that tuberculosis may still occur if other protective measures are not used.

Testing for TST response soon after BCG vaccination is not recommended. More information on BCG vaccine is provided in Appendix 29.

\begin{itemize}
\item Determine the BCG immunization status (BCG scar check);
\item Perform a baseline chest x-ray;
\item Perform a baseline tuberculin skin test (TST);
\item HIV testing is strongly recommended.
\end{itemize}

\textbf{Notas}

(a) Pregnancy is not an absolute contra-indication but generally live vaccines should not be administered.

\textsuperscript{[1]}
Referencias


15.3 Follow-up

Follow-up of the staff routinely exposed includes:

- Clinical examination once per year;
- Assessment of TB and HIV for any symptomatic staff;
- Chest x-ray if clinical signs are observed (not routinely).

Staff presenting with a recent risk of an immunocompromised state (HIV infection, immuno-suppressive treatment, etc.) and newly pregnant women should not remain exposed. According to the context and the level of risk, they should be transferred to another department or to the least TB-exposed position (*Chapter 14*).

Long-term (at least 36 months) isoniazid preventive therapy is recommended for all HIV-infected health staff known to be TST-positive, including those who convert from TST-negative to TST-positive (see *Chapter 16* for more information).

Chapter 16: Treatment of latent tuberculosis infection

16.1 Introduction

16.2 Target populations

16.3 Latent tuberculosis infection treatment regimens

16.4 Latent tuberculosis infection in HIV-infected patients

16.5 Latent tuberculosis infection in household contacts

16.6 Latent tuberculosis infection in other individuals at risk

16.7 Latent tuberculosis infection and multidrug-resistant tuberculosis
16.1 Introduction

Exposure to *M. tuberculosis* may result in latent tuberculosis infection (LTBI). WHO defines LTBI as a state of persistent immune response to stimulation by *M. tuberculosis* antigens with no evidence of clinically manifest active tuberculosis (TB)\(^1\). This is also referred to as “tuberculosis infection”.

Identification and treatment of LTBI can reduce TB morbidity and mortality, as well as TB transmission.

Tuberculin skin test (TST) or interferon-gamma release assay (IGRA) can be used to detect LTBI (Chapter 3).

The goal of LTBI treatment is to reduce the risk of progression to active TB. It must be initiated only once active TB has been ruled out by appropriate evaluation.

If a patient develops signs and symptoms of active TB while on LTBI treatment, a specimen should be taken for diagnosis and detection of drug resistance (Xpert MTB/RIF, Xpert MTB/XDR, culture and drug susceptibility test, DST) and according to the results, TB treatment should be initiated.

Referencias

TST or IGRA cannot predict which patients with LTBI are likely to develop active TB. Therefore, widespread LTBI testing and treatment are not recommended.

However, in certain populations, the risk of progression to active TB significantly exceeds that of the general population. For these at-risk populations, the benefits of LTBI treatment of preventing active TB and TB transmission outweigh the potential risks.

Populations who benefit most from LTBI treatment include:

- HIV-infected individuals.
- Household contacts of patients with bacteriologically confirmed pulmonary TB (PTB), in particular children under 5 years.
- Other individuals or populations at risk (e.g. health staff, prisoners).

### 16.3 Latent tuberculosis infection treatment regimens

There are 3 recommended LTBI treatment regimens and 2 alternative treatment regimens[1]. The decision to prescribe one regimen rather than the other should take into consideration:

- Drug-susceptibility of the strain of the presumed source patient, if known.
- Co-morbidities (e.g. HIV infection, pre-existing hepatic disease or neuropathy).
- Risk of drug interactions (especially with antiretrovirals), tolerability, length of treatment and likelihood of adherence.
- Individual characteristics (e.g. age, pregnancy, living conditions, individual preference).
- Epidemiological and programmatic aspects (e.g. HIV prevalence, available drugs, national recommendations).

| Table 16.1 - LTBI treatment regimens |
### Recommended regimens

<table>
<thead>
<tr>
<th>Isoniazid daily for 6 months (6H) or 36 months (36H)</th>
<th>Isoniazid PO once daily:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 30 kg: 10 mg/kg (7 to 15 mg/kg)</td>
</tr>
<tr>
<td></td>
<td>≥ 30 kg: 5 mg/kg (4 to 6 mg/kg)</td>
</tr>
<tr>
<td></td>
<td>(max. dose 300 mg daily)</td>
</tr>
<tr>
<td>OR</td>
<td>Isoniazid + rifapentine weekly for 3 months (3HP)</td>
</tr>
<tr>
<td></td>
<td>Isoniazid PO once weekly:</td>
</tr>
<tr>
<td></td>
<td>&lt; 30 kg and ≥ 2 years: 20 to 30 mg/kg</td>
</tr>
<tr>
<td></td>
<td>≥ 30 kg: 900 mg</td>
</tr>
<tr>
<td></td>
<td>+ Rifapentine PO once weekly:[2]</td>
</tr>
<tr>
<td></td>
<td>10 to 14 kg and ≥ 2 years: 300 mg</td>
</tr>
<tr>
<td></td>
<td>14.1 to 25 kg and ≥ 2 years: 450 mg</td>
</tr>
<tr>
<td></td>
<td>25.1 to 32 kg: 600 mg</td>
</tr>
<tr>
<td></td>
<td>32.1 to 49.9 kg: 750 mg</td>
</tr>
<tr>
<td></td>
<td>≥ 50 kg: 900 mg max.</td>
</tr>
<tr>
<td>OR</td>
<td>Isoniazid + rifampicin daily for 3 months (3HR)</td>
</tr>
<tr>
<td></td>
<td>Isoniazid PO once daily:</td>
</tr>
<tr>
<td></td>
<td>&lt; 30 kg: 10 mg/kg (7 to 15 mg/kg)</td>
</tr>
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<tr>
<td></td>
<td>(max. dose 300 mg daily)</td>
</tr>
<tr>
<td></td>
<td>+ Rifampicin PO once daily:</td>
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<tr>
<td></td>
<td>&lt; 30 kg: 15 mg/kg</td>
</tr>
<tr>
<td></td>
<td>≥ 30 kg: 10 mg/kg</td>
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<tr>
<td></td>
<td>(max. dose 600 mg daily)</td>
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</tbody>
</table>

### Alternative regimens

<table>
<thead>
<tr>
<th>Isoniazid + rifapentine daily for 1 month (1HP)</th>
<th>Isoniazid PO once daily:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥ 13 years: 300 mg</td>
</tr>
<tr>
<td></td>
<td>+ Rifapentine PO once daily:</td>
</tr>
<tr>
<td></td>
<td>≥ 13 years: 600 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OR</th>
<th>Rifampicin daily for 4 months (4R)</th>
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<tbody>
<tr>
<td></td>
<td>Rifampicin PO once daily:</td>
</tr>
<tr>
<td></td>
<td>&lt; 30 kg: 15 mg/kg</td>
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<tr>
<td></td>
<td>≥ 30 kg: 10 mg/kg</td>
</tr>
<tr>
<td></td>
<td>(max. dose 600 mg daily)</td>
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</tbody>
</table>
16.3.1 Isoniazid monotherapy

Isoniazid monotherapy (or isoniazid preventive therapy, IPT) is the treatment currently most often used for LTBI. This treatment has proven to be effective in preventing active TB in both HIV-infected and non-HIV-infected patients\textsuperscript{3,4}. WHO recommends this treatment in all patients regardless of their HIV status, including children of any age and pregnant women.

The main disadvantage of isoniazid monotherapy is the length of treatment. Patients are usually healthy and may not be motivated to complete a 6-month therapy. Adverse effects (e.g. peripheral neuropathy, hepatotoxicity) can also lead to treatment interruption. All patients at risk of peripheral neuropathy should receive pyridoxine (vitamin B\textsubscript{6}) for the entire duration of treatment to prevent this risk (for doses see Appendix 17).

In HIV-infected patients, the treatment may be difficult due to additive adverse effects of antiretrovirals and isoniazid, the extending of the duration of treatment to 36 months in some adolescents and adults (Section 16.4.2) and the high number of tablets to be taken daily. The number of tablets can be reduced using a fixed-dose combination (FDC) of isoniazid/cotrimoxazole/pyridoxine.

16.3.2 Rifapentine-containing regimens

Combination isoniazid-rifapentine once weekly for 3 months (3HP)

This treatment has proven to be effective in preventing active TB in both HIV-infected and non-HIV-infected patients. WHO recommends this treatment in children 2 years and over, adolescents and adults, regardless of their HIV status.

It is short, requires few doses, has a high completion rate and the risk of hepatotoxicity is low\textsuperscript{5,6}. The disadvantages of this regimen are the lack of FDC and the development of hypersensitivity reaction in almost 4% of patients\textsuperscript{4} (Section 16.8.3).

Combination isoniazid-rifapentine once daily for 1 month (1HP)

This treatment has proven to be effective in preventing active TB in HIV-infected patients. WHO recommends this treatment as an alternative regimen in patients 13 years and over, regardless of their weight and HIV status.

The treatment is short, has a high completion rate and the risk of hepatotoxicity is low\textsuperscript{7}. However, cutaneous reactions (rash, itching) are common.

Rifapentine containing regimens are not currently recommended for pregnant women. Despite some reassuring data\textsuperscript{8}, safety is not definitively established.

16.3.3 Rifampicin-containing regimens

Combination isoniazid-rifampicin once daily for 3 months (3HR)
This treatment has proven to be effective in preventing active TB in both HIV-infected and non-HIV-infected patients. WHO recommends this treatment in all patients regardless of their HIV status, including children of any age and pregnant women. It is short, safe, has a good completion rate and FDC are available for children and adults. Hypersensitivity reaction may occur in approximately 2% of patients.

**Rifampicin monotherapy once daily for 4 months (4R)**

This treatment has proven to be effective in preventing active TB in non-HIV-infected patients of all ages. WHO recommends this regimen as an alternative regimen in all patients regardless of their HIV status, including children of any age and pregnant women. The advantages of this regimen (better safety profile and completion rate compared to 6H) should be weighed against the risk associated with use of rifampicin in monotherapy (development of resistance to rifampicin in patients with undiagnosed active TB).

**Notes on rifamycin-containing regimens:**
- Rifapentine and rifampicin have interactions with many drugs, particularly antiretrovirals (Appendix 19) and contraceptives (Chapter 9).
- For pregnant women taking rifampicin, administer phytomenadione (vitamin K) in the last few weeks of pregnancy (Chapter 9).
- Rifapentine and rifampicin are not interchangeable.
- Rifabutin can replace rifampicin if rifampicin cannot be used due to drug interactions.

**Referencias**


16.4 Latent tuberculosis infection in HIV-infected patients

Treatment of LTBI reduces the risk of active TB by 33-64% [1].

For patients not yet on antiretroviral treatment (ART), ART initiation should take priority over initiation of LTBI treatment.

Among these patients, there is a high proportion of undiagnosed, asymptomatic TB cases and it is important to use all existing diagnostic means to rule out active TB.

**Note:** a treatment programme for LTBI should be combined with a screening programme for active TB in HIV-infected patients (Chapter 6).

16.4.1 Children

HIV-exposed children and HIV-infected children and who do not have active TB (for evaluation, see Chapter 5) should receive LTBI treatment:

- After contact with a TB case, including smear-positive, smear-negative and extrapulmonary TB (EPTB), regardless of their age;
- In high TB transmission areas: if aged 12 months and over, regardless of their contact history.


In addition, for children treated for active TB and living in high TB transmission areas, LTBI treatment may also be prescribed immediately after the successful completion of TB treatment to reduce the risk of reinfection.

16.4.2 Adolescents and adults

HIV-infected adolescents and adults who do not have active TB should receive LTBI treatment, regardless of contact history and TB prevalence in the area. In areas with high TB transmission, HIV-infected adolescents and adults with a LTBI test positive or unknown and who are unlikely to have active TB (no cough, no fever, no weight loss, no night sweats) should receive the treatment for at least 36 months (long-term regimen). This regimen is more effective in preventing TB in HIV-infected adults with a positive TST than those with a negative TST [2].

If TST is not feasible, or where the national guidelines do not recommend long-term isoniazid monotherapy, HIV-infected adolescents and adults without any TB symptoms should receive another LTBI treatment (6H or a rifapentine- or rifampicin-containing regimen).

Table 16.2 – LTBI treatments for HIV-infected patients

<table>
<thead>
<tr>
<th>Age</th>
<th>Recommended regimens</th>
<th>Alternative regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child &lt; 2 years</td>
<td>6H or 3RH</td>
<td>4R</td>
</tr>
<tr>
<td>Child ≥ 2 years</td>
<td>6H or 3HP or 3RH</td>
<td>4R</td>
</tr>
<tr>
<td>Adolescent and adult</td>
<td>6H or 3HP or 3RH or 36H</td>
<td>1HP (if ≥ 13 years) or 4R</td>
</tr>
</tbody>
</table>

Notas

(a) HIV-exposed children are children born to HIV-infected women whose HIV status has not been established and/or are still at risk of infection (e.g. still breastfed).

Referencias


16.5 Latent tuberculosis infection in household contacts

A household contact is a person who has shared the same enclosed living space as the index case for one or more nights or for frequent or extended daytime periods during 3 months before the start of the current treatment\textsuperscript{[1]}.

16.5.1 Neonates of mothers with active pulmonary tuberculosis

All neonates born to mothers with active PTB should receive treatment for LTBI, after exclusion of active TB, if the mother:

- Has been treated for PTB less than 2 weeks at the time of birth, or
- Has a positive smear microscopy result on a sputum sample collected at birth or close to the time of birth\textsuperscript{[2]}.

A test Xpert MTB/RIF and Xpert MTB/XDR should be performed to rule out resistance to rifampicin and isoniazid before starting LTBI treatment.

The recommended regimens are 3HR or 6H. For HIV-exposed neonates receiving nevirapine, only 6H is recommended.

BCG vaccine should be administered just after LTBI treatment completion (not during the treatment).

If a TST is feasible and the regimen chosen is 6H:

- Administer isoniazid for 3 months, then perform a TST.
- If the TST is positive, complete isoniazid monotherapy.
- If the TST is negative, stop isoniazid and administer the BCG vaccine.

Notes:

- A neonate should not be separated from its mother unless severely ill.
- Breastfeeding should continue, and breastfed neonates should receive pyridoxine (vitamin B\textsubscript{6}).

16.5.2 Other household contacts

Children under 5 years

It is not mandatory to perform TST or IGRA prior to LTBI treatment.

All children < 5 years in contact with a confirmed PTB case and who do not have active TB (for evaluation, see Chapter 5) should receive LTBI treatment, regardless of their HIV and BCG vaccination status.

If LTBI treatment is contra-indicated or in case of parental refusal, monitor the child closely for one year to enable the early detection of active TB.
Children 5 years and older, adolescents and adults

A TST or IGRA should be performed prior to LTBI treatment. If this is not feasible, LTBI treatment may be considered, weighing benefits and risks.

- Children 5 years and over in contact with a confirmed PTB case and who do not have active TB (for evaluation, see Chapter 5) may receive LTBI treatment, regardless of their HIV status.
- Adolescents and adults in contact with a confirmed PTB case and who do not have active TB (no TB symptoms and no abnormality on CXR) may receive LTBI treatment, regardless of their HIV status.

Table 16.3 - LTBI regimens for household contacts

<table>
<thead>
<tr>
<th>Age</th>
<th>Recommended regimens</th>
<th>Alternative regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child &lt; 2 years</td>
<td>6H or 3RH</td>
<td>4R</td>
</tr>
<tr>
<td>Child ≥ 2 years and &lt; 5 years</td>
<td>6H or 3HP or 3RH</td>
<td>4R</td>
</tr>
<tr>
<td>Child ≥ 5 years, adolescent, adult</td>
<td>6H or 3HP or 3RH</td>
<td>1HP (if ≥ 13 years) or 4R</td>
</tr>
</tbody>
</table>

Referencias


16.6 Latent tuberculosis infection in other individuals at risk

Routine LTBI testing (TST or IGRA) and treatment after exclusion of active TB:
Latent tuberculosis infection and multidrug-resistant tuberculosis

Due to limited evidence, routine LTBI treatment for all household contacts of multidrug-resistant TB (MDR-TB) patients cannot be recommended at this time.

However, treatment of LTBI should be considered in certain high-risk household contacts based on an individual risk-benefit assessment.

Individual assessment includes:

- High risk of progression to active TB: children under 5 years, individuals with HIV infection or on immunosuppressive therapy.
- Resistance pattern of the source case: the LTBI treatment regimen must be individually tailored as contacts of MDR-TB patients are often infected with the same strain\(^1\).
- Intensity of exposure.
- Contra-indication or risk of adverse drug reactions.

A TST or IGRA should be performed prior to LTBI treatment. If not feasible, LTBI treatment may be considered, weighing benefits and risks.

16.7.1 Household contacts of multidrug-resistant tuberculosis cases eligible for treatment

Evidence is lacking on the choice of treatment to prevent disease in MDR-TB contacts. Few observational studies, primarily using a fluoroquinolone (FQ) for 6 months, reported promising results\(^2\)\(^3\). Randomized clinical trials are ongoing\(^4\)\(^5\).

For contacts of FQ-susceptible MDR-TB patients, **levofloxacin** PO for 6 months can be proposed at the following doses:
If active TB develops during LTBI treatment, DST including resistance to FQs is necessary due to the potential risk associated with use of FQs in monotherapy (development of resistance to FQs in patients with undiagnosed active TB).

Independent of LTBI treatment, monitor these patients for 2 years for the development of active TB.

### 16.7.2 Household contacts of multidrug-resistant tuberculosis cases not eligible for treatment

If the contact is not eligible for LTBI treatment, closely monitor for signs and symptoms of active TB every 3 months for the next 2 years.

If active TB develops, initiate TB treatment promptly with a regimen designed according to the DST. If DST is not feasible, a regimen can be designed according to the resistance profile of the source case.

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**Referencias**


5. Tuberculosis child multidrug-resistant preventive therapy: TB CHAMP trial. [https://doi.org/10.1186/ISRCTN92634082](https://doi.org/10.1186/ISRCTN92634082)
16.8 Follow-up for patients treated for latent tuberculosis infection

For the modality of administration of LTBI treatments see Chapter 13.

16.8.1 Baseline assessment of liver function

Before initiating LTBI treatment, look for clinical signs of hepatic disease and specific risks of hepatotoxicity.

For patients with hepatic disease, baseline liver function tests (LFTs), i.e. aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin should be performed. The benefit of LTBI treatment should be weighed against the potential risk of aggravation of existing hepatic disease. LTBI treatment is contra-indicated in patients with end-stage hepatic disease or LFTs > 5 times the upper limit of normal (ULN) and should be used with caution in patients with LFTs > 3 times ULN\(^1\).

Depending on available resources, baseline LFTs can be performed in groups at risk for hepatotoxicity (e.g. patients with HIV infection, women during pregnancy and post-partum period, chronic alcohol consumption, age > 35 years, concomitant use of hepatotoxic drugs, history of hepatic disease).

16.8.2 Follow-up

All patients should be evaluated monthly for signs and symptoms of active TB, adverse effects and adherence.

TST or IGRA should not be repeated.

In patients with pre-existing hepatic disease:

- Baseline LFTS are normal: monitor LFTs monthly.
- Baseline LFTs are elevated or LFTs increase during LTBI treatment: monitor LFTs once a week\(^2\).

Other patients should be tested if they develop symptoms of hepatotoxicity.

Any problems with adherence should be addressed with the patient.

If signs and symptoms of active TB develop, the patient should undergo full evaluation (Chapter 3, Chapter 4 and Chapter 5).

16.8.3 Management of adverse effects

Hepatotoxicity
Clinical features resemble that of viral hepatitis. Early symptoms include malaise, fatigue, loss of appetite, muscle and joint pain. Nausea, vomiting and abdominal pain are common in severe disease. Jaundice, scleral icterus, dark (tea-coloured) urine and discoloured stool are signs of clinical worsening. Clinical hepatitis can be fatal, so action should be taken immediately.

- Patient with symptoms of hepatitis:
  Stop all TB drugs and perform LFTs:
  a) AST or ALT or bilirubin ≥ 3 times ULN or severe symptoms: do not re-initiate LTBI treatment.
  b) AST, ALT, and bilirubin < 3 times ULN and mild symptoms (no jaundice): after discussion with the patient on benefits and risk, treatment may be re-initiated. Closely monitor the patient and perform LFTs once a week. Continue treatment as long as LFTs levels remain < 3 ULN and there are no signs of worsening hepatitis.
  c) If LFTs are not available, do not re-initiate LTBI treatment.

- Patient without symptoms of hepatitis, but elevated LFTs:
  a) AST or ALT ≥ 5 times ULN or bilirubin ≥ 3 ULN: stop and do not re-initiate LTBI treatment.
  b) AST and ALT < 5 times ULN and bilirubin < 3 ULN: stop LTBI treatment. Perform LFTs once a week. If LFTs return to normal, after discussion with the patient on benefits and risk, treatment may be re-initiated. Closely monitor the patient and perform LFTs once a week.

**Note:** 10-20% of patients taking isoniazid alone may have a mild, transient, asymptomatic elevation of LFTs (AST and/or ALT). In most cases, this does not require treatment interruption.

**Hypersensitivity reaction**

Approximately 2% of patients on 3HR regimen and 4% of patients on 3HP regimen have hypersensitivity reaction, typically after the first 3 to 4 doses[^3]. Symptoms may include fever, headache, dizziness, nausea and vomiting, muscle and bone pain, rash, itching, red eyes, angioedema, shortness of breath and, more rarely, hypotension and altered consciousness.

In case of hypersensitivity reaction, treatment should be stopped immediately. Symptoms usually resolve within 24 hours after TB drug withdrawal. In case of mild reaction (fever, rash, itching), consider re-initiating the treatment. In this case, the patient should be observed at least 4 hours after each dose is administered to detect first signs of hypersensitivity reaction.

**Other adverse effects**

See Appendix 17.

**Referencias**

Chapter 17: Monitoring and evaluation

17.1 Introduction

Monitoring and evaluation rely on both quantitative and qualitative information in order to provide information on the following:

- Programme performance (e.g. number of patients started on anti-TB treatment, treatment results, number of patients tested for MDR-TB, etc.);
- Planning for human resources, patient support, diagnostic tests and drug orders, etc.;
- Evaluation of the functioning of the programme (quality of drugs, diagnostics, patient support, etc.).

Recording and reporting are based on a set of standard case and outcome definitions.

Case definitions are presented in Chapter 7.

17.2 Definitions of treatment outcomes
For all forms of TB, outcome definitions have many similarities. These are:
- Outcome assignment is standardized, as to permit comparisons across clinicians, time and sites.
- Outcome assignment relies heavily, but not exclusively, on bacteriologic endpoints (smear or culture).
- Outcomes are mutually exclusive and exhaustive.

For all forms of TB, definitions exist for:
- Interim outcomes (intended to have an indication on how the programme is functioning before final outcomes are available);
- Final outcomes (cure, completion, failure, treatment interruption, death or not evaluated).

### 17.2.1 Interim outcomes for drug-susceptible TB and MDR-TB

Given that TB treatment is long (6 to 18 months or more), interim outcomes provide early indicators of programme results. Table 17.1 provides a summary on interim outcomes.

<table>
<thead>
<tr>
<th>TB</th>
<th>Interim outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-susceptible TB</td>
<td>At 2-3 and 4-5 months:</td>
</tr>
<tr>
<td></td>
<td>• Bacteriological status (smear negative/positive/no information)</td>
</tr>
<tr>
<td></td>
<td>• Final outcomes in patient who had already interrupted or died</td>
</tr>
<tr>
<td>MDR-TB</td>
<td>At 6 months:</td>
</tr>
<tr>
<td></td>
<td>• Bacteriological status (negative/positive/no information) based on smear and culture</td>
</tr>
<tr>
<td></td>
<td>• Final outcomes in patient who had already interrupted or died</td>
</tr>
</tbody>
</table>

### 17.2.2 Final outcomes for drug-susceptible TB and DR-TB

Table 17.2 provides definitions for the final outcomes.

Table 17.2 - Summary table of final outcome definitions[1][2]
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>TB</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DS TB</td>
<td>Patient initially bacteriologically confirmed (microscopy, culture or molecular test) who completed treatment AND shows no signs of continued active disease AND has at least 2 negative smears or cultures: one at 4-5 months and the other at the end of treatment AND does not meet the definition of failure.</td>
</tr>
<tr>
<td>Cured</td>
<td>PDR-TB</td>
<td>Patient initially bacteriologically confirmed (culture or molecular test), who completed treatment AND has been consistently culture-negative with at least 3 results on sputum tested at least one month apart for the final 6 months of treatment AND does not meet the definition of failure.</td>
</tr>
<tr>
<td></td>
<td>MDR-TB</td>
<td>Patient initially bacteriologically confirmed (culture or molecular test), who completed treatment AND with at least 3 negative cultures in the last 8 months of treatment AND does not meet the definition of failure. If there is a lone positive culture or smear reported during that time, and no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of 3 consecutive negative cultures taken at least 30 days apart.</td>
</tr>
<tr>
<td>Completed</td>
<td>All</td>
<td>Patient who completed treatment AND has no signs of continued active disease AND does not meet the bacteriological criteria for cure.</td>
</tr>
<tr>
<td>Failure</td>
<td>DS TB</td>
<td>Patient with signs of continued active disease or deterioration requiring a treatment change: • Any patient with positive smear or culture at 4-5 months of treatment or thereafter. • Any patient with no significant clinical improvement, no significant gain of weight after 4-5 months of treatment and for whom the diagnosis of failure is established by a clinician.</td>
</tr>
<tr>
<td></td>
<td>DR-TB (a)</td>
<td>Treatment terminated or need for permanent treatment change of at least 2 classes of anti-TB drugs because of one or more of the following:</td>
</tr>
<tr>
<td></td>
<td>(b) (c)</td>
<td></td>
</tr>
</tbody>
</table>
If treatment is continuing at the time of a cohort analysis, an outcome of “still on treatment” may be provisionally assigned.

### Treatment Outcomes

<table>
<thead>
<tr>
<th>Category</th>
<th>Regimen</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interrupted</strong></td>
<td>All</td>
<td>Patient who interrupted treatment for 2 months or more.</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>All</td>
<td>Patient who died on TB treatment or while awaiting TB treatment, irrespective of the cause of death. The cause of death should be recorded.</td>
</tr>
<tr>
<td><strong>Treatment adapted</strong></td>
<td>DS TB</td>
<td>Patient initially treated with a standard regimen and for whom the treatment is secondarily adapted according to the results of DST (and not because of a treatment failure).</td>
</tr>
<tr>
<td><strong>Not evaluated</strong></td>
<td>All</td>
<td>Patient whose treatment outcome is unknown (including patients “transferred out” to another treatment centre, for whom the outcome is unknown).</td>
</tr>
</tbody>
</table>

(a) A patient registered as “failure” can be re-registered as DR-TB “previously treated 2nd line” and started again on a new regimen if possible.

(b) This category does not include the changing of one drug due to an adverse effect or a temporary cessation of drugs in order to manage severe adverse event.

(c) If a patient was defined as a “failure”, and no appropriate treatment was possible, but the treatment was continued and the patient subsequently interrupted the treatment or died, the outcome is “failure” (the first outcome is recorded).

(d) For programmes that report using the WHO’s mutually exclusive six outcomes, the “treatment adapted” outcome can be added to failures for reporting purposes, but should also be kept track of separately for good programmatic monitoring and evaluation.

(e) Not applicable for DR-TB.

If treatment is continuing at the time of a cohort analysis, an outcome of “still on treatment” may be provisionally assigned.

**Notas**

(a) Molecular techniques are not used to monitor treatment response or to declare failure. These tests may...
identify dead bacilli for a long time and can even be positive after a patient is truly cured.

Referencias


   http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf

17.3 Recording tools

Forms used in recording and reporting can be found in the appendices. They are intended to be examples that programmes or country can use to produce their own forms.

17.3.1 Drug-susceptible TB treatment card and drug-susceptible TB register

Drug-susceptible TB treatment card and drug-susceptible TB register (Appendix 23 and Appendix 24) are used for all new patients or previously treated patients treated by standard first-line regimens (with or without confirmation of the drug susceptibility by a DST).

17.3.2 DR-TB treatment card and DR-TB register

DR-TB treatment card (Appendix 25) tracks, in particular, each dose of each drug taken during the full course of treatment. The number of actually observed doses and the number of expected observed doses are reported each month. In addition to the treatment card, it is recommended to keep a medical chart with a full admission note at the time of enrolment and a progress note at each medical encounter.

DR-TB register (Appendix 26) includes data on case definition, bacteriological exams (indicate date of specimen collection and not the date of result), type of treatment and treatment outcome. It is a separate register from the drug-susceptible TB register.

Each DR-TB patient detected should be registered, including patients who refuse treatment.

Transfer of patients from the drug-susceptible TB register to the DR-TB register is done usually while on treatment when DST results are available. Patient’s outcome is reported as ‘treatment adapted’ in the comment row of the drug-susceptible TB register (Appendix 24).

17.3.3 Laboratory request form(s) and register(s)
17.3.4 Drug-O-Gram

The Drug-O-Gram is a summary of the patient’s treatment history. It includes consecutive DST and treatment changes presented in a chronological order and gives a short summary of the patient status (Appendix 31).

17.4 Reporting

The key evaluation tool for all forms of TB is the periodic report. It must be presented in a standardized manner in two parts: case enrolment and treatment outcomes. The data presented in the report comes from the TB register. It is generally completed by quarter for drug-susceptible TB and by semester for DR-TB.

Evaluation of interim and final treatment outcomes is a fundamental stage in the evaluation. This evaluation is done through a cohort analysis. A "cohort" is a group of individuals presenting certain common characteristics and undergoing the same events. In respect to the evaluation of TB patients, a cohort is represented by patients all put under treatment within a given period of time (usually a quarter for drug-susceptible TB and a semester for DR-TB). At the end of treatment, a final outcome is assigned to each patient (Table 17.1).

Notes:
- The number of patients in each group should, in principle, be identical to those registered for the same interval in the case enrolment part of the corresponding periodic report. If it is different, an explanation should be given (e.g., patients “interrupting before treatment” can be excluded from the outcome analysis).
- The outcomes of patients "transferred in" should not be included in the outcomes of the facility to which they were transferred. Their outcome results should be recorded in the facility that initially enrolled the patient in TB treatment.

17.4.1 Case detection and enrolment report for TB

The elements necessary for defining a TB case (treatment history, bacteriological status, anatomical site of the disease, and HIV status) are defined in Chapter 7.

See Quarterly report for case enrolment, Appendix 32.

Main indicators
- Proportion of confirmed pulmonary TB (PTB)
  \[= \text{Number of PTB cases confirmed enrolled}/ \text{Total number of TB cases enrolled for the period}\]
With the introduction of automated molecular tests and rapid cultures, it is expected that the proportion of confirmed PTB cases will increase as compared to programmes where only smear microscopy is available.

- **Proportion of smear-negative PTB**
  \[ \text{Proportion of smear-negative PTB} = \frac{\text{Number of smear-negative PTB cases enrolled}}{\text{Total number of TB cases enrolled for the period}} \]
  This indicator essentially depends on the following: the quality of microscopy, the number of children under treatment (children are rarely smear-positive), the prevalence of HIV infection within the population (these patients present more smear-negative PTB), and the other diagnostics used (culture, Xpert MTB/RIF, etc).
  The proportion of smear-negative PTB is about 20% when HIV prevalence is low. It is 40 to 60% when HIV prevalence is high. Proportions that differ significantly from these should make one consider the possibility of under- or over-diagnosis of smear-negative forms.

- **Proportion of smear-positive PTB**
  \[ \text{Proportion of smear-positive PTB} = \frac{\text{Number of smear-positive PTB cases enrolled}}{\text{Total number of TB cases enrolled for the period}} \]
  In practice, the proportion of smear-positive PTB should correspond to roughly half of all patients. This proportion is lower, however, in areas where HIV prevalence is high. Proportion of smear-positive PTB is around 60% where HIV prevalence is low, and it is 30 to 40% where HIV prevalence is high. Proportions that differ significantly from these should make one consider the possibility of under- or over-diagnosis of smear-negative pulmonary TB and extra-pulmonary B forms.

- **Proportion of new cases**
  \[ \text{Proportion of new cases} = \frac{\text{Number of new TB cases enrolled}}{\text{Total number of cases enrolled for the period}} \]
  This indicator indirectly reflects the relapse and failure rates and possible parallel treatments outside the programme.

- **Proportion of children**
  \[ \text{Proportion of children} = \frac{\text{Number of TB patients less than 15 years enrolled}}{\text{Total number of TB cases enrolled for the period}} \]
  Children should represent approximately 10 to 15% of the total number of patients. Proportions that differ significantly from these should make one consider the possibility of under- or over-diagnosis of TB in children.

- **Proportion of detected cases enrolled under treatment**
  \[ \text{Proportion of detected cases enrolled under treatment} = \frac{\text{Number of cases enrolled under treatment}}{\text{Total number of cases detected for the period}} \]
  Patients enrolled are counted from the TB register. Patients detected are counted from the laboratory register and include patients who “interrupted before treatment”.

- **Case detection rate**
  \[ \text{Case detection rate} = \frac{\text{Number of new smear-positive PTB cases detected}}{\text{Expected number of smear-positive PTB cases for the period}} \]
  A rough estimate of the expected number of new smear-positive cases can be obtained using the estimated TB incidence given by the WHO in the country profile, which allows an estimate of detection efficacy.
Note: even the best programmes often do not detect more than 60 to 70% of expected new smear-positive cases within a population. In addition, patients might come from outside the target area.

17.4.2 Case detection and enrolment report for DR-TB

See standard DR-TB case detection and enrolment reports in Appendix 33.

Early detection of resistance is intended to ensure that an appropriate treatment is initiated from the start. DST is usually performed for patients at risk of DR-TB. Target groups vary according to local situation, but should at a minimum always include patients who have been previously treated and contacts of confirmed MDR-TB patients.

The indicators for detection aim at measuring the access of TB patients to DST. The frequency of MDR-TB among individuals in different risk groups is also evaluated.

All patients in whom DR-TB is highly suspected or detected should be started on appropriate treatment in the shortest time possible.

A comparison of enrolled patients under treatment to detected DR-TB cases gives an indication of access to care, though some patients started on treatment may have been detected prior to the period of assessment.

The period of assessment is six calendar months. This is usually counted from January to the end of June and July to the end of December. Indicators are measured three months after the end of the six-month period. All data can be extracted from the DR-TB register (Appendix 26), the laboratory register for culture and DST and the Xpert register (Appendix 30).

Each indicator should be calculated for all patients and for each risk group of patients, including: all cases, previously treated cases, failures, household contacts and other local risk groups according to the strategy.

Case detection indicators

- Proportion of TB patients detected with DST result for isoniazid and rifampicin (for each risk group during the period)  
  \[ \text{Proportion} = \frac{\text{Number of TB cases detected with DST result for both isoniazid and rifampicin}}{\text{Total number of TB cases detected}} \]

- Proportion of TB patients detected with Xpert MTB/RIF result (for each risk group during the period)  
  \[ \text{Proportion} = \frac{\text{Number of TB cases detected with Xpert MTB/RIF result}}{\text{Total number of TB cases detected}} \]

- Proportion of confirmed MDR-TB cases detected among TB patients tested for isoniazid and rifampicin DST (for each risk group during the period)  
  \[ \text{Proportion} = \frac{\text{Number of TB cases with confirmed resistance to isoniazid and rifampicin}}{\text{Total number of TB cases tested for these 2 drugs}} \]

- Proportion of Xpert RIF resistant cases detected among patients tested by Xpert MTB/RIF (for each risk group during the period)  
  \[ \text{Proportion} = \frac{\text{Number of Xpert RIF resistant cases}}{\text{Total number of TB cases with Xpert MTB/RIF result}} \]
Enrolment indicators

- Proportion of confirmed MDR-TB cases enrolled on MDR-TB treatment
  \[= \frac{\text{Number of confirmed MDR-TB cases registered and started on MDR-TB treatment}}{\text{Total number of confirmed MDR-TB cases detected}}\]
  This can also be calculated for rifampicin resistant TB cases.

- Proportion of confirmed PDR-TB cases enrolled on PDR-TB treatment
  \[= \frac{\text{Number of confirmed PDR-TB cases registered and started on PDR-TB treatment}}{\text{Total number of confirmed PDR-TB cases detected}}\]
  This calculation does not include rifampicin resistance and unknown isoniazid resistance.

17.4.3 Interim treatment outcomes for drug-susceptible TB and DR-TB

Interim analysis should be completed approximately 3 months after all patients who were registered during a particular interval completed the intensive phase of treatment (three months should allow culture results for all those patients).

Interim treatment outcomes for drug-susceptible TB

Interim results at Month 2 or 3 should be evaluated for all patients treated as new or previously treated patients by standard first-line regimens (with or without confirmation of the drug susceptibility by a DST). These results may be disaggregated by treatment history (new, previously treated, and by type of previous treatment).

At the beginning of a programme, when it is not yet possible to do cohort analysis, the conversion rate at Month 2-3 is a proxy indicator of the effectiveness of treatment, and it allows early detection of potential problems. The smear conversion rate of new smear-positive patients is the proportion of new smear-positive patients who are smear-negative at Month 2. The smear conversion rate of previously treated smear-positive patients is the proportion of previously treated smear-positive patients who are smear-negative at Month 3.

Interim treatment outcomes for DR-TB

The period of assessment is six calendar months, usually counted from January to end June, July to end December. All patients registered and starting treatment during the period of assessment are included in the calculation. The interim report form should be completed 9 months after the closing day of the cohort. This allows culture information at 6 months of treatment to be included for all patients in the cohort. For instance, interim results of TB patients who started treatment during the first semester of a year (1 January to 30 June), should be calculated at the beginning of April of the following year.

Culture conversion (for confirmed DR-TB cases) and death by six months are used as proxies for final outcomes. Information on treatment interruption by six months is helpful. It is also useful to know how many patients started on second-line drugs for MDR-TB turned out not to be MDR.

All data can be extracted from the DR-TB register (Appendix 26).
At six months:

- **Proportion of death**
  \[\text{Proportion of death} = \frac{\text{Number of confirmed MDR-TB cases registered and started on MDR-TB treatment who died of any cause by the end of Month 6}}{\text{Total number of confirmed MDR-TB cases started on treatment for MDR-TB during the period}}\]

- **Proportion of treatment interrupted**
  \[\text{Proportion of treatment interrupted} = \frac{\text{Number of confirmed MDR-TB cases started on MDR-TB treatment who interrupted by the end of Month 6}}{\text{Total number of confirmed MDR-TB cases started on treatment for MDR-TB during the period}}\]

- **Proportion with negative culture**
  \[\text{Proportion with negative culture} = \frac{\text{Number of bacteriologically confirmed pulmonary MDR-TB cases registered and started on MDR-TB treatment with negative culture at Month 6}}{\text{Total number of bacteriologically confirmed pulmonary MDR-TB cases registered and started on treatment for MDR-TB during the period}}\]

- **Proportion with positive culture**
  \[\text{Proportion with positive culture} = \frac{\text{Number of bacteriologically confirmed pulmonary MDR-TB cases registered and started on MDR-TB treatment with positive culture at Month 6}}{\text{Total number of bacteriologically confirmed pulmonary MDR-TB cases registered and started on treatment for MDR-TB during the period}}\]

- **Proportion found not to have MDR-TB**
  \[\text{Proportion found not to have MDR-TB} = \frac{\text{Number of patients started on MDR-TB treatment during the period and later found not to be MDR}}{\text{Total number of patients started on MDR-TB treatment during the period}}\]

17.4.4 Final treatment outcomes for TB

See standard TB treatment outcomes reports ([Appendix 32](#) and [Appendix 33](#)).

The final outcome is the most important direct measurement of the effectiveness of a TB programme in terms of patient care. All patients entered on the TB register should be assigned one of six mutually exclusive outcomes at the end of their therapy. All patients should be assigned the first outcome they experience for the treatment being evaluated.[1]

Final treatment outcome cohort analysis could be carried out when all patients admitted in a given period of time had a chance to complete their treatment. In practice:

- For drug-susceptible TB (and all patients treated by standard first-line regimens) cohort results are analysed quarterly, one year after inclusion of the last patient of the cohort (e.g. cohort of patients admitted during the first quarter 2014 will be evaluated at the end of the first quarter 2015).
- For DR-TB, evaluation occurs 27 months after inclusion of the last patient in the cohort in order to have the results of cultures performed at 24 months. The period of assessment is six calendar months, usually counted from January to the end of June and July to the end of December. All patients starting treatment during this period are included in the calculation. Indicators are measured 24 months after the end of the semester of assessment. All data can be extracted from the DR-TB register.
Although the timing of the analysis is different for drug-susceptible TB and DR-TB, the indicators are the same.

Indicators should be calculated for patients treated by standard first-line regimens (with or without confirmation of drug-susceptible TB by a DST), and for patients with PDR-TB and MDR-TB. The most important indicators are:

- **Proportion of cured**
  \[ \frac{\text{Number of confirmed TB cases declared “cured”}}{\text{Total number of confirmed TB cases put under treatment during the period}} \]
  This indicator is calculated for all confirmed drug-susceptible TB cases and DR-TB cases. It is the best indicator of the success of a programme for confirmed TB patients. Though the effectiveness of the treatment for drug-susceptible TB is theoretically above 90%, the proportion of cure is rarely above 70%. For MDR-TB this indicator rarely exceeds 50%.

- **Proportion of treatment completed**
  \[ \frac{\text{Number of patients registered as “treatment completed”}}{\text{Total number of patients put under treatment for the period}} \]
  A high proportion of patients completing treatment is a positive sign for not confirmed PTB and EPTB. For confirmed TB, it indicates insufficient bacteriological verification at the end of treatment, thus, suggesting that a step should therefore be reinforced.

- **Proportion with successful outcome**
  \[ \frac{\text{Number of patients registered as “cured” or “treatment completed”}}{\text{Total number of patients put under treatment during the period}} \]
  This is the best indicator to measure the efficacy of a programme for all forms of TB (confirmed and not confirmed, PTB and EPTB). This indicator rarely exceeds 80% for drug-susceptible TB and 60% for MDR-TB.

- **Proportion of treatment interrupted**
  \[ \frac{\text{Number of patients registered as “treatment interrupted”}}{\text{Total number of patients put under treatment during the period}} \]
  Patients who interrupted treatment are at risk of not being cured or of relapsing. Treatment interruption indicates a failure of the programme in supporting the patient to be able to successfully complete treatment.

- **Proportion of death**
  \[ \frac{\text{Number of patients registered as “death”}}{\text{Total number of patients put under treatment during the period}} \]
  This ratio usually does not exceed 5% for drug-susceptible TB. Over-mortality may be related to the poor functioning of a programme. It may also be due to a high prevalence of HIV infection among cases or late referrals.

- **Proportion of failure**
  \[ \frac{\text{Number of patients registered as “failures”}}{\text{Total number of patients put under treatment during the period}} \]
  A high failure rate in new cases can be related to poor treatment adherence, high rate of primary
resistance or poor quality of anti-TB drugs. The failure rate should not be over 2% in new cases under treatment.

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

This is one of the indicators that help evaluate the integration of TB and HIV services.

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

In high HIV-prevalence regions, co-infection rate may exceed 80%. This information is important in assessing other indicators, in particular the proportion of death.


### 17.5 Programme assessment

To be complete, evaluation should look at how well the programme functions, particularly with respect to three aspects: organization of care, established procedures and human resources. A set of quality criteria is evaluated for each of these aspects. The criteria may be either qualitative (description) or quantitative (indicators). The following tables can be used as a rough guide.

### 17.5.1 Organization
<table>
<thead>
<tr>
<th>Criteria</th>
<th>Indicators</th>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Access to care</strong></td>
<td></td>
<td>Easy access to care during the intensive/continuation phases</td>
</tr>
<tr>
<td></td>
<td>• Accessibility of treatment facilities, decentralization, etc.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Home-based treatment available when appropriate.</td>
<td></td>
</tr>
<tr>
<td><strong>Patient comfort</strong></td>
<td></td>
<td>According to needs</td>
</tr>
<tr>
<td></td>
<td>• Patient welcome</td>
<td>• Bed occupancy rate ≤ 100%</td>
</tr>
<tr>
<td></td>
<td>• Condition of the facility, heating (or cooling), overall organization and cleanliness.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Food during hospitalization and/or for outpatients (supplemental rations, quantities, organization in charge).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bed occupancy rate of the TB ward.</td>
<td></td>
</tr>
<tr>
<td><strong>Information and therapeutic education</strong></td>
<td>Patient interviews conducted.</td>
<td>Patient understanding of treatment</td>
</tr>
<tr>
<td><strong>Hospital hygiene</strong></td>
<td>• Equipment (respirators, masks, gloves, gowns, autoclaves, cleaning supplies, etc.)</td>
<td>All necessary equipment is available and used.</td>
</tr>
<tr>
<td></td>
<td>• Waste management (sorting, incinerator, etc.)</td>
<td></td>
</tr>
<tr>
<td><strong>Constant supply of lab materials</strong></td>
<td></td>
<td>3-month buffer stock</td>
</tr>
<tr>
<td></td>
<td>• Supplied by (government, agency or facility, other)</td>
<td>• No shortages</td>
</tr>
<tr>
<td></td>
<td>• Buffer stock</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Number and duration of shortages</td>
<td></td>
</tr>
<tr>
<td><strong>Constant supply of quality-assured anti-TB drugs</strong></td>
<td>• Stock card maintenance</td>
<td>Stock cards up-to-dated</td>
</tr>
<tr>
<td></td>
<td>• Order frequency, delivery time, buffer stock</td>
<td>One person in charge of the pharmacy</td>
</tr>
<tr>
<td></td>
<td>• Shortage(s)</td>
<td>All adequate</td>
</tr>
<tr>
<td></td>
<td>• Drug sources</td>
<td>No shortages</td>
</tr>
<tr>
<td></td>
<td>• Institution in charge of supply</td>
<td>WHO-prequalified sources (or equivalent)</td>
</tr>
<tr>
<td></td>
<td>• Use of FDCs first-line drugs</td>
<td>Use of FDCs</td>
</tr>
<tr>
<td></td>
<td>• Storage conditions</td>
<td>Appropriate storage conditions</td>
</tr>
<tr>
<td></td>
<td>• Organization of supply for peripheral facilities</td>
<td>Regular supply</td>
</tr>
<tr>
<td><strong>Case detection</strong></td>
<td>• Type of case detection (active or passive)</td>
<td>Know the type, in order to</td>
</tr>
</tbody>
</table>
### 17.5.2 Procedures

<table>
<thead>
<tr>
<th>Contacts screening</th>
<th>Detection rate of new smear-positive cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection rate of MDR-TB</td>
<td>interpret the quantitative results of case detection</td>
</tr>
<tr>
<td>Percentage of smear-positive patients out of the total number of patients who had a sputum smear.</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Depends on the context</td>
</tr>
<tr>
<td></td>
<td>&lt; 20%</td>
</tr>
<tr>
<td></td>
<td>Depends on the context</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis of smear-negative PTB and EP forms</th>
<th>Automated molecular test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Culture or molecular techniques</td>
</tr>
<tr>
<td></td>
<td>X-rays</td>
</tr>
<tr>
<td></td>
<td>Others (e.g. ADA, Pandy, Rivalta, FNAC)</td>
</tr>
<tr>
<td></td>
<td>Algorithms used</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DST</th>
<th>DST possible (methods, quality control)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Detection of DR-TB</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment support</th>
<th>Number of patients receiving treatment support/month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100% of those eligible for support</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Identification of non-adherent patients</th>
<th>System for identifying and looking for non-adherent patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Percentage of patients who resumed treatment among those missing for less than 2 months who had to be looked for</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>&gt; 90%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Integrated TB/HIV care</th>
<th>Access to voluntary counselling and testing (VCT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Access to ART</td>
</tr>
<tr>
<td></td>
<td>Access to cotrimoxazole prophylaxis</td>
</tr>
<tr>
<td></td>
<td>HIV treatment integrated in the TB service (or TB treatment in the HIV service)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

---

**Note:** The table above outlines various procedures and their respective methodologies and percentages, ensuring a comprehensive approach to tuberculosis (TB) and multidrug-resistant TB (MDR-TB) management.
<table>
<thead>
<tr>
<th>Criteria</th>
<th>Indicators</th>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registers/records</td>
<td>Description of the documents</td>
<td>Records reliable</td>
</tr>
<tr>
<td></td>
<td>• Consistency between TB registers and treatment cards</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>• Consistency between TB register and lab registers</td>
<td>100%</td>
</tr>
<tr>
<td>Standard case definitions</td>
<td>Percentage of patients with exact case definition out of a randomized sample of patients</td>
<td>100%</td>
</tr>
<tr>
<td>Adequate standard treatment regimens and follow-up</td>
<td>• Percentage of new cases correctly treated (combinations, dosage, duration) out of a randomized sample of patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Percentage of patients who did not have bacteriological follow-up according to schedule out of a randomized sample of patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Percentage of MDR-TB patients who did not have biochemistry tests according to schedule out of a randomized sample of patients</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>HIV testing</td>
<td>Percentage of new cases tested for HIV</td>
<td>100%</td>
</tr>
<tr>
<td>ART</td>
<td>Percentage of HIV-positive TB cases started on ART</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>ART started within:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• &lt; 2 weeks; 2 weeks-&lt; 2 months; ≥ 2 months</td>
<td></td>
</tr>
<tr>
<td>Criteria for cure</td>
<td>Percentage of confirmed cases declared cured who actually met the definition of cure out of a randomized sample of patients</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>Regular monitoring of drug-susceptible TB and DR-TB</td>
<td>• Quarterly report and cohort analysis for drug-susceptible TB</td>
<td>Quantitative data on inclusions and results collected</td>
</tr>
<tr>
<td></td>
<td>• Bi-annual report and cohort analysis for DR-TB</td>
<td>Rapid detection of potential problems</td>
</tr>
<tr>
<td>Adherence</td>
<td>• Percentage of patients coming in for their</td>
<td>&gt; 90% in both the</td>
</tr>
</tbody>
</table>
### 17.5.3 Human resources

<table>
<thead>
<tr>
<th>Monitoring</th>
<th>Description</th>
<th>Intensive and continuation phases</th>
</tr>
</thead>
</table>
|             | appointment out of number of patients expected  
|             | - Percentage of doses given under DOT for DR-TB treatment in a randomized sample of patients | 100% |

| Prevention of *M. tuberculosis* airborne transmission in TB facilities | Isolation  
| Building ventilation, lights, UV lamps (hospital wards, outpatient clinics, laboratory); respirators for staff and visitors in contact with contagious patients; masks for contagious patients (if they move about)  
| Written prevention plan?  
| Person in charge identified? | Isolation of smear positive patients  
| Isolation of DR smear positive patients  
| Appropriate use of means | Yes  
| Yes |

<table>
<thead>
<tr>
<th>Standard precautions</th>
<th>Description</th>
<th>Standard precautions followed</th>
</tr>
</thead>
</table>

| Laboratory quality control | Regular evaluation of laboratory functioning  
| Quarterly EQA of smear microscopy  
| Annual EQA of DST | Ensure the quality of laboratory analyses for bacteriological diagnosis  
| Results according to standards  
| Results according to standards |
A grid for evaluating TB clinic operations can be found in Appendix 35. Each criterion is rated either “satisfactory” or “unsatisfactory”.

### Table: Criteria, Indicators, and Goals

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Indicators</th>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staff</strong></td>
<td>• Job descriptions (doctors, nurses, lab technicians, cleaning staff, etc.)&lt;br&gt;• Medical staff-to-patient ratio</td>
<td>On average: &lt;br&gt;• One nurse for 10-15 patients&lt;br&gt;• One doctor for 40-50 patients</td>
</tr>
<tr>
<td><strong>Training</strong></td>
<td>Refer to training programme evaluation criteria</td>
<td>Competent staff</td>
</tr>
<tr>
<td><strong>Other contributors</strong></td>
<td>Description: other NGOs, local associations, etc.</td>
<td></td>
</tr>
</tbody>
</table>

A grid for evaluating TB clinic operations can be found in Appendix 35. Each criterion is rated either “satisfactory” or “unsatisfactory”.

**Appendices**

- **Appendix 3. Sputum specimen: collection, storage and shipment**
- **Appendix 3. Xpert MTB/RIF**
- **Appendix 4. Sputum smear microscopy**
- **Appendix 6. Adenosine desaminase assay (ADA)**
- **Appendix 7. Lymph node fine needle aspiration**
- **Appendix 7. Ventilated work station (VWS) and bio-safety cabinet (BSC)**
- **Appendix 8. Protein estimation**
- **Appendix 8. Daily dose of anti-TB drugs using FDCs**
  - **Appendix 8a. New paediatric FDCs**
  - **Appendix 8b. Former paediatric FDCs**
- **Appendix 9. Tuberculin skin test**
- **Appendix 10. Tuberculosis drug information sheets and patient instructions**
  - **Tuberculosis drug information sheets**
  - **Amikacin (Am)**
  - **Amoxicillin/clavulanic acid ratio 4:1 (Amx/Clv)**
  - **Clofazimine (Cfz)**
Cycloserine (Cs) or terizidone (Trd)
Ethambutol (E)
Ethionamide (Eto) or prothionamide (Pto)
Imipenem/cilastatin (Ipm/Cln)
Isoniazid - Standard dose (H)
Levofloxacin (Lfx)
Linezolid (Lzd)
Meropenem (Mpm)
Moxifloxacin (Mfx)
Para-aminosalicylic acid (PAS) and sodium salt of PAS
Pyrazinamide (Z)
Rifabutin (Rfb)
Rifampicin (R)
Streptomycin (S)
  Patient instructions
Patients on drug-susceptible TB treatment
Patients on drug-resistant TB treatment
Appendix 11. Compassionate use
Appendix 12. Dose adjustments in renal insufficiency
Appendix 16. Basic TB infection control risk assessment tool
Appendix 17. Management of adverse effects
  Gastrointestinal disorders
Abdominal pain
Diarrhoea
Epigastric pain
Hepatotoxicity
Metallic taste
Nausea and vomiting
  Neurotoxicity
Depression
Headache
Optic neuritis
Ototoxicity
Peripheral neuropathy
Psychosis
Seizures
  Endocrine disorders
Gynecomastia
Hypothyroidism
  Dermatological disorders
Alopecia
Fungal infection
Photosensitivity
Skin reactions
  Musculoskeletal disorders
Arthralgias
Tendinitis/tendon rupture
  Miscellaneous
Electrolyte disorders
Haematologic disorders
Lactic acidosis
Nephrotoxicity
QT prolongation

Appendix 17. Air change per hour (ACH) measurement recommendations
Appendix 18. Advantages and disadvantages of ventilation techniques
Appendix 19. Potential overlapping toxicities of ARVs and anti-TB drugs
Appendix 19. Upper room ultraviolet germicidal irradiation (UVGI) system
Appendix 20. Treatment supporters
Appendix 21. Informing the patient
Appendix 3. Sputum specimen: collection, storage and shipment

3.1 Sputum collection techniques

Regardless the collection technique used, staff member present during sputum collection should wear a respirator to prevent bacilli inhalation.

3.1.1 Sputum obtained spontaneously

Two specimens are to be collected. When possible, specimens should be collected outside in the open air and far away from other people.
The first sample is collected on the spot, at the consultation, when the patient is identified as suspected TB case. If the patient has recently eaten, ask him/her to rinse his/her mouth with water in order to avoid the presence of food in the sample.

The second sample is collected the day after, in the early morning, right after the patient wakes up and before eating. The second sample may be collected at home then the patient brings it to the health facility.

Alternatively, two sputum specimens can be collected one hour apart (frontloaded microscopy).

Collection technique:
- The patient must be given a labelled sputum container (or a Falcon® tube, if the sample is to be shipped by air).
- Have the patient take a deep breath, hold for a few seconds, exhale, repeat two or three times, then cough: sputum is material brought up from the lungs after a productive cough. One or two minutes of chest clapping are of benefit.
- Collect at least 3 ml and close the container hermetically.

The quality of sample determines the reliability of the result. Always check that the sample contains solid or purulent material and not only saliva. Take a new sample if unsatisfactory.

If the sample is collected at home, make sure that the patient has understood the technique, including closing the container hermetically after collecting the sputum.

### 3.1.2 Sputum induction

Sputum induction is sometimes used in children when sputa cannot be spontaneously expectorated, and only in order to perform cultures or Xpert MTB/RIF.

Sputum induction must be performed under close medical supervision. The child should be observed for respiratory distress during, and for 15 minutes after, the procedure. Bronchospasm may occur. Salbutamol spray and oxygen must be ready at hand.

#### Equipment
- Gloves and respirator
- Suction catheter (6, 7, 8F)
- Sputum container
- 50 ml syringe, needle
- Mask and tubing for nebulizer
- Holding chamber with child’s mask (to be sterilized between each patient)
- Sterile hypertonic solution of 5% sodium chloride (to be kept refrigerated)
- Sterile solution of 0.9% sodium chloride (for the specimen)
- Salbutamol spray
- Oxygen

#### Procedure

The child should fast for at least 2 hours before the procedure.
- Prior to nebulization:
Gastric aspiration

Gastric aspiration is sometimes used in children when sputa cannot be spontaneously expectorated nor induced using hypertonic saline, and only in order to perform cultures or Xpert MTB/RIF.

### Equipment
- Gloves and respirator
- Suction catheter (6, 7, 8F)
- Sputum container
- 50 ml syringe
- Sterile water

### Procedure
- Prior to inserting the suction catheter:
  - Explain the procedure to the child and/or the person accompanying him/her (this person must wear a respirator);
  - Place the child in a half-sitting or sitting position in the adult’s arms.
- Insert a nasogastric tube and check that it is correctly placed.
- First suction to collect the gastric fluid and place it in the sputum container, then rinse the stomach with 30 ml of sterile water and suction again. Add the suctioned fluid to the first sample.
• Start culture within 4 hours of collecting the sample. If there will be more than four hours’ delay, neutralize with 100 mg of sodium bicarbonate.

### 3.2 Sputum specimen storage

When examinations are not performed on the site of collection:

#### Specimen for smear microscopy

Smears should be performed within three-four days of collection and in the meanwhile stored refrigerated (2 to 8 °C) and protected from light. Contamination does not affect microscopy but heat make specimen liquefy, with selection of mucopurulent part of the sample more difficult.

#### Specimen for culture in liquid medium

Keep the specimen refrigerated (2 to 8 °C), protected from light. Do not use cethylpyrodinium chloride (CPC) as it is not compatible with MGIT. The specimen should be processed as soon as possible.

#### Specimen for culture on Lowenstein-Jensen medium (LJ)

- Specimens that can be cultured in less than 3 days after collection: Keep refrigerated (2 to 8 °C) and protected from light until transport OR immediately transport to the laboratory for processing.
- Specimens that will be cultured more than 3 days after collection: Use Falcon tubes and add 1% CPC to preserve the specimen for up to 2 weeks. Specimens with CPC should not be refrigerated, as the CPC will crystallize and be ineffective. Samples with CPC can be inoculated on LJ. For inoculation on agar, they require prior neutralization by neutralizing buffer (Difco®). CPC can be used for specimens tested by Xpert MTB/RIF.

### 3.3 Sputum specimen shipment

#### To a local laboratory

- Without CPC transport medium: between 2 and 8 °C and protected from light;
- With CPC transport medium: should not be refrigerated because at low temperatures the CPC will crystallize and ruin the sample. Specimens should be kept at room temperature, protected from heat and light.

#### By air to a reference laboratory for culture

Samples are collected and shipped in 50 ml Falcon® conical tubes with screw caps. The tubes are labelled UN 3373, corresponding to Category B infectious substances. If transport times are less than 12 hours, even specimens without CPC can be transported at room temperature.
Samples are triple-packaged, in accordance with IATA packing instruction 650:
1. Primary container holding the sputum sample: tube tightly closed and placed into a latex glove;
2. Secondary container intended to protect the primary container: leak-proof box with enough absorbent material to absorb the entire sample, should the primary container break;
3. Outer packaging intended to protect the secondary container, with UN 3373 labelling.

Information to be provided:
- Primary container: label with the patient’s name or identification number and the sample collection date and location;
- Outer package: indicate the name of the receiving laboratory, the complete address (name, street, postal code, locality, country), and telephone number.
- All samples must be accompanied by the corresponding laboratory test request form (including clinical information).

Notes:
- Procedures for shipping bacterial strains obtained after culture are different, more complicated, and rarely feasible in practice. Cultures are classified as Category A infectious substances (UN 2814).
- For a detailed description of the shipment procedures, see MSF Medical catalogue, volume 4.

Appendix 3. Xpert MTB/RIF

Xpert MTB/RIF assay is based on hemi-nested real time PCR for simultaneous detection of *M. tuberculosis* (MTB) and rifampicin (RIF) resistance. The target is the rpoB gene, critical for detection of mutations associated to rifampicin resistance.

Xpert MTB/RIF automates all aspects of real time PCR analysis, with results available in 2 hours.

3.1 Sample processing

The test can be performed using fresh sputum samples or decontaminated samples prior culture inoculation.

Procedure with fresh sputum samples

- Ask the patient to rinse the mouth twice before collecting the sample.
- Collect a minimum of 1.5 ml good quality sputum.
- Follow the procedures outlined below:

Procedure for Xpert MTB/RIF*
### Procedure for sediment samples

- Sediments can be prepared according to standard decontamination procedure (NALCNaOH method) and re-suspend with phosphate buffer.
- Ensure 0.5 ml is available for the test; add 1.5 ml of reagent for 0.5 ml of re-suspended sediment.
- Follow the procedure described in the above figure.

### 3.2 Interpretation of the results

Proper test performance is ensured by 2 internal controls:
- Sample processing control (SPC) ensures adequate processing and monitors presence of inhibition.
- Probe check control (PCC) verifies that the steps of the tests (rehydration, filling of the cartridge, etc.) take place correctly.

When the test is completed the display can show:
- “MTB detected” expressed by levels (the higher the level, the higher the amount of MTB detected in the sample) or “MTB not detected”;
- RIF results expressed as “detected”, “not detected” or “indeterminate” are available only if MTB is detected.

Other possible results:
- Invalid: MTB invalid and SPC failed due to one of several reasons, such as inhibition;
- Error: MTB no result, SPC no result, PCC failed; fail of system components;
- No result: e.g. tests stopped during processing.

### 3.3 Storage of samples and cartridges

**Samples**

- Add the reagent 2:1 (v/v) to the sample and shake 10-20 times. Incubate at room temperature for 15 min.; during incubation repeat once shaking for 10-20 times.
- With a pipette transfer the diluted sample into a cartridge.
- Insert the cartridge in the machine and start the test.

*Source: National Health Laboratory Services, South Africa.*
• For a period ≤ 3 days: store at 35 °C maximum. A cold chain is not required for up to 3 days after collection. During this period of time, overgrowth of normal flora does not have negative influence on the test. However, if a cold chain is available, samples should be stored at 2 to 8 °C in order to help their preservation.
• For a period of 4 to 10 days: store refrigerated at 2 to 8 °C. If samples require other testing (i.e. smear microscopy and/or culture), sample storing conditions adequate for microscopy and culture have to be followed. CPC does not interfere with Xpert MTB/RIF testing.

**Cartridges**

• To be stored at 2 to 28 °C.
• The cartridge should be used within 30 minutes of opening the cartridge lid.
• Cartridges are stable for 7 days after opening the packaging.

### 3.4 Logistic requirements

**Power supply**

The device requires stable and uninterrupted power supply. Each GeneXpert instrument will need a uninterruptible power supply (UPS). The minimum requirement for the functioning of the GeneXpert instrument is to have a 800VA UPS.

**Operating temperature**

The operating temperature for GeneXpert instrument device is 15 to 30 °C. According to climate conditions, the installation of air conditioning can be recommended to keep the area within the temperature ranges indicated by the manufacturer.

**Calibration**

The GeneXpert modules require annual calibration, which must be performed by an authorised service provider or carried out by swapping out the modules. A detailed commercial sales contract and customer support plan should be negotiated with the supplier, guaranteeing regular maintenance, calibration, repair and replacement (when needed).

**Cartridges and reagents shelf-life**

12 months from date of production.

**Storage space**

Each kit contains 10 cartridges and all reagents necessary to run 10 tests. The dimensions of the kit are 27 x 20 x 17 cm and the weight is 800 g.

**Lab space**
The GeneXpert IV instrument (4 modules allowing the processing of 4 specimens at the same time) has the following dimensions: 29.8 cm wide, 35.6 cm high, 31.1 cm deep; weight: 12 kg.

It is designed for indoor use only.

Provide at least 5 cm of clearance on each side of the instrument to ensure adequate ventilation.

Do not place the instrument close to the vents of other instruments or air-handling units.

**Safety**

The personal protection requirements for microscopy should be adopted, including use of gloves and respirators.

**Waste disposal**

Same procedure as for sputum containers. To be noted is the large volume of additional waste generated by Xpert MTB/RIF compared to smear microscopy.

**3.5 Predictive values for detection of rifampicin resistance with Xpert MTB/RIF**

Positive predictive value (PPV) is defined as the proportion of subjects with a positive test result who are correctly diagnosed. A high PPV means that when the test yields a positive result, it is most likely correct. Negative predictive value (NPV) is defined as the proportion of subjects with a negative test result who are correctly diagnosed. A high NPV means that when the test yields a negative result, it is most likely correct. PPV and NPV are influenced by the prevalence of disease in the population being tested.

**Predictive values according to the prevalence of rifampicin resistance**

*Source: World Health Organization. Rapid implementation of the Xpert MTB/RIF diagnostic test*.1
<table>
<thead>
<tr>
<th>Rifampicin resistance prevalence</th>
<th>PPV</th>
<th>NPV</th>
<th>True positive (a)</th>
<th>False negative (a)</th>
<th>False positive (a)</th>
<th>True negative (a)</th>
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<tbody>
<tr>
<td>1%</td>
<td>32.4%</td>
<td>99.9%</td>
<td>9.5</td>
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<td>1</td>
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</table>

(a) Sensitivity (95%) and specificity (98%) for Xpert MTB/RIF rifampicin resistance, compared with reference method (culture).
Appendix 4. Sputum smear microscopy

Update: January 2022

4.1 Sputum smear preparation

Staff members present during sputum smear preparation should wear a respirator to prevent the inhalation of bacilli.
Sputum smears should be prepared promptly after sputum collection.

Equipment

- Gloves
- Respirator (FFF2 or N95)
- New, clean glass slides (never re-use sputum smear slides)
- Wooden applicator sticks

Technique

- Label one end of the slide with the date of sputum collection and laboratory serial number.
- Select a mucopurulent or blood-stained portion of the sputum sample.
- Use an applicator stick to transfer to the slide.
- Smear the specimen over an area of 1.5 to 2 cm x 2 to 3 cm. Make it thin enough to be able to read through it.
- Allow the smear to air dry for 15 minutes. Do not dry the smear in direct sunlight or over a flame.
- Fix the smear by passing the underside of the slide through a flame for 2 to 3 seconds. Repeat 3 or 4 times.
- Allow to cool before staining.

4.2 Ziehl-Neelsen staining

Equipment

- Gloves
- Distilled or filtered water
- 0.3% carbol fuchsin
• 3% acid-alcohol
• 0.3% methylene blue
• Binocular microscope with oil immersion objective (100x magnification)

Technique

• Flood the slide with 0.3% carbol fuchsin (after filtering the carbol fuchsin).
• Gently heat the underside of the slide. Begin timing as soon as steam appears. Let it steam for 5 minutes. Do not let the stain boil or dry.
• Gently rinse the slide until the water runs clear, then drain off excess water.
• Flood the slide with 3% acid-alcohol for 2 to 3 minutes, then drain. Repeat this operation if the slide is not completely decolourised.
• Gently rinse the slide, then drain off excess water.
• Flood the slide with 0.3% methylene blue for one minute, then drain.
• Gently rinse the slide until the water runs clear, then drain off excess water.
• Allow to air dry. Do not wipe or blot.

Reading

• The slides should be examined by an experienced technician. Technicians must be given sufficient time to accurately read slides.
• Before reading the slide, apply a drop of immersion oil to the left edge of the stained smear. Do not touch the slide with the immersion oil applicator (risk of AFB transfer into the oil bottle and onto another slide).
• Examine at least one length (100 high power fields, HPF) before giving a negative result (this should take at least 5 minutes).
• AFB are red, straight or slightly curved rods. They may be found singly or in small groups. The background stains blue.

Reporting

Table 4.1 - Grading AFB scale (WHO-IUATLD)\(^1\)

<table>
<thead>
<tr>
<th>Number of AFB (1000x magnification: one length = 100 HPF)</th>
<th>Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero AFB/one length</td>
<td>No AFB</td>
</tr>
<tr>
<td>1-9 AFB/one length or 100 HPF</td>
<td>Report exact number of AFB</td>
</tr>
<tr>
<td>10-99 AFB/one length or 100 HPF</td>
<td>1+</td>
</tr>
<tr>
<td>1-10 AFB/one HPF in at least 50 fields</td>
<td>2+</td>
</tr>
<tr>
<td>&gt; 10 AFB/one HPF in at least 20 fields</td>
<td>3+</td>
</tr>
</tbody>
</table>
Note: 1-9 AFB per 100 HPF is a positive result. Note that 1-9 AFB per 100 HPF was previously reported as “scanty” followed by the number of AFB seen in 100 HPF (e.g. “scanty 3” meant there were 3 AFB in 100 HPF). Do not confuse “scanty 3” (3 AFB in 100 HPF) with AFB 3+ (more than 10 AFB per HPF).

4.3 Auramine O or auramine/rhodamine staining

Equipment

- Gloves
- Distilled or filtered (not chlorinated) water
- 0.1% auramine O or auramine/rhodamine solution
- 0.5% acid alcohol
- 0.5% potassium permanganate or 0.3% methylene blue
- Fluorescence microscope (or a LED device that can be attached to a standard light microscope)

Technique

- Flood the slide with auramine O or auramine/rhodamine solution for 15 minutes. Ensure that the staining solution remains on the smear.
- Gently rinse, then drain off excess water. Do not use chlorinated water to avoid disturbing the fluorescence reading.
- Flood the slide with 0.5% acid-alcohol for one minute, then drain.
- Gently rinse, then drain off excess water.
- Flood the slide with 0.5% potassium permanganate solution or 0.3% methylene blue for one minute, then drain.
- Gently rinse, then drain off excess water.
- Allow to air dry. Do not wipe or blot.

Note: to control the quality of the colouration include at least one known positive smear in the batch.

Reading

- The slides should be examined by an experienced technician (artefacts are frequent). Technicians must be given sufficient time to read slides.
- Use a 20x objective to screen the smear.
- Examine one length before giving a negative result.
- Always read the positive control smear first. If the positive control is not positive do not continue with the patient smears, but re-stain the batch.
- AFB are bright yellow, straight or slightly curved rods. They may be found singly or in small groups. The background is dark. Non-specific debris stains pale yellow.

Reporting
Table 4.2 - Grading AFB scale (WHO-IUATLD)[1]

<table>
<thead>
<tr>
<th>Number of AFB (200-250x magnification: one length = 300 HPF)</th>
<th>Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero AFB/one length</td>
<td>No AFB</td>
</tr>
<tr>
<td>1-29 AFB/one length</td>
<td>Report exact number of AFB</td>
</tr>
<tr>
<td>30-299 AFB/one length</td>
<td>1+</td>
</tr>
<tr>
<td>10-100 AFB/one field on average</td>
<td>2+</td>
</tr>
<tr>
<td>&gt; 100 AFB/one field on average</td>
<td>3+</td>
</tr>
</tbody>
</table>

Note: the fluorescence stain remains stable when sheltered from light for only 3 days. Quality control should be done within this time.

Referencias


Appendix 6. Adenosine desaminase assay (ADA)

Adenosine desaminase is an enzyme that is necessary for the maturation and differentiation of lymphoid cells. It is useful surrogate marker for TB in pleural and peritoneal fluids. ADA testing is not widely available but can be done relatively easily and cheaply if a spectrophotometer is available. Kits can be purchased to perform the test (see MSF *Medical catalogue*, volume 4).

Pleural fluid
ADA is typically greater than 50 U/litre in TB pleural effusions. Pleural effusions with an ADA level below 40 U/litre are much less likely due to TB. The specificity is increased when ADA is greater than 50 and the lymphocyte-neutrophil ratio is greater than 0.75.

**Peritoneal fluid**

A meta-analysis suggests the optimal cut off values of greater than 39 U/litre likely to be due to TB. However, the sensitivity of ADA in peritoneal fluid is substantially lower in patients with cirrhosis.

**Notes:**
- HIV-infected patients and patients already on TB medications may have lower levels of ADA.
- ADA is generally not a good test in cerebrospinal fluid.

**Appendix 7. Lymph node fine needle aspiration**

FNAC is used to obtain material from lymph nodes. The material is expressed onto slides and prepared for examination.

Two smears will be prepared with Giemsa stain to look for caseum, granuloma, giants cells, and epithelioid cells or histocytes and 1 or 2 will be prepared with Ziehl-Neelsen (ZN) stain to look for acid-fast bacilli (AFB).

**Equipment**
- Needle 23G (in very few cases, it would be possible to use 19G)
- 10 ml syringe
- 2 slides for Giemsa + one or 2 slides for ZN stain
- 10% povidone iodine, sterile gauze, gloves

**Technique**
- Disinfect the area.
- With the needle attached to the syringe, insert the needle deep into the lymph node.
- After the needle has entered the mass, pull back on the syringe plunger to create a vacuum.
- Rapidly move the needle in a to-and-fro fashion to allow material entering the needle.
- When blood or material appears in the needle hub the aspiration should be stopped. Try to aspirate as much as possible of materials, the amount of materials that has been aspirated would have effect on the specificity and sensitivity of diagnosis.
- Release the negative pressure before to take out the needle from the lymph node. Do not continue sucking while taking out the needle, this will avoid aspiration of materiel into the barrel of the syringe and avoid mixing the sample with the possible peripheral blood in the skin.
Slide preparation

Slide should be identified prior to the aspiration and prepared immediately after the aspiration.

- Detach the needle from the syringe immediately after the aspiration.
- Fill the syringe with air (needle is still detached).

Prepare the smear as follow:

- Giemsa
  - Reattach the needle to the syringe and carefully release one small drop of sample onto one end of the slide by pushing down the plunger of the syringe (if the drop is placed in the middle of slide it would be difficult to make smear afterwards).
  - Put another slide over the sample.
  - Slide the two slides against each other, in opposite directions, to spread the sample out completely between them. Do not press the slides together forcefully, to avoid crushing the cells.
  - Allow to air dry.
  - Fix the smears by methanol when they are completely dry.
  - Proceed to Giemsa staining.

- Ziehl-Neelsen
  - Place a small drop of ganglion aspirate on the slide.
  - Make a smear that is neither too thin or too thick.
  - Allow to air dry.
  - Fix the smear by flame when it is completely dry.
  - Proceed to ZN staining.

Reading after Giemsa staining

On each slide, one or several of the following aspects can be found:

- Caseation necrosis (caseum): a uniform, acellular, pinkish substance.
- Granuloma: cluster of epithelioid cells and lymphocytes scattered throughout smear with or without caseous necrosis.
- Epithelioid cells: elongated, often semi-lunar cells with a fine granular nuclear chromatin surrounded by pink cytoplasm.
- Giant cells: huge multinuclear cells.

Notes:

- It would be better to look for granuloma and necrosis with the 10x and 40x power of microscope then to look for epithelioid cells and giant cells with 100x power.
- Observation of smear requires a competent reader with skills in cytology. Slides have to be sent to a referral cytopathology laboratory for quality control or confirmation.
- The quality of the specimen and the preparation are essential. The smear is to be done by skilled technicians.
7.1 Ventilated workstation (VWS)

The VWS provides a safe work environment while preparing sputum smears for AFB staining and Xpert MTB/RIF. It is used when adequate natural ventilation cannot be achieved. Designed to be placed over a bench, it is constituted by a rectangular box ducted to the outside, where the duct is connected to an extraction fan. VWS are used without filter and do not provide product protection. They should never be used for preparing cultures.

7.2 Class II BSC

A Class II BSC protects not only the operator and the environment, but also the material being manipulated inside the cabinet. The room air and the air circulating within the cabinet are drawn by a downward flowing current through a grate then, through a HEPA filter, which protects both the operator and the product. The air exiting the cabinet is filtered through a HEPA filter to protect the environment. Class II BSCs are required for performing cultures.

Notes:
- Class I BSCs cannot be used for performing cultures and VWS are sufficient for preparing samples for microscopy and tests Xpert MTB/RIF. Therefore, their use is not recommended in this manual.
- Class III BSCs are generally not used for TB.

Appendix 8. Protein estimation

Update: January 2022

8.1 Pandy test
Pandy test is used to detect an increase of protein in the cerebrospinal fluid (CSF). The normal range of protein in CSF is 0.20 to 0.45 g/litre. The Pandy test is positive when protein is superior to 0.45 g/litre.

**Equipment**

- Disposable gloves
- Pandy reagent
- Pasteur pipettes
- Conical centrifuge glass tube or test tube
- 1 ml pipettes

**Preparation of 500 ml of Pandy reagent**

Pandy is a saturated phenol solution.

- Weigh 30 g of phenol and transfer it into a 1000 ml bottle.
- Add 500 ml of distilled water and shake vigorously.
- Leave to stand for one 24 hours.
- Check that some phenol remains undissolved:
  - If so, filter: the solution is ready.
  - If all the phenol has dissolved, add a further 10 g of phenol and wait another 24 hours before filtering.

Pandy reagent is a highly corrosive and toxic solution:

- Label the bottle and mark it corrosive and poisonous.
- Wash hands after preparation.

**Technique**

- Place 1 ml of Pandy reagent in a centrifuge tube.
- Add 3 drops of CSF, drop by drop.
- After each drop, look for a white cloud in the tube.
- To facilitate the reading, place a black surface behind the tube.

**Results**

- Presence of a white precipitate: Pandy test
- Absence of a white precipitate: Pandy test

**8.2 Rivalta test**

The Rivalta test is used to detect an increase of protein in the body fluid (pleural fluid, ascites). The test is positive when the proteins are superior to 30 g/litre.

**Equipment**

- Disposable gloves
- Rivalta reagent
- Pasteur pipettes
- Conical centrifuge glass tube or test tube
- 5 ml pipette

**Preparation of 100 ml of Rivalta reagent**

- Place 50 ml of distilled water in a 100 ml measuring cylinder.
- With a 5 ml pipette, add 3 ml of glacial acetic acid and make up to the 100 ml mark with the remaining 50 ml of distilled water.
- Transfer the solution into a bottle.

**Technique**

- Place 2 ml of Rivalta reagent in a centrifuge tube.
- Add 3 drops of pleural fluid/ascites, drop by drop.
- After each drop, look for a white cloud in the tube.
- To facilitate the reading, place a dark surface behind the tube.

**Results**

- Presence of a white precipitate: Rivalta test positive.
- Absence of a white precipitate: Rivalta test negative.

**Appendix 8. Daily dose of anti-TB drugs using FDCs**

- [Appendix 8a. New paediatric FDCs](#)
- [Appendix 8b. Former paediatric FDCs](#)

**Appendix 8a. New paediatric FDCs**

**Intensive phase**
For example:

– A child weighing 9 kg takes 2 tablets of HZR (50 mg/150 mg/75 mg) + 2 tablets of E (100 mg) once daily.

– A child weighing 20 kg takes 4 tablets of HZR (50 mg/150 mg/75 mg) + 1 tablet of E (400 mg) once daily.

**TABLETS ARE TO BE TAKEN ON AN EMPTY STOMACH.**

**Continuation phase**

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Paediatric formulations</th>
<th>Adult formulations</th>
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</thead>
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<td></td>
<td>HZR 50/150/75</td>
<td>E 100</td>
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For example:

– A child weighing 9 kg takes 2 tablets of HZR (50 mg/150 mg/75 mg) + 2 tablets of E (100 mg) once daily.

– A child weighing 20 kg takes 4 tablets of HZR (50 mg/150 mg/75 mg) + 1 tablet of E (400 mg) once daily.

**TABLETS ARE TO BE TAKEN ON AN EMPTY STOMACH.**

**Continuation phase**
### Appendix 8b. Former paediatric FDCs

**Intensive phase**

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<th>Adult formulation</th>
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<tr>
<td>&gt;70</td>
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</table>

#### Daily dosing in patients < 30 kg

<table>
<thead>
<tr>
<th></th>
<th>Daily dosing in patients &lt; 30 kg</th>
<th>Daily dosing in patients ≥ 30 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>15 to 25 mg/kg once daily</td>
<td>15 to 25 mg/kg once daily</td>
</tr>
<tr>
<td>H</td>
<td>7 to 15 mg/kg once daily</td>
<td>4 to 6 mg/kg once daily</td>
</tr>
<tr>
<td>Z</td>
<td>30 to 40 mg/kg once daily</td>
<td>20 to 30 mg/kg once daily</td>
</tr>
<tr>
<td>R</td>
<td>10 to 20 mg/kg once daily</td>
<td>8 to 12 mg/kg once daily</td>
</tr>
</tbody>
</table>
For example:

- A child weighing 9 kg takes 2 tablets of HZR (30 mg/150 mg/60 mg) + 2 tablets of E (100 mg) once daily.
- A child weighing 20 kg takes 5 tablets of HZR (30 mg/150 mg/60 mg) + 1 tablet of E (400 mg) once daily.

TABLETS ARE TO BE TAKEN ON A EMPTY STOMACH.

**Continuation phase**
## Appendix 9. Tuberculin skin test

Update: January 2022

### 9.1 Introduction

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Paediatric formulation</th>
<th>Adult formulation</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>HR 30/60</td>
<td>HR 75/150</td>
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<tr>
<td>4</td>
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<td>30-34</td>
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<td>35-39</td>
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<td>40-54</td>
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<td>55-70</td>
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<tr>
<td>&gt; 70</td>
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</tr>
</tbody>
</table>

### Daily dosing in patients < 30 kg vs. ≥ 30 kg

<table>
<thead>
<tr>
<th></th>
<th>Daily dosing in patients &lt; 30 kg</th>
<th>Daily dosing in patients ≥ 30 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>15 to 25 mg/kg once daily</td>
<td>15 to 25 mg/kg once daily</td>
</tr>
<tr>
<td>H</td>
<td>7 to 15 mg/kg once daily</td>
<td>4 to 6 mg/kg once daily</td>
</tr>
<tr>
<td>Z</td>
<td>30 to 40 mg/kg once daily</td>
<td>20 to 30 mg/kg once daily</td>
</tr>
<tr>
<td>R</td>
<td>10 to 20 mg/kg once daily</td>
<td>8 to 12 mg/kg once daily</td>
</tr>
</tbody>
</table>
A delayed hypersensitivity reaction occurs after an intradermal injection of tuberculin (tuberculin skin test, TST) in persons infected by *M. tuberculosis* or vaccinated with BCG.

The test is performed by injecting 5 international units of tuberculin (purified protein derivative, PPD) intradermally on the ventral surface of the forearm (side of forearm exposed with palm facing up)\(^8\) .

The test, which should be performed by a trained healthcare worker, requires 2 visits. The reading is done on the second visit, 48 to 72 hours after the tuberculin injection.

If the patient does not return within 72 hours, another TST should be performed.

The result is determined by the diameter of the reaction and individual characteristics of the person being tested (Table 9.1). It should be recorded in millimetres, not as “positive” or “negative”.

The reaction is the area of induration (swelling that can be felt) around the injection site.

Using a ruler, the diameter of induration is measured transversely. The erythema (redness) around the indurated area is not the reaction and should not be measured.

A reaction that appears several minutes, hours or even 24 hours after injection, but disappears on the day after its appearance, is of no significance.

There is no correlation between the diameter of the induration and:

- likelihood of active TB,
- risk of developing active TB,
- protection against TB disease in vaccinated people.

### 9.2 Positive TST

A positive TST signifies that a *M. tuberculosis* infection has occurred.

However, TST cannot differentiate between active and latent infection.

A positive test supports the diagnosis of latent TB when other diagnostic tools have been used to rule out active TB.

In children, a positive TST may be one element among many to establish the diagnosis of active TB.

Table 9.1 - Positive TST results
A highly positive (induration diameter > 20 mm) or phlyctenular reaction should be considered as an argument in favour of active TB but is not enough to decide on treatment.

Some persons may have a positive TST result even if they have not been infected with *M. tuberculosis*.

Causes of false positive results include:
- Errors in tuberculin administration
- Previous BCG vaccination
- Infection with non-tuberculosis mycobacteria
- Low specificity of TST

BCG is given at birth so previous BCG vaccination has limited impact on the interpretation of TST results, except in small children. The average diameter of the TST reaction 1 year after BCG vaccination is 10 mm, with extremes ranging from 4 to 20 mm. The reaction becomes weaker over time and disappears 5 to 10 years post-vaccination.

### 9.3 Negative TST

Usually, a negative TST result signifies that no *M. tuberculosis* infection has occurred. However, a negative TST result does not rule out TB infection.

Causes of false negative results include:
- Errors in tuberculin administration

<table>
<thead>
<tr>
<th>Individual characteristics</th>
<th>Diameter of induration</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-infected persons</td>
<td>≥ 5 mm</td>
</tr>
<tr>
<td>Severely malnourished children</td>
<td></td>
</tr>
<tr>
<td>Patients taking corticosteroids (e.g. prednisolone ≥ 15 mg daily ≥ 1 month) or immunosuppressants</td>
<td></td>
</tr>
<tr>
<td>Recent contacts of TB patients</td>
<td></td>
</tr>
<tr>
<td>Persons with fibrotic changes on CXR consistent with prior TB</td>
<td></td>
</tr>
<tr>
<td>Persons from countries with high TB prevalence</td>
<td>≥ 10 mm</td>
</tr>
<tr>
<td>Mycobacteriology laboratory personnel</td>
<td></td>
</tr>
<tr>
<td>Persons working and/or living in congregate settings, including healthcare facilities, prisons, homeless shelters, etc.</td>
<td></td>
</tr>
<tr>
<td>Children &lt; 5 years</td>
<td></td>
</tr>
<tr>
<td>Children &gt; 5 years and adolescents exposed to adults at risk of TB</td>
<td></td>
</tr>
<tr>
<td>Other at-risk categories (e.g. diabetes, injecting drug users, end-stage renal disease, leukemia, low body mass index)</td>
<td></td>
</tr>
<tr>
<td>All other children and adults with no other risk factors or exposure to TB</td>
<td>≥ 15 mm</td>
</tr>
</tbody>
</table>
Recent viral illness or live virus vaccination (e.g. measles)
Severe TB disease (e.g. TB meningitis or miliary TB)
Recent (< 12 weeks) or very old (many years) TB infection
Immunodepression or a weak immune response (e.g. the very elderly, children < 5 years, malnutrition, patients taking corticosteroids or immunosuppressants)
Persons with diseases that result in anergy (e.g. AIDS, haemopathy, sarcoidosis)
Natural extinction of post-vaccination reaction from the 5th year following BCG

Notas

Appendix 10. Tuberculosis drug information sheets and patient instructions

Update: January 2022

- Tuberculosis drug information sheets
  - Amikacin (Am)
  - Amoxicillin/clavulanic acid ratio 4:1 (Amx/Clv)
  - Clofazimine (Cfz)
  - Cycloserine (Cs) or terizidone (Trd)
  - Ethambutol (E)
  - Ethionamide (Eto) or prothionamide (Pto)
  - Imipenem/cilastatin (Ipm/Cln)
  - Isoniazid - Standard dose (H)
  - Levofloxacin (Lfx)
  - Linezolid (Lzd)
  - Meropenem (Mpm)
  - Moxifloxacin (Mfx)
  - Para-aminosalicylic acid (PAS) and sodium salt of PAS
  - Pyrazinamide (Z)
  - Rifabutin (Rfb)
Tuberculosis drug information sheets

Update: January 2022

- **Amikacin (Am)**
- **Amoxicillin/clavulanic acid ratio 4:1 (Amx/Clv)**
- **Clofazimine (Cfz)**
- **Cycloserine (Cs) or terizidone (Trd)**
- **Ethambutol (E)**
- **Ethionamide (Eto) or prothionamide (Pto)**
- **Imipenem/cilastatin (Ipm/Cln)**
- **Isoniazid - Standard dose (H)**
- **Levofloxacin (Lfx)**
- **Linezolid (Lzd)**
- **Meropenem (Mpm)**
- **Moxifloxacin (Mfx)**
- **Para-aminosalicylic acid (PAS) and sodium salt of PAS**
- **Pyrazinamide (Z)**
- **Rifabutin (Rfb)**
- **Rifampicin (R)**
- **Streptomycin (S)**

### Amikacin (Am)

**Forms, strengths and route of administration**

- 500 mg amikacin base, in 2 ml ampoule (250 mg/ml), for IM injection

**Dosage**

- Child and adult: 15 to 20 mg/kg once daily
- Patient 60 years and over: 15 mg/kg 3 times a week
- Maximum dose: 1000 mg daily
- Renal insufficiency: 12 to 15 mg/kg 2 or 3 times a week
<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Daily dose (mg)</th>
<th>Daily dose (ml) - IM injection(^{(a)}) (500 mg in 2 ml = 250 mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>75-100</td>
<td>0.4 ml</td>
</tr>
<tr>
<td>6</td>
<td>90-120</td>
<td>0.4 ml</td>
</tr>
<tr>
<td>7</td>
<td>105-140</td>
<td>0.6 ml</td>
</tr>
<tr>
<td>8</td>
<td>120-160</td>
<td>0.6 ml</td>
</tr>
<tr>
<td>9</td>
<td>135-180</td>
<td>0.6 ml</td>
</tr>
<tr>
<td>10</td>
<td>150-200</td>
<td>0.8 ml</td>
</tr>
<tr>
<td>11</td>
<td>165-220</td>
<td>0.8 ml</td>
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<tr>
<td>12</td>
<td>180-240</td>
<td>0.8 ml</td>
</tr>
<tr>
<td>13</td>
<td>195-260</td>
<td>1 ml</td>
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<tr>
<td>14</td>
<td>210-280</td>
<td>1 ml</td>
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<tr>
<td>15</td>
<td>225-300</td>
<td>1 ml</td>
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<tr>
<td>16</td>
<td>240-320</td>
<td>1.2 ml</td>
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<td>17</td>
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<td>18</td>
<td>270-360</td>
<td>1.2 ml</td>
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<td>19</td>
<td>285-380</td>
<td>1.5 ml</td>
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<td>330-440</td>
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<td>375-500</td>
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<td>25</td>
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<td>26</td>
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<td>28</td>
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<td>29</td>
<td>435-580</td>
<td>2 ml</td>
</tr>
<tr>
<td>30-35</td>
<td>625</td>
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</tr>
<tr>
<td>36-45</td>
<td>750</td>
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</tr>
<tr>
<td>46-55</td>
<td>875</td>
<td>3.5 ml</td>
</tr>
<tr>
<td>56-70</td>
<td>1000</td>
<td>4 ml</td>
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<tr>
<td>&gt; 70</td>
<td>1000</td>
<td>4 ml</td>
</tr>
</tbody>
</table>

(a) For doses less than 1 ml, use a 1 ml syringe graduated in 0.01 ml.

**Contra-indications, adverse effects, precautions**

- Do not administer to patients with allergy to aminoglycosides.
- Administer with caution to patients 60 years and over or patients with pre-existing renal, vestibular, auditory or severe hepatic impairment.
- May cause:
  - nephrotoxicity, ototoxicity, electrolyte disturbances; rarely, hypersensitivity reactions;
  - local pain after injection.
- For the management of adverse effects see Appendix 17.
- Avoid or monitor combination with other ototoxic and/or nephrotoxic drugs (furosemide, amphotericin B, tenofovir, etc.).
- **Pregnancy**: CONTRA-INDICATED
- **Breastfeeding**: no contra-indication

**Monitoring**

- Symptomatic monitoring.
- Audiometry, serum creatinine and electrolytes (K, Ca, Mg).
Patient instructions

- Maintain a good fluid intake to limit renal problems.

Remarks

- Use a different site for each injection (absorption may be delayed if the same site is used repeatedly).

Storage

- Below 25 °C

Solution may darken from colourless to a pale yellow, but this does not indicate a loss of potency.

Amoxicillin/clavulanic acid ratio 4:1 (Amx/Clv)

Forms and strengths

- 500 mg amoxicillin/125 mg clavulanic acid tablet
- 250 mg amoxicillin/62.5 mg clavulanic acid per 5 ml, powder for oral suspension

Dosage (expressed in clavulanic acid)

- Child under 30 kg: 3 mg (0.25 ml)/kg of clavulanic acid 3 times daily, 60 minutes before each dose of meropenem
- Adolescent ≥ 15 years and ≥ 30 kg and adult: 125 mg of clavulanic acid 2 times daily, 60 minutes before each dose of carbapenem
- Maximum dose: 250 mg daily
<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Daily dose (mg)</th>
<th>500 mg/125 mg tablet</th>
<th>250 mg/62.5 mg per 5 ml oral suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>50</td>
<td>–</td>
<td>1.3 ml x 3</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
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<td>1.5 ml x 3</td>
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<tr>
<td>7</td>
<td>70</td>
<td>–</td>
<td>2 ml x 3</td>
</tr>
<tr>
<td>8</td>
<td>80</td>
<td>–</td>
<td>2 ml x 3</td>
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<tr>
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<td>3 ml x 3</td>
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<tr>
<td>12</td>
<td>120</td>
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<td>13</td>
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<td>4 ml x 3</td>
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<td>16</td>
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<tr>
<td>18</td>
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<td>21</td>
<td>210</td>
<td>–</td>
<td>5.5 ml x 3</td>
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<tr>
<td>22</td>
<td>220</td>
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<td>6 ml x 3</td>
</tr>
<tr>
<td>23</td>
<td>230</td>
<td>–</td>
<td>6 ml x 3</td>
</tr>
<tr>
<td>24</td>
<td>240</td>
<td>–</td>
<td>6.5 ml x 3</td>
</tr>
</tbody>
</table>
Contra-indications, adverse effects, precautions

- Do not administer to penicillin-allergic patients and patients with history of hepatic disorders during a previous treatment with amoxicillin/clavulanic acid.
- Administer with caution to patients allergic to betalactams (cross-hypersensitivity may occur) and to patients with hepatic impairment.
- May cause: gastrointestinal disturbances (mainly diarrhoea), hypersensitivity reactions, hepatotoxicity.
- For the management of adverse effects see Appendix 17.
- Pregnancy: no contra-indication
- Breastfeeding: no contra-indication

Monitoring

- Symptomatic monitoring

Patient instructions

- Take with food.
Storage

- Below 25 °C
  - Powder for oral suspension: between 15 °C and 25 °C
  - Once reconstituted, the oral suspension must be kept refrigerated (between 2 °C and 8 °C) and may be used for up to 7 days.

Clofazimine (Cfz)

Therapeutic action

- Antibacterial with in vitro activity (no evidence in vivo)

Presentation

- 50 mg and 100 mg soft capsules

Dosage

- Child under 30 kg: 2 to 3 mg/kg/day
- Child over 30 kg and adult: 200 to 300 mg/day for 2 months then 100 mg/day

The daily dose is administered in 2 divided doses or once daily, depending on tolerance and available formulation.
<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Daily dose (mg)</th>
<th>100 mg capsule</th>
<th>50 mg capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>10-15</td>
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<tr>
<td>6</td>
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<td>26-39</td>
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<td>16</td>
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</tr>
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<td>19</td>
<td>38-57</td>
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<td>42-63</td>
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<td>44-66</td>
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<td>1 caps</td>
</tr>
<tr>
<td>23</td>
<td>46-69</td>
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<td>1 caps</td>
</tr>
<tr>
<td>24</td>
<td>48-72</td>
<td>–</td>
<td>1 caps</td>
</tr>
</tbody>
</table>
### Contra-indications, adverse effects, precautions

- Do not administer to patients with history of allergy to clofazimine.
- Administer with caution to patients with severe hepatic impairment.
- May cause:
  - gastrointestinal disturbances (nausea, vomiting, abdominal pain, diarrhoea) sometimes severe (acute abdomen presentation, intestinal bleeding);
  - pink, red or brownish-black discolouration of skin, body fluids and faeces;
  - eye and skin dryness and irritation, hypersensitivity reactions, photosensitivity;
  - QT prolongation (newly reported).
- For the management of adverse effects, see Appendix 17.
- **Pregnancy:** not recommended (safety is not established)
- **Breast-feeding:** can be used; may cause breast milk discolouration and reversible skin discolouration in breastfed infants.

### Monitoring
- Symptomatic monitoring

### Patient instructions

<table>
<thead>
<tr>
<th>25</th>
<th>50-75</th>
<th>–</th>
<th>1 caps</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>52-78</td>
<td>–</td>
<td>1 caps</td>
</tr>
<tr>
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<td>54-81</td>
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<tr>
<td>28</td>
<td>56-84</td>
<td>–</td>
<td>1 caps</td>
</tr>
<tr>
<td>29</td>
<td>58-87</td>
<td>–</td>
<td>1 caps</td>
</tr>
</tbody>
</table>

| 30-35 | First 2 months: 200 to 300 mg then reduce to 100 mg | First 2 months: 1 caps x 2 or 2 caps (morning) + 1 caps (evening) then 1 caps |
| 36-45 | – | – |
| 46-55 | – | – |
| 56-70 | – | – |

| > 70 | – | – | – | – |
• Take with food to improve gastrointestinal tolerance.
• Protect your skin from sun.
• Clofazimine may cause reversible discolouration of the skin, conjunctiva, faeces, urine, sweat, tears, saliva, sputum, breast-milk, etc. However, it may take months to years to disappear after stopping treatment.

Storage

🌡 – Below 25 °C

Cycloserine (Cs) or terizidone (Trd)

Forms and strengths

• 250 mg and 125 mg capsules

Dosage

• Child under 30 kg: 7.5 to 10 mg/kg 2 times daily (or 15 to 20 mg/kg once daily if tolerated)
• Child 30 kg and over and adult: 5 to 7.5 mg/kg 2 times daily (or 10 to 15 mg/kg once daily if tolerated)
• Maximum dose: 1000 mg daily
• Renal insufficiency: 250 mg once daily or 500 mg 3 times a week
<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Daily dose (mg)</th>
<th>250 mg capsule</th>
<th>125 mg capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>75-100</td>
<td>–</td>
<td>1 caps</td>
</tr>
<tr>
<td>6</td>
<td>90-120</td>
<td>–</td>
<td>1 caps</td>
</tr>
<tr>
<td>7</td>
<td>105-140</td>
<td>–</td>
<td>1 caps</td>
</tr>
<tr>
<td>8</td>
<td>120-160</td>
<td>–</td>
<td>1 caps</td>
</tr>
<tr>
<td>9</td>
<td>135-180</td>
<td>–</td>
<td>1 caps</td>
</tr>
<tr>
<td>10</td>
<td>150-200</td>
<td>–</td>
<td>1 caps x 2</td>
</tr>
<tr>
<td>11</td>
<td>165-220</td>
<td>–</td>
<td>1 caps x 2</td>
</tr>
<tr>
<td>12</td>
<td>180-240</td>
<td>–</td>
<td>1 caps x 2</td>
</tr>
<tr>
<td>13</td>
<td>195-260</td>
<td>–</td>
<td>1 caps x 2</td>
</tr>
<tr>
<td>14</td>
<td>210-280</td>
<td>–</td>
<td>1 caps x 2</td>
</tr>
<tr>
<td>15</td>
<td>225-300</td>
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<td>1 caps x 2</td>
</tr>
<tr>
<td>16</td>
<td>240-320</td>
<td>–</td>
<td>1 caps (morning) + 2 caps (evening)</td>
</tr>
<tr>
<td>17</td>
<td>255-340</td>
<td>–</td>
<td>1 caps (morning) + 2 caps (evening)</td>
</tr>
<tr>
<td>18</td>
<td>270-360</td>
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<td>1 caps (morning) + 2 caps (evening)</td>
</tr>
<tr>
<td>19</td>
<td>285-380</td>
<td>–</td>
<td>1 caps (morning) + 2 caps (evening)</td>
</tr>
<tr>
<td>20</td>
<td>300-400</td>
<td>–</td>
<td>1 caps (morning) + 2 caps (evening)</td>
</tr>
<tr>
<td>21</td>
<td>315-420</td>
<td>–</td>
<td>1 caps (morning) + 2 caps (evening)</td>
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<tr>
<td>22</td>
<td>330-440</td>
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<td>1 caps (morning) + 2 caps (evening)</td>
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<tr>
<td>23</td>
<td>345-460</td>
<td>–</td>
<td>1 caps (morning) + 2 caps (evening)</td>
</tr>
<tr>
<td>24</td>
<td>360-480</td>
<td>1 caps x 2</td>
<td>–</td>
</tr>
</tbody>
</table>
### Contra-indications, adverse effects, precautions

- Avoid in patients with epilepsy, depression, psychosis, severe anxiety, history of neurological or psychiatric disorders, chronic alcohol use. However, if essential to the regimen, it can be administered under close monitoring.

- May cause:
  - neurotoxicity: seizure, headache, lethargy, confusion, mood change, drowsiness, anxiety, psychosis, depression, suicidal ideation, peripheral neuropathy; rarely, vestibular toxicity;
  - hypersensitivity reactions.

- For the management of adverse effects see Appendix 17.

- Avoid or monitor combination with isoniazid and thionamides (increased risk of neurotoxicity).

- Administer concomitantly pyridoxine (vitamin B₆); child: 1 to 2 mg/kg (usual range: 10 to 50 mg) once daily; adult: 100 mg once daily.

- **Pregnancy**: use if the benefits outweigh the risks. Administer pyridoxine to the mother (as above).

- **Breastfeeding**: no contra-indication. Administer pyridoxine to the mother (as above) and the breast-fed neonate or infant (1 to 2 mg/kg once daily).

### Monitoring

- Symptomatic monitoring.

### Table

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Daily Dose</th>
<th>Administration</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-35</td>
<td>500</td>
<td>1 caps x 2</td>
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<tr>
<td>36-45</td>
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</tr>
<tr>
<td>46-55</td>
<td>750</td>
<td>1 caps (morning) + 2 caps (evening)</td>
<td>–</td>
</tr>
<tr>
<td>56-70</td>
<td>750</td>
<td>1 caps (morning) + 2 caps (evening)</td>
<td>–</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>750</td>
<td>1 caps (morning) + 2 caps (evening)</td>
<td>–</td>
</tr>
</tbody>
</table>
Patient instructions

- Take capsules with water before or after meals.
- Avoid alcohol during treatment.

Remarks

- To increase tolerance, start with a low dose (e.g. 250 mg daily in adults), then increase over 1 to 2 weeks to achieve the requested dose.

Storage

°C - Below 25 °C

Ethambutol (E)

Forms and strengths

- 100 mg and 400 mg tablets
- 100 mg dispersible tablet

Dosage

- Child and adult: 15 to 25 mg/kg once daily
- Maximum dose: 1200 mg daily
- Renal insufficiency: 15 to 25 mg/kg 3 times a week
<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Daily dose (mg)</th>
<th>400 mg tablet</th>
<th>100 mg tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>75-125</td>
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<tr>
<td>6</td>
<td>90-150</td>
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<td>2 tab</td>
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<td>10</td>
<td>150-250</td>
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<td>2 tab</td>
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<td>11</td>
<td>165-275</td>
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<td>2 tab</td>
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<td>180-300</td>
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<td>Dosage</td>
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<tr>
<td>25-26</td>
<td>375-625</td>
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<td>28-29</td>
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<td>36-45</td>
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<td>2 tab</td>
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</tr>
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<td>56-70</td>
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</tr>
<tr>
<td>&gt;70</td>
<td>1200</td>
<td>3 tab</td>
<td>–</td>
</tr>
</tbody>
</table>

**Contra-indications, adverse effects, precautions**

- Do not administer to patients with severe renal impairment or pre-existing optic neuritis (e.g. diabetic retinopathy).
- May cause: dose-related retrobulbar optic neuritis, exacerbated in renal impairment.
- The dosage must be carefully adjusted to the weight, especially for children under 5 years, as it is more difficult to detect visual changes at this age.
- For the management of adverse effects see **Appendix 17**.
- **Pregnancy**: no contra-indication
- **Breastfeeding**: no contra-indication

**Monitoring**

- Symptomatic monitoring.

**Patient instructions**

- Take with or without food.

**Remarks**
• For adults on drug-susceptible TB treatment, ethambutol is given as part of a fixed-dose combination.
• Ethambutol is also used in the treatment of drug-resistant TB treatment for longer duration. For treatment > 2 months, daily doses should be closer to 15 mg/kg and visual acuity and colour discrimination should be monitored.

Storage

☀️ – 🌡️ – Below 25 °C

**Ethionamide (Eto) or prothionamide (Pto)**

**Forms and strengths**

• 250 mg tablet (ethionamide or prothionamide)
• 125 mg dispersible tablet (ethionamide)

**Dosage**

• Child and adult: 15 to 20 mg/kg once daily
• Maximum dose: 1000 mg daily
<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Daily dose (mg)</th>
<th>250 mg tablet</th>
<th>125 mg dispersible tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
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<td>345-460</td>
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<td>3 tab</td>
</tr>
<tr>
<td>24</td>
<td>360-480</td>
<td>–</td>
<td>3 tab</td>
</tr>
</tbody>
</table>
Contra-indications, adverse effects, precautions

- Do not administer to patients with severe hepatic impairment.
- Administer with caution to patients with hepatic disease, diabetes or depression.
- May cause:
  - frequently: gastrointestinal disturbances (abdominal or epigastric pain, diarrhoea, metallic taste, nausea and vomiting, stomatitis, etc.);
  - occasionally: endocrine disorders (gynecomastia, hypothyroidism), alopecia, depression, anxiety, psychosis, hypoglycaemia, vestibular disorders, hepatotoxicity, peripheral neuropathy, optic neuritis, hypersensitivity reactions, seizures
- For the management of adverse effects see Appendix 17.
- Monitor combination with: cycloserine or terizidone (increased risk of seizures) and para-aminosalicylic acid (increased risk of gastrointestinal disturbances and hypothyroidism).
- Administer concomitantly pyridoxine (vitamin B₆); child: 1 to 2 mg/kg (usual range: 10 to 50 mg) once daily; adult: 100 mg once daily.
- **Pregnancy:** CONTRA-INDICATED
- **Breastfeeding:** administer pyridoxine to the mother (as above). Observe the breast-fed neonate or infant for adverse effects and supplement it with pyridoxine (1 to 2 mg/kg once daily).

**Monitoring**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>375-500</td>
<td>2 tab</td>
<td>–</td>
<td></td>
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<td>26</td>
<td>390-520</td>
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<td>29</td>
<td>435-580</td>
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<tr>
<td>30-35</td>
<td>500</td>
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</tr>
<tr>
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</tr>
<tr>
<td>&gt; 70</td>
<td>1000</td>
<td>4 tab</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>
Patient instructions

- Symptomatic monitoring.
- Liver function and thyroid function.

- Take with food and/or at bedtime to limit gastrointestinal disturbances.
- Avoid alcohol during treatment.

Remarks

- To improve tolerance, start with a low dose (e.g. 250 mg daily in adults), then increase over 1 to 2 weeks to achieve the requested dose.
- For the 6HRZEt regimen for drug-susceptible TB meningitis, the dose is 20 mg/kg once daily (max. 750 mg daily).

Storage

- Below 25 °C

Imipenem/cilastatin (Ipm/Cln)

Forms, strengths and route of administration

- Powder for injection, in vial of 500 mg imipenem monohydrate/500 mg cilastatin sodium, to be reconstituted with 20 ml of 0.9% sodium chloride (25 mg imipenem/ml).
- Each dose is to be diluted in 100 ml of 0.9% sodium chloride and to be administered by IV infusion:
  - over 30 minutes for doses ≤ 500 mg/500 mg
  - over 60 minutes for doses > 500 mg/500 mg
- Use a deep line, preferably an implantable venous access device (Port-a-Cath).

Dosage (expressed in imipenem)

- Adolescent 15 years and over (and ≥ 30 kg) and adult: 1000 mg (2 vials) 2 times daily with 10 hours minimum between infusions
- Maximum dose: 2000 mg daily
- Renal insufficiency: 750 mg every 12 hours for CrCl 20-40 ml/minute; 500 mg every 12 hours for CrCl < 20 ml/minute
<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Daily dose (mg)</th>
<th>Daily dose (ml) - IV infusion (500 mg/500 mg per vial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-29</td>
<td></td>
<td>Do not used in patients &lt; 15 years and &lt; 30 kg</td>
</tr>
<tr>
<td>30-33</td>
<td>2000</td>
<td>2 vials (40 ml) in 100 ml of 0.9% NaCl x 2</td>
</tr>
<tr>
<td>34-40</td>
<td>2000</td>
<td>2 vials (40 ml) in 100 ml of 0.9% NaCl x 2</td>
</tr>
<tr>
<td>41-45</td>
<td>2000</td>
<td>2 vials (40 ml) in 100 ml of 0.9% NaCl x 2</td>
</tr>
<tr>
<td>46-50</td>
<td>2000</td>
<td>2 vials (40 ml) in 100 ml of 0.9% NaCl x 2</td>
</tr>
<tr>
<td>51-70</td>
<td>2000</td>
<td>2 vials (40 ml) in 100 ml of 0.9% NaCl x 2</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>2000</td>
<td>2 vials (40 ml) in 100 ml of 0.9% NaCl x 2</td>
</tr>
</tbody>
</table>

**Contra-indications, adverse effects, precautions**

- Do not administer to patients with allergy to carbapenems.
- Administer with caution to patients allergic to other betalactams (cross-hypersensitivity may occur).
- May cause:
  - nausea, vomiting (the infusion rate may be slowed down in case of nausea), diarrhoea;
  - neurotoxicity: confusional state, seizures (most frequently in patients with history of seizures or renal impairment);
  - hypersensitivity reactions;
  - local reactions (phlebitis/thrombophlebitis).
- For the management of adverse effects see Appendix 17.
- Avoid or monitor combination with: valproic acid (decreased plasma concentration of valproic acid and risk of seizures), oral or injectable ganciclovir (risk of seizures).
- **Pregnancy and breastfeeding:** avoid unless the benefits outweigh the risks

**Monitoring**

- Symptomatic monitoring.

**Remarks**

- Administer clavulanic acid 60 minutes before each dose of imipenem/cilastatin.
- Do not mix with Ringer lactate (incompatibility) but may be administered via Y-site.
• Do not mix with other drugs in the infusion bag.

**Storage**

![°C] – Below 25 °C

• Once reconstituted, solution:
  ▪ remains stable 4 hours at room temperature or 24 hours between 2 to 8 °C;
  ▪ may darken from colourless to yellow (this does not indicate a loss of potency);
  ▪ should be discarded if it becomes brown.

**Isoniazid - Standard dose (H)**

**Forms and strengths**

• 100 mg and 300 mg tablets
• 100 mg dispersible tablet

**Dosage**

• Child under 30 kg: 10 mg/kg (7 to 15 mg/kg) once daily
• Child 30 kg and over and adult: 5 mg/kg (4 to 6 mg/kg) once daily
• Maximum dose: 300 mg daily
<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Daily dose (mg)</th>
<th>300 mg tablet</th>
<th>100 mg tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>35-75</td>
<td>–</td>
<td>½ tab</td>
</tr>
<tr>
<td>6</td>
<td>42-90</td>
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<tr>
<td>7</td>
<td>49-105</td>
<td>–</td>
<td>1 tab</td>
</tr>
<tr>
<td>8</td>
<td>56-120</td>
<td>–</td>
<td>1 tab</td>
</tr>
<tr>
<td>9</td>
<td>63-135</td>
<td>–</td>
<td>1 tab</td>
</tr>
<tr>
<td>10</td>
<td>70-150</td>
<td>–</td>
<td>1½ tab</td>
</tr>
<tr>
<td>11</td>
<td>77-165</td>
<td>–</td>
<td>1½ tab</td>
</tr>
<tr>
<td>12</td>
<td>84-180</td>
<td>–</td>
<td>1½ tab</td>
</tr>
<tr>
<td>13</td>
<td>91-195</td>
<td>–</td>
<td>2 tab</td>
</tr>
<tr>
<td>14</td>
<td>98-210</td>
<td>–</td>
<td>2 tab</td>
</tr>
<tr>
<td>15</td>
<td>105-225</td>
<td>–</td>
<td>2 tab</td>
</tr>
<tr>
<td>16</td>
<td>112-240</td>
<td>–</td>
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<tr>
<td>17</td>
<td>119-255</td>
<td>–</td>
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<td>18</td>
<td>126-270</td>
<td>–</td>
<td>2 tab</td>
</tr>
<tr>
<td>19</td>
<td>133-285</td>
<td>–</td>
<td>2 tab</td>
</tr>
<tr>
<td>20</td>
<td>140-300</td>
<td>–</td>
<td>2 tab</td>
</tr>
<tr>
<td>21</td>
<td>147-300</td>
<td>1 tab</td>
<td>–</td>
</tr>
<tr>
<td>22</td>
<td>154-300</td>
<td>1 tab</td>
<td>–</td>
</tr>
<tr>
<td>23</td>
<td>161-300</td>
<td>1 tab</td>
<td>–</td>
</tr>
<tr>
<td>24</td>
<td>168-300</td>
<td>1 tab</td>
<td>–</td>
</tr>
</tbody>
</table>
### Contra-indications, adverse effects, precautions

- Do not administer to patients with severe hepatic impairment.
- May cause:
  - peripheral neuropathy;
  - hepatotoxicity;
  - hypersensitivity reactions, psychotic reactions, seizures and depression.
- Monitor closely:
  - pregnant and breastfeeding women, patients with renal impairment or diabetes; malnourished or HIV-infected patients (increased risk of neuropathy);
  - alcoholic patients (increased risk of neuropathy and hepatotoxicity);
  - patients with chronic hepatic disease or taking rifampicin or ≥ 35 years (increased risk of hepatotoxicity);
  - patients taking anticonvulsants, benzodiazepines (risk of toxicity), warfarin (risk of bleeding).
  - Dose adjustment may be required.
- For the management of adverse effects see Appendix 17.
- Administer concomitantly pyridoxine (vitamin B<sub>6</sub>), to patients at risk of peripheral neuropathy (child: 5 to 10 mg once daily; adult: 10 mg once daily).
- **Pregnancy and breastfeeding**: no contra-indication. Administer pyridoxine to the mother (as above) and the breast-fed neonate or infant (5 mg once daily).

<table>
<thead>
<tr>
<th></th>
<th>Range</th>
<th>Unit</th>
<th></th>
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<td>27</td>
<td>189-300</td>
<td>1 tab</td>
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<td>−</td>
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<td>28</td>
<td>196-300</td>
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<td>−</td>
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<td>29</td>
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<td>−</td>
</tr>
<tr>
<td>30-35</td>
<td>150</td>
<td>½ tab</td>
<td></td>
<td>−</td>
</tr>
<tr>
<td>36-45</td>
<td>300</td>
<td>1 tab</td>
<td></td>
<td>−</td>
</tr>
<tr>
<td>46-55</td>
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<td></td>
<td>−</td>
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<tr>
<td>56-70</td>
<td>300</td>
<td>1 tab</td>
<td></td>
<td>−</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>300</td>
<td>1 tab</td>
<td></td>
<td>−</td>
</tr>
</tbody>
</table>
Monitoring

- Symptomatic monitoring.
- Liver function in patients with hepatic disease.

Patient instructions

- Take without food.
- Avoid alcohol during treatment.

Remarks

- For patients on drug-susceptible TB treatment, isoniazid is given as part of a fixed-dose combination.
- For the 6HRZEto regimen for drug-susceptible TB meningitis, the dose of isoniazid is 20 mg/kg once daily (max. 400 mg daily).
- Isoniazid is also used in the treatment of latent TB infection and multidrug-resistant TB treatment (at high dose - H₇).

Storage

🌞 - 🛡️ - Below 25 °C

Levofloxacin (Lfx)

Therapeutic action

- Antibacterial (fluoroquinolone) with bactericidal activity

Presentation

- 250 mg and 500 mg tablets

Dosage

- Child under 30 kg:
  - 6 months-under 5 years: 15 to 20 mg/kg/day in 2 divided doses
  - 5 years and over: 10 mg/kg once daily
- Child over 30 kg and adult: 750 to 1000 mg once daily
- Maximum dose: 1000 mg daily
- Patient with severe renal impairment: 750 to 1000 mg/dose, 3 times per week
<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Daily dose (mg)</th>
<th>500 mg tablet</th>
<th>250 mg tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>75-100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>90-120</td>
<td>-</td>
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<tr>
<td>7</td>
<td>105-140</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>120-160</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>135-180</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>150-200</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>165-220</td>
<td>-</td>
<td>½ tab x 2</td>
</tr>
<tr>
<td>12</td>
<td>180-240</td>
<td>-</td>
<td>½ tab x 2</td>
</tr>
<tr>
<td>13</td>
<td>195-260</td>
<td>-</td>
<td>½ tab x 2</td>
</tr>
<tr>
<td>14</td>
<td>210-280</td>
<td>-</td>
<td>½ tab x 2</td>
</tr>
<tr>
<td>15</td>
<td>225-300</td>
<td>-</td>
<td>½ tab x 2</td>
</tr>
<tr>
<td>16</td>
<td>240-320</td>
<td>-</td>
<td>½ tab x 2</td>
</tr>
<tr>
<td>17</td>
<td>255-340</td>
<td>-</td>
<td>½ tab x 2</td>
</tr>
<tr>
<td>18</td>
<td>270-360</td>
<td>-</td>
<td>½ tab x 2</td>
</tr>
<tr>
<td>19</td>
<td>285-380</td>
<td>-</td>
<td>½ tab x 2</td>
</tr>
<tr>
<td>20</td>
<td>200</td>
<td>-</td>
<td>1 tab</td>
</tr>
<tr>
<td>21</td>
<td>210</td>
<td>-</td>
<td>1 tab</td>
</tr>
<tr>
<td>22</td>
<td>220</td>
<td>-</td>
<td>1 tab</td>
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<tr>
<td>23</td>
<td>230</td>
<td>-</td>
<td>1 tab</td>
</tr>
<tr>
<td>24</td>
<td>240</td>
<td>-</td>
<td>1 tab</td>
</tr>
</tbody>
</table>
Contra-indications, adverse effects, precautions

- Do not administer to patients with history of allergy or tendon damage during a previous treatment with a fluoroquinolone.
- Administer with caution to children, adolescents and patients over 60 years (increased risk of tendon damage); patients with risk factors for QT interval prolongation (heart failure, bradycardia, hypokalaemia, etc.) or history of psychiatric disorders or seizures.
- May cause: gastrointestinal disturbances, headache, central nervous system disorders (dizziness, insomnia, depression, etc.), hypersensitivity reactions, photosensitivity, peripheral neuropathy, myalgia, tendinitis, tendon rupture; rarely, crystalluria.
- For the management of adverse effects, see Appendix 17.
- Avoid or monitor combination with drugs that prolong QT interval (amiodarone, bedaquiline, clofazimine, erythromycin, fluconazole, lopinavir, mefloquine, ondansetron, pentamidine, quinine, etc.) and warfarin.
- Do not administer simultaneously with antacids containing magnesium or aluminium, calcium, iron and zinc salts, didanosine (except enteric-coated formulation): administer 2 hours apart.
- Pregnancy and breastfeeding: safety is not established, considered as acceptable if vital for the mother.

Monitoring
Patient instructions

- May be taken with food but do not take milk-based product or antacids or multivitamins when taking a tablet, wait two hours.
- Maintain a good fluid intake.
- Protect your skin from sun.

Remarks

- An oral suspension (25 mg/ml) is available, however because of its high concentration of benzyl alcohol, it is contraindicated in children under 3 years. For long-term use in children no safety data are available.

Storage

- Below 25 °C

Linezolid (Lzd)

Therapeutic action

- Antibacterial (oxazolidinone) with bactericidal activity

Presentation

- 600 mg tablet
  Also comes in 400 mg tablet and 100 mg/5 ml powder for oral suspension.

Dosage

- Child under 30 kg: 30 mg/kg/day in 3 divided doses
- Child over 30 kg and adult: 600 mg once daily
- Maximum dose: 600 mg daily
<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Daily dose (mg)</th>
<th>600 mg tablet</th>
<th>100 mg per 5 ml oral suspension</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>150</td>
<td>–</td>
<td>2.5 ml x 3</td>
</tr>
<tr>
<td>6</td>
<td>180</td>
<td>–</td>
<td>3 ml x 3</td>
</tr>
<tr>
<td>7</td>
<td>210</td>
<td>–</td>
<td>3.5 ml x 3</td>
</tr>
<tr>
<td>8</td>
<td>240</td>
<td>–</td>
<td>4 ml x 3</td>
</tr>
<tr>
<td>9</td>
<td>270</td>
<td>–</td>
<td>4.5 ml x 3</td>
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<tr>
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<td>5 ml x 3</td>
</tr>
<tr>
<td>11</td>
<td>330</td>
<td>–</td>
<td>5.5 ml x 3</td>
</tr>
<tr>
<td>12</td>
<td>360</td>
<td>–</td>
<td>6 ml x 3</td>
</tr>
<tr>
<td>13</td>
<td>390</td>
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<td>18</td>
<td>540</td>
<td>–</td>
<td>9 ml x 3</td>
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<td>21</td>
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<td>–</td>
<td>10 ml x 3</td>
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<tr>
<td>22</td>
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<td>10 ml x 3</td>
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<tr>
<td>23</td>
<td>600</td>
<td>–</td>
<td>10 ml x 3</td>
</tr>
<tr>
<td>24</td>
<td>600</td>
<td>–</td>
<td>10 ml x 3</td>
</tr>
</tbody>
</table>
Contra-indications, adverse effects, precautions

- Administer with caution to patients with blood disorders or hypertension.
- May cause:
  - myelosuppression (decreased level of platelets after 10-14 days of treatment, decreased level of white blood cells, and anaemia), lactic acidosis;
  - optic and peripheral neuropathy (can be irreversible), diarrhoea, nausea.
- For the management of adverse effects, see Appendix 17.
- Avoid or monitor combination with serotonergic drugs such as tricyclic antidepressants (e.g. amitriptyline), selective serotonin reuptake inhibitors (e.g. fluoxetine, paroxetine), lithium, etc., as it may cause a serotonin syndrome.
- Administer concomitantly pyridoxine (vitamin $B_6$) to prevent neurotoxic effects (child: 5 to 10 mg/day; adult: 50 mg/day).
- **Pregnancy**: avoid (safety is not established), except if vital. To prevent neurotoxic effects, administer pyridoxine as above.
- **Breast-feeding**: avoid (safety is not established), except if vital. To prevent neurotoxic effects, administer pyridoxine as above. Supplement the breast-fed infant with pyridoxine (5 mg/day).

Monitoring
Patient instructions

• Take with or without food.

Storage

• No special temperature requirements

Meropenem (Mpm)

Forms, strengths and route of administration

• Powder for injection, in 500 mg vial, to be reconstituted with 10 ml of water for injection (50 mg meropenem/ml).
• Each dose is to be diluted in 5 ml/kg of 0.9% sodium chloride in children under 20 kg and in 100 ml of 0.9% sodium chloride in children 20 kg and over and adults and to be administered by IV infusion over 15 to 30 minutes.
• Use a deep line, preferably an implantable venous access device (Port-a-Cath).

Dosage

• Child under 30 kg: 20 to 40 mg/kg every 8 hours
• Child 30 kg and over and adult: 1500 to 2000 mg 2 times daily with 10 hours minimum between infusions
• Maximum dose: 6000 mg daily
• Renal insufficiency: 750 mg every 12 hours for CrCl 20-40 ml/minute; 500 mg every 12 hours for CrCl < 20 ml/minute

Symptomatic monitoring, visual acuity and colour discrimination before and during treatment; complete blood count weekly (first month), then monthly, and as needed based on symptoms.
<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Daily dose (mg)</th>
<th>Daily dose (ml) – IV infusion (500 mg per vial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>300</td>
<td>2 ml in 25 ml of 0.9% NaCl x 3</td>
</tr>
<tr>
<td>6</td>
<td>300</td>
<td>2 ml in 30 ml of 0.9% NaCl x 3</td>
</tr>
<tr>
<td>7</td>
<td>600</td>
<td>4 ml in 35 ml of 0.9% NaCl x 3</td>
</tr>
<tr>
<td>8</td>
<td>600</td>
<td>4 ml in 40 ml of 0.9% NaCl x 3</td>
</tr>
<tr>
<td>9</td>
<td>600</td>
<td>4 ml in 45 ml of 0.9% NaCl x 3</td>
</tr>
<tr>
<td>10</td>
<td>900</td>
<td>6 ml in 50 ml of 0.9% NaCl x 3</td>
</tr>
<tr>
<td>11</td>
<td>900</td>
<td>6 ml in 55 ml of 0.9% NaCl x 3</td>
</tr>
<tr>
<td>12</td>
<td>900</td>
<td>6 ml in 60 ml of 0.9% NaCl x 3</td>
</tr>
<tr>
<td>13</td>
<td>900</td>
<td>6 ml in 65 ml of 0.9% NaCl x 3</td>
</tr>
<tr>
<td>14</td>
<td>900</td>
<td>6 ml in 70 ml of 0.9% NaCl x 3</td>
</tr>
<tr>
<td>15</td>
<td>900</td>
<td>6 ml in 75 ml of 0.9% NaCl x 3</td>
</tr>
<tr>
<td>16</td>
<td>1200</td>
<td>8 ml in 80 ml of 0.9% NaCl x 3</td>
</tr>
<tr>
<td>17</td>
<td>1200</td>
<td>8 ml in 85 ml of 0.9% NaCl x 3</td>
</tr>
<tr>
<td>18</td>
<td>1200</td>
<td>8 ml in 90 ml of 0.9% NaCl x 3</td>
</tr>
<tr>
<td>19</td>
<td>1200</td>
<td>8 ml in 95 ml of 0.9% NaCl x 3</td>
</tr>
<tr>
<td>20</td>
<td>1200</td>
<td>8 ml in 100 ml of 0.9% NaCl x 3</td>
</tr>
<tr>
<td>21</td>
<td>1200</td>
<td>8 ml in 100 ml of 0.9% NaCl x 3</td>
</tr>
<tr>
<td>22</td>
<td>1200</td>
<td>8 ml in 100 ml of 0.9% NaCl x 3</td>
</tr>
<tr>
<td>23</td>
<td>1200</td>
<td>8 ml in 100 ml of 0.9% NaCl x 3</td>
</tr>
<tr>
<td>24</td>
<td>1650</td>
<td>11 ml in 100 ml of 0.9% NaCl x 3</td>
</tr>
</tbody>
</table>
Contra-indications, adverse effects, precautions

- Do not administer to patients with history of allergy to carbapenems.
- Administer with caution to patients allergic to cephalosporins (cross-hypersensitivity may occur).
- May cause:
  - nausea, vomiting (the infusion rate may be slowed down in case of nausea), diarrhoea;
  - neurotoxicity: confusional state, seizures (rarely compared to imipenem/cilastatin, most frequently in patients with history of seizures or renal impairment);
  - hypersensitivity reactions;
  - local reactions (phlebitis/thrombophlebitis).
- For the management of adverse effects see Appendix 17.
- Avoid or monitor combination with valproic acid (decreased concentration of valproic acid and risk of seizures).
- Pregnancy and breastfeeding: avoid unless the benefits outweigh the risks.

Monitoring

- Symptomatic monitoring.
Remarks

- Administer clavulanic acid 60 minutes before each dose of meropenem.
- Do not mix with other drugs in the infusion bag.

Storage

- Below 25 °C

Once reconstituted, solution should be used immediately (within 1 hour of preparation)

Moxifloxacin (Mfx)

Therapeutic action

- Antibacterial (fluoroquinolone) with bactericidal activity

Presentation

- 400 mg tablet

Dosage

- Child under 30 kg: 7.5 to 10 mg/kg once daily
- Child over 30 kg and adult: 400 mg once daily
- Maximum dose: 400 mg daily
<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Daily dose (mg)</th>
<th>400 mg tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>37.5-50</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>45-60</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>52.5-70</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>60-80</td>
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<td>16</td>
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<td>½ tab</td>
</tr>
<tr>
<td>24</td>
<td>180-240</td>
<td>½ tab</td>
</tr>
</tbody>
</table>
### Contra-indications, adverse effects, precautions

- Do not administer to patients with history of allergy or tendon damage during a previous treatment with a fluoroquinolone.
- Administer with caution to children, adolescents and patients over 60 years (increased risk of tendon damage); patients with risk factors for QT interval prolongation (heart failure, bradycardia, hypokalaemia, etc.) or history of psychiatric disorders or seizures.
- May cause: gastrointestinal disturbances, headache, central nervous system disorders (dizziness, insomnia, depression, etc.), hypersensitivity reactions, photosensitivity, peripheral neuropathy, myalgia, tendinitis, tendon rupture, QT prolongation; rarely, crystalluria.
- For the management of adverse effects see Appendix 17.
- Avoid or monitor combination with drugs that prolong QT interval (amiodarone, bedaquiline, clofazimine, erythromycin, fluconazole, lopinavir, mefloquine, ondansetron, pentamidine, quinine, etc.) and warfarin.
- Do not administer simultaneously with antacids containing magnesium or aluminium, calcium, iron and zinc salts, didanosine (except enteric-coated formulation): administer 2 hours apart.
- **Pregnancy and breastfeeding:** safety is not established, considered as acceptable when vital for the mother.

### Monitoring

<table>
<thead>
<tr>
<th>25</th>
<th>187.5-250</th>
<th>½ tab</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>&gt; 70</td>
<td>400</td>
<td>1 tab</td>
</tr>
</tbody>
</table>
Patient instructions

- May be taken with food but do not take milk-based product and antacids and multivitamins when taking a tablet, wait two hours.
- Maintain a good fluid intake.
- Protect your skin from sun.

Remarks

- Moxifloxacin is more frequently associated with QT prolongation than levofloxacin and ofloxacin.

Storage

- Below 25 °C

Para-aminosalicylic acid (PAS) and sodium salt of PAS

Therapeutic action

- Antibacterial with bacteriostatic activity

Presentation

- Para-aminosalicylic acid (PAS): delayed-release granules, 4 g sachet (PASER® Jacobus)
- Para-aminosalicylate sodium (sodium salt of PAS or PAS-sodium):
  - Powder for oral solution, 5.52 g sachet (PAS-Na® Olainfarm)
  - 60% w/w delayed-release granules, 9.2 g sachet or 100 g jar (MONOPAS® Macleods)

One 4 g sachet of PAS (PASER® Jacobus) = one 5.52 g sachet of PAS-sodium (PAS-Na® Olainfarm) = one 9.2 g sachet of PAS sodium 60% w/w (MONOPAS® Macleods).

Dosage (expressed in PAS)

- Child under 30 kg: 200 to 300 mg/kg/day in 2 to 3 divided doses (max. 8 g daily)
- Child over 30 kg and adult: 8 g once daily if tolerated or in 2 divided doses (max. 12 g daily)
- Patient with severe renal impairment: 8 g/day in 2 divided doses

For paediatric dosing: PAS (Jacobus) comes with a dosage scoop graduated in milligrams; PAS sodium (Macleods) with a measuring spoon graduated in grams.
<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Daily dose (in mg of PAS)</th>
<th>PASER® Jacobus (mg)</th>
<th>PAS-Na® Olainfarm (sachet)</th>
<th>MONOPAS 9.2 g® Mcleods (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>1000-1500</td>
<td>500 mg x 2</td>
<td>−</td>
<td>1.5 g x 2</td>
</tr>
<tr>
<td>6</td>
<td>1200-1800</td>
<td>750 mg x 2</td>
<td>−</td>
<td>1.5 g x 2</td>
</tr>
<tr>
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<td>750 mg x 2</td>
<td>−</td>
<td>2 g x 2</td>
</tr>
<tr>
<td>8</td>
<td>1600-2400</td>
<td>1000 mg x 2</td>
<td>−</td>
<td>2 g x 2</td>
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<td>−</td>
<td>3 g x 2</td>
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<td>−</td>
<td>3 g x 2</td>
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<tr>
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<td>2600-3900</td>
<td>1500 mg x 2</td>
<td>−</td>
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<tr>
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<td>2800-4200</td>
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<td>−</td>
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<td>−</td>
<td>4 g x 2</td>
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<td>−</td>
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<td>−</td>
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</tr>
<tr>
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<td>3600-5400</td>
<td>2000 mg x 2</td>
<td>−</td>
<td>4 g x 2</td>
</tr>
<tr>
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<td>3800-5700</td>
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<td>−</td>
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<td>−</td>
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<td>4200-6300</td>
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<td>−</td>
<td>6 g x 2</td>
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<td>4400-6600</td>
<td>2500 mg x 2</td>
<td>−</td>
<td>6 g x 2</td>
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<tr>
<td>23</td>
<td>4600-6900</td>
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<td>−</td>
<td>6 g x 2</td>
</tr>
<tr>
<td>24</td>
<td>4800-7200</td>
<td>3000 mg x 2</td>
<td>−</td>
<td>6 g x 2</td>
</tr>
</tbody>
</table>
Contra-indications, adverse effects, precautions

- Avoid or administer with caution to patients with hepatic or renal impairment or gastric ulcer.
- May cause:
  - frequent gastrointestinal disturbances (nausea, vomiting, gastritis, diarrhoea);
  - rarely: hypothyroidism, hepatitis, blood disorders, hypersensitivity reactions.
- For the management of adverse effects see Appendix 17.
- Monitor combination with ethionamide/prothionamide (increased risk of hypothyroidism and gastrointestinal disturbances).
- Pregnancy: safety is not established, no known teratogenicity.
- Breast-feeding: no contra-indication

Monitoring

- Symptomatic monitoring, liver and thyroid function

Patient instructions

- Take the granules mixed with acidic juices (apple or orange).
- Do not chew the granules.
- Do not use if the sachet is swollen or if granules are dark brown or purple.
- Shells of the granules may appear in the stool.

Remarks

- To increase tolerance, start with a low dose (4 g/day in 2 divided doses) then, increase the dose over 1 to 2 weeks to achieve the target dose.
• PAS and PAS-sodium may come in various strengths or proportions. As daily dosages are expressed in PAS, always check the content of PAS in the product: 1 g of PAS is equivalent to 1.38 g of PAS-sodium (e.g. one 9.2 g sachet of MONOPAS® 60% w/w contains 600 mg of PAS-sodium equivalent to approximately 435 mg of PAS per 1 g of granules).

Storage

☀ - ☀
• PAS: below 15 °C; may be stored at 40°C for 8 weeks maximum;
• PAS-sodium: below 25 °C

Pyrazinamide (Z)

Forms and strengths

• 400 mg tablet
• 150 mg dispersible tablet

Dosage

• Child under 30 kg: 35 mg/kg (30 to 40 mg/kg) once daily
• Child 30 kg and over and adult: 25 mg/kg (20 to 30 mg/kg) once daily
• Maximum dose: 2000 mg daily
• Renal insufficiency: 25 mg/kg 3 times a week
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<thead>
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<td>2 tab</td>
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<tr>
<td>8</td>
<td>240-320</td>
<td>–</td>
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<tr>
<td>9</td>
<td>270-360</td>
<td>–</td>
<td>2 tab</td>
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<tr>
<td>10</td>
<td>300-400</td>
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<tr>
<td>24</td>
<td>720-960</td>
<td>2½ tab</td>
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</table>
### Contra-indications, adverse effects, precautions

- Do not administer to patients with allergy to pyrazinamide, severe hepatic impairment or severe gout.
- May cause: gout and arthralgias, hepatotoxicity, gastrointestinal disturbances (epigastric pain, nausea and vomiting), hypersensitivity reactions; rarely, photosensitivity.
- For the management of adverse effects see Appendix 17.
- **Pregnancy:** no contra-indication
- **Breastfeeding:** no contra-indication

### Monitoring

- Symptomatic monitoring.
- Liver function in patients with hepatic impairment or under drug-resistant TB treatment.

### Patient instructions

- Take with or without food.
- Protect your skin from sun.

### Remarks
• For patients on drug-susceptible TB treatment, pyrazinamide is given as part of a fixed-dose combination.
• For the 6HRZEto regimen for drug-susceptible TB meningitis, the dose of pyrazinamide is 40 mg/kg once daily (max. 2000 mg daily).

Storage

itories – Below 25 ºC

Rifabutin (Rfb)

Forms and strengths

• 150 mg capsule

Dosage

• Child and adult: 5 to 10 mg/kg once daily
• Maximum dose: 300 mg daily
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<thead>
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<th>Daily dose (mg)</th>
<th>150 mg capsule</th>
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</thead>
<tbody>
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<td>1 caps</td>
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<tr>
<td>19</td>
<td>95-190</td>
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<tr>
<td>20</td>
<td>100-200</td>
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<tr>
<td>21</td>
<td>105-210</td>
<td>1 caps</td>
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<tr>
<td>22</td>
<td>110-220</td>
<td>1 caps</td>
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<tr>
<td>23</td>
<td>115-230</td>
<td>1 caps</td>
</tr>
<tr>
<td>24</td>
<td>120-240</td>
<td>1 caps</td>
</tr>
</tbody>
</table>
Contra-indications, adverse effects, precautions

- Do not administer to patients with hypersensitivity to rifamycins or history of severe haematological disorders (thrombocytopenia, purpura) during a previous treatment with a rifamycin.
- Administer with caution to patients with severe renal impairment or hepatic or haematological disorders.
- May cause:
  - gastrointestinal disturbances, hepatotoxicity;
  - haematological disorders (leukopenia, anaemia, thrombocytopenia), hypersensitivity reactions;
  - reversible uveitis.
- For the management of adverse effects see Appendix 17.
- Reduce the dose of rifabutin:
  - in patients taking boosted protease inhibitors (Appendix 19);
  - if rifabutin toxicity is suspected in patients taking clarithromycin, fluconazole or itraconazole.
- Rifabutin reduces the effect of many drugs (macrolides, some antiretrovirals, some hormones, warfarin, etc.):
  - in patients taking antiretrovirals, see Appendix 19;
  - in women using contraception, use injectable medroxyprogesterone or an intrauterine device;
  - for the other drugs, adjust dosage if necessary.

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<table>
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<tbody>
<tr>
<td>25</td>
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<td>1 caps</td>
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<tr>
<td>30-35</td>
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<tr>
<td>36-45</td>
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<tr>
<td>46-55</td>
<td>300</td>
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<tr>
<td>56-70</td>
<td>300</td>
<td>2 caps</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>300</td>
<td>2 caps</td>
</tr>
</tbody>
</table>
• Pregnancy and breastfeeding: avoid (safety not established). If used in late pregnancy, administer phytonemadione (vitamin K₁) to the mother and the neonate.

**Monitoring**

• Symptomatic monitoring.
• Liver function in patients with hepatic disease.
• Full blood count.

**Patient instructions**

• Take with or without food.
• Harmless orange-red discoloration of the urine, faeces, sweat, saliva, sputum, tears and other body fluids.

**Storage**

☀ - ⚫ - Below 25 °C

**Rifampicin (R)**

**Forms and strengths**

• 300 mg capsule and 150 mg tablet

**Dosage**

• Child under 30 kg: 15 mg/kg (10 to 20 mg/kg) once daily
• Child 30 kg and over and adult: 10 mg/kg (8 to 12 mg/kg) once daily
• Maximum dose: 600 mg daily
• Hepatic impairment: 8 mg/kg once daily max.
<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Daily dose (mg)</th>
<th>300 mg capsule</th>
<th>150 mg tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
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<td>160-320</td>
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<tr>
<td>24</td>
<td>240-480</td>
<td>1 tab</td>
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</tr>
</tbody>
</table>
Contra-indications, adverse effects, precautions

- Do not administer to patients with hypersensitivity to rifamycins or history of severe haematological disorders (thrombocytopenia, purpura) during a previous treatment with a rifamycin.
- Avoid or administer with caution to patients with hepatic disorders.
- May cause:
  - gastrointestinal disturbances, headache, drowsiness, hepatotoxicity;
  - influenza-like symptoms, thrombocytopenia, hypersensitivity reactions.
- For the management of adverse effects, see Appendix 17.
- Rifampicin reduces the effect of many drugs (antimicrobials, some antiretrovirals, some hormones, antidiabetics, corticosteroids, phenytoin, direct-acting antivirals for chronic hepatitis C, warfarin, etc.):
  - in patients taking antiretrovirals, see Appendix 19;
  - in women using contraception, use injectable medroxyprogesterone or an intrauterine device;
  - in the event of concomitant fluconazole administration, administer each drug 12 hours apart (rifampicin in the morning, fluconazole in the evening);
  - for the other drugs, adjust dosage if necessary.
- Pregnancy and breastfeeding: no contra-indication. If used in late pregnancy, administer phytomenadione (vitamin K₁) to the mother and the neonate.
Monitoring

- Symptomatic monitoring.
- Liver function in patients with hepatic disease.

Patient instructions

- Take without food (or with a small amount of food to increase gastrointestinal tolerance).
- Harmless orange-red discoloration of the urine, faeces, sweat, saliva, sputum, tears and other body fluids.

Remarks

- For patients on drug-susceptible TB treatment, rifampicin is given as part of a fixed-dose combination.
- For the 6HRZEO regimen for drug-susceptible TB meningitis, the dose of rifampicin is 20 mg/kg once daily (max. 600 mg daily).
- Rifampicin is also used in the treatment of latent TB infection.

Storage

🌞 – 🌫 – Below 25 °C

Streptomycin (S)

Forms, strengths and route of administration

- Powder for injection, in vial of 1 g streptomycin base, to be dissolved in 4 ml of water for injection, for IM injection
  DO NOT ADMINISTER BY IV INJECTION.

Dosage

- Adolescent 30 kg and over and adult: 12 to 18 mg/kg once daily
- Adult 60 years and over: 15 mg/kg 3 times a week
- Maximum dose: 1000 mg daily
- Renal insufficiency: 12 to 15 mg/kg 2 or 3 times a week

The daily doses take into account the displacement volume (see note below).
**Note**: displacement volume
Powders for injection are usually formulated such that after reconstitution the final content of the vial corresponds to an adult dose. Errors may occur when only part of the reconstituted solution is to be administered and no allowance is made for the displacement volume. The risk of error increases the greater the weight of the powder and the smaller the volume of solvent used.

**Contra-indications, adverse effects, precautions**
- Do not administer to children or adolescents under 30 kg and patients with allergy to aminoglycosides.
- Administer with caution to patients 60 years and over or patients with pre-existing renal, vestibular, auditory or severe hepatic impairment.
- May cause:
  - ototoxicity, nephrotoxicity, electrolyte disturbances; rarely, hypersensitivity reactions;
  - local pain after injection.
- For the management of adverse effects see Appendix 17.
- Avoid or monitor combination with other ototoxic and/or nephrotoxic drugs (furosemide, amphotericin B, tenofovir, etc.)
- **Pregnancy**: CONTRA-INDICATED
- **Breastfeeding**: no contra-indication

### Monitoring

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Daily dose (mg)</th>
<th>Daily dose (ml) - IM injection (1 g in 4 ml of water for injection; final volume 4.83 ml; 207 mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-29</td>
<td></td>
<td>Not used in patients &lt; 30 kg</td>
</tr>
<tr>
<td>30-33</td>
<td>500</td>
<td>2.4 ml</td>
</tr>
<tr>
<td>34-40</td>
<td>600</td>
<td>2.8 ml</td>
</tr>
<tr>
<td>41-45</td>
<td>700</td>
<td>3.4 ml</td>
</tr>
<tr>
<td>46-50</td>
<td>800</td>
<td>4 ml</td>
</tr>
<tr>
<td>51-70</td>
<td>900</td>
<td>4.4 ml</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>1000</td>
<td>Entire volume</td>
</tr>
</tbody>
</table>
Patient instructions

- Symptomatic monitoring.
- Audiometry, serum creatinine and electrolytes (K, Ca, Mg).

Patient instructions

- Maintain a good fluid intake to limit renal problems.

Remarks

- Use a different site for each injection (absorption may be delayed if the same site is used repeatedly).

Storage

- Below 25 °C

Patient instructions

Update: January 2022

- Patients on drug-susceptible TB treatment
- Patients on drug-resistant TB treatment

Patients on drug-susceptible TB treatment

TB drugs are usually well tolerated. However, inform patients that they should immediately seek medical attention in the event of:

- Skin rash
- Yellowing of the skin or eyes or dark urine
- Numbness or tingling of fingers or toes
- Decreased urination
- Palpitations
- Blurred vision, reduced visual acuity, blind spot, green-red colour blindness, eye pain, sensitivity to light
- Pain, burning, swelling of a tendon or muscle
- Pain or swelling in the joints
Patients on drug-resistant TB treatment

Inform patients that they should immediately seek medical attention in the event of:

- Skin rash
- Yellowing of the skin or eyes or dark urine
- Numbness or tingling of fingers or toes
- Decreased urination
- Palpitations
- Dizziness or hearing loss
- Blurred vision, reduced visual acuity, blind spot, green-red colour blindness, eye pain, sensitivity to light
- Muscle cramps, spasms, or weakness
- Pain, burning, swelling of a tendon or muscle
- Pain or swelling in the joints
- Personality changes (depression, aggressive behaviour, anxiety)
- Severe abdominal upset or severe nausea, vomiting, black or bloody stools
- Unusual bleeding

Appendix 11. Compassionate use

11.1 Definitions

The term “compassionate use” refers to the use of potentially life-saving experimental treatments to patients suffering from a disease for which no satisfactory authorised therapy exists and/or who cannot enter a clinical trial. For many patients, these treatments represent their last hope. Experimental treatment is below referred to as investigational new drug (IND).

11.2 Indications

Both MDR-TB and XDR-TB can be life-threatening diseases for which approved drugs alone may be ineffective. In some cases, experimental TB drugs, used in combination with approved drugs, could potentially be effective or life-saving.

Compassionate use may be considered for patients presenting with a life-threatening condition (e.g. deteriorating clinical condition due to TB and/or severe immune depression) when:

- Available treatments have failed or are very likely to fail (e.g. regimen comprises less than 3 highly likely effective drugs and/or clinical evolution shows that the treatment is not effective).
- No medical or surgical options are appropriate.
- At least one highly likely effective drug is available (based in the DST result and previous use by the patient). The IND should never be used in monotherapy. It should always be used in conjunction with
other drug(s) with proven or probable efficacy in order to prevent emergence of resistance to the IND. In that respect, will be taken into consideration on a case by case basis:

- the number of remaining drug(s) and their bactericidal or bacteriostatic activity: at least one bactericidal or 2 bacteriostatic drugs could be considered as a minimum;
- the reliability of the DST to the remaining drug(s), treatment history prior to the last DST result;
- the vulnerability to resistance amplification of the IND if known;
- the use of the IND does not result in the discontinuation of an essential effective drug. Special attention will be paid if the use of the IND imposes the replacement of an anti-TB drug by a less effective one.

Compassionate use might be considered for a single patient or a group of patients presenting similar characteristics.

The use of two INDs would basically follow the same indications and conditions. Possible interactions and overlapping toxicity between the INDs have to be taken into consideration.

### 11.3 Minimal requirements

Compassionate use should only be considered if conditions for an adequate management of DR-TB patients are in place: optimal treatment regimen; clinical, biological and bacteriological monitoring; adherence support and follow-up. Results of DST by a validated laboratory are critical to decision making.

In addition to the basic components of regular DR-TB case management a specific monitoring might be required for the use of an IND.

It is essential that a reporting system is in place in order to diligently report any adverse events.

### 11.4 National regulations

In most countries, only drugs for which a marketing authorization has been granted by the national regulatory agency can be used in humans. Some national regulatory agencies have developed mechanisms to facilitate the access to new drugs at different stages of development, but before market approval. In this case, a party can apply for approval of an IND and then seek the proper permission to import the drug to a country. The use of an IND requires permission from the proper national regulatory authorities and/or country ethic boards.

### Appendix 12. Dose adjustments in renal insufficiency

**Update: January 2022**

### 12.1 Normal values for creatinine clearance (CrCl)
12.2 Estimation of CrCl (Cockcroft-Gault method)

12.2.1 If serum creatinine is in µmol/litre

\[
\text{Weight (kg)} \times (140 - \text{age}) \times (\text{constant})
\]
\[
\frac{\text{Serum creatinine (µmol/litre)}}{}
\]

The constant = 1.04 for women and 1.23 for men

12.2.2 If serum creatinine is in mg/dl

\[
\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dl)}}
\]

For women, the result must be multiplied by 0.85.

Example (calculation with serum creatinine in µmol/litre)\(^a\):
A woman on cyclosine (Cs), 50 kg, 46 years, serum creatinine = 212 µmol/litre

- **Step 1** - Calculate the CrCl:
  \[50 \times (140 - 46) \times 1.04 = 4,888\]
  \[4,888 \div 212 = 23.1\]
  For this patient, the CrCl is 23.1 ml/minute

- **Step 2** - CrCl is < 30 ml/minute, administer 250 mg of Cs once daily or 500 mg 3 times a week.

- **Step 3** - Adjust each drug as required according to the table below.

12.2.3 Overweight and obese patients

For overweight (BMI > 25) or obese (BMI > 30) patients, use the ideal body weight (IBW) rather than the actual body weight to avoid overestimation of the CrCl.

The IBW is calculated using the patient's height\(^b\):

IBW women (kg) = 45.4 + 0.89 (height in cm – 152.4)
IBW men (kg) = 49.9 + 0.89 (height in cm – 152.4)

Example:
A woman, weight 70 kg, height 160 cm (BMI = 27.3, i.e. overweight)
\[45.4 + 0.89 (160 - 152.4) = 45.4 + 0.89 (7.6) = 45.4 + 6.76 = 52.2\]
For this patient, the IBW is 52 kg.

12.3 Dosing of TB drugs in renal insufficiency
<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose and frequency if Clcr &lt; 30 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>No change</td>
</tr>
<tr>
<td>R</td>
<td>No change</td>
</tr>
<tr>
<td>Z</td>
<td>25 mg/kg 3 times a week (not daily)</td>
</tr>
<tr>
<td>E</td>
<td>15-25 mg/kg 3 times a week (not daily)</td>
</tr>
<tr>
<td>Rfb</td>
<td>No change</td>
</tr>
<tr>
<td>Mfx</td>
<td>No change</td>
</tr>
<tr>
<td>Lfx</td>
<td>750-1000 mg 3 times a week (not daily)</td>
</tr>
<tr>
<td>Bdq(^{(a)})</td>
<td>No change</td>
</tr>
<tr>
<td>Lzd</td>
<td>No change</td>
</tr>
<tr>
<td>Cfz</td>
<td>No change</td>
</tr>
<tr>
<td>Cs(^{(b)})</td>
<td>250 mg once daily or 500 mg 3 times a week</td>
</tr>
<tr>
<td>Dlm(^{(a)})</td>
<td>No change</td>
</tr>
</tbody>
</table>
| Ipm/Cln | 750 mg every 12 hours for CrCl 20-40 ml/min  
          | 500 mg every 12 hours for CrCl < 20 ml/min |
| Mpm   | 750 mg every 12 hours for CrCl 20-40 ml/min  
          | 500 mg every 12 hours for CrCl < 20 ml/min |
| Am\(^{(c)}\) | 12-15 mg/kg 2 or 3 times a week (not daily) |
| S\(^{(c)}\) | 12-15 mg/kg 2 or 3 times a week (not daily) |
| Eto/Pto | No change    |
| PAS\(^{(d)}\) | 4 g 2 times daily |
| H\(^{h}\) | No information |

\(^{(a)}\) indicate different dosing schedules.

\(^{(b)}\) Dosing may vary based on specific patient conditions.

\(^{(c)}\) Dosing may be adjusted based on weight.

\(^{(d)}\) PAS dosing may require monitoring for side effects.

\(^{(h)}\) H dosing may vary based on individual patient response.
Appendix 16. Basic TB infection control risk assessment tool

<table>
<thead>
<tr>
<th>Amx/Clv</th>
<th>No change</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>No change</td>
</tr>
<tr>
<td>Pa</td>
<td>No information</td>
</tr>
</tbody>
</table>

(a) Use with caution in case of severe renal insufficiency or dialysis (limited data).
(b) Monitor carefully for signs of neurotoxicity.
(c) Use with caution in case of severe renal insufficiency or dialysis (increased risk of nephrotoxicity and ototoxicity).
(d) Avoid sodium salt formulations of PAS in patients with renal disease (risk of excessive sodium load).
(e) On a case-by-case basis, consider once daily dosing (e.g. 500/125 mg every 24 hours) for patients with CrCl < 10 ml/minute.

Notas
(a) If possible use a calculator to avoid errors, e.g.:
   https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation
(b) If possible use a calculator to avoid errors, e.g.:
   https://www.mdcalc.com/ideal-body-weight-adjusted-body-weight

Appendix 17. Management of adverse effects

Update: January 2022

- Gastrointestinal disorders
  - Abdominal pain
Gastrointestinal disorders

- Diarrhoea
- Epigastric pain
- Hepatotoxicity
- Metallic taste
- Nausea and vomiting

- Neurotoxicity
  - Depression
  - Headache
  - Optic neuritis
  - Ototoxicity
  - Peripheral neuropathy
  - Psychosis
  - Seizures

- Endocrine disorders
  - Gynecomastia
  - Hypothyroidism

- Dermatological disorders
  - Alopecia
  - Fungal infection
  - Photosensitivity
  - Skin reactions

- Musculoskeletal disorders
  - Arthralgias
  - Tendinitis/tendon rupture

- Miscellaneous
  - Electrolyte disorders
  - Haematologic disorders
  - Lactic acidosis
  - Nephrotoxicity
  - QT prolongation

Gastrointestinal disorders

- Abdominal pain
- Diarrhoea
- Epigastric pain
- Hepatotoxicity
- Metallic taste
- Nausea and vomiting
Abdominal pain

Eto or Pto, PAS, Cfz, Lzd, FQs, H, Z

Abdominal pain is common with MDR/RR-TB treatment. It can be the early sign of severe adverse effects such as hepatitis, pancreatitis, or lactic acidosis.

Deposition of Cfz crystals may cause severe abdominal pain (presentation of acute abdomen). In this case, stop Cfz until symptoms resolve.

Diarrhoea

PAS, FQs, Eto or Pto, Amx/Clv, Ipm/Cln or Mpm

Diarrhoea, along with cramping, can cause significant difficulty and lead to discontinuation of treatment.

PAS often causes diarrhoea at treatment initiation. It usually resolves or improves substantially after some weeks.

For diarrhoea with no blood in stools and no fever, loperamide PO (adult: 4 mg followed by 2 mg after each loose stool to a maximum of 10 mg daily) may be used intermittently, especially when the patient needs to attend social functions or return to work, but not on a daily basis.

Encourage the patient to tolerate some degree of diarrhoea. Prevent (encourage fluid intake including oral rehydration solution) or treat dehydration.

In the event of severe diarrhoea, particularly if associated with blood in stools, severe abdominal pain, or fever > 38.5 °C, consider other causes such as acute bacterial enteritis, or pseudo-membranous colitis (C. difficile) due to FQs. Do not use loperamide in bloody diarrhoea or diarrhoea associated with fever.

Monitor serum electrolytes in patients with severe diarrhoea on QT prolonging drugs.

Epigastric pain
GAstritis (epigastric burning or cramp relieved by eating) or dyspepsia (epigastric pain or discomfort following meals, often accompanied by bloating, sensation of fullness and nausea) are frequent with PAS, Eto or Pto.

- For gastritis: 
  **omeprazole** PO: 20 mg once daily in the morning for 7 to 10 days. In severe or recurrent cases, dose may be increased to 40 mg once daily and the treatment may be prolonged for up to 8 weeks. Histamine H2-antagonists (e.g., ranitidine) may be an alternative.

- For dyspepsia: 
  **omeprazole** PO: 10 mg once daily in the morning for 4 weeks

Haematemesis (vomiting of blood) and melena (black stools) are symptoms of a bleeding gastric ulcer and require urgent intervention.

## Hepatotoxicity

**Z, H, R, Eto or Pto, PAS, Bdq, Amx/Clv**

All TB drugs may cause hepatotoxicity. However, certain drugs are likely more responsible than others for this adverse effect.

The liver function tests (LFTs) used for the diagnosis and monitoring of hepatotoxicity are serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin.

A mild, transient elevation of ALT and AST may be observed during treatment and usually remains asymptomatic. Significant hepatotoxicity is usually symptomatic.

Clinical features resemble that of viral hepatitis. Early symptoms include malaise, fatigue, loss of appetite, muscle and joint pain. Nausea, vomiting and abdominal pain are common in severe toxicity. Jaundice, scleral icterus, dark (tea-coloured) urine and discoloured stool are signs of clinical worsening. Differential diagnosis includes infections (e.g. viral hepatitis, cytomegalovirus, leptospirosis, yellow fever, rubella), chronic alcohol use and hepatotoxicity due to other drugs (e.g. anti-epileptics, paracetamol, sulfa drugs, erythromycin).

Clinical hepatitis can be fatal and action should be taken immediately.

### 1) General management

- Patient with symptoms of hepatitis: 
  Stop all TB drugs and perform LFTs:
    a) AST or ALT or bilirubin ≥ 3 times upper limit of normal (ULN): wait for resolution of symptoms,
perform LFTs weekly and restart TB treatment when LFTs are < 3 times ULN.

b) AST, ALT and bilirubin < 3 times ULN and mild symptoms (no jaundice): restart TB treatment, closely monitor the patient and perform LFTs weekly. Continue TB treatment as long as LFTs levels remain < 3 ULN and there are no signs of worsening hepatitis.

- Patient without symptoms of hepatitis, but elevated LFTs:
  a) AST or ALT ≥ 5 times ULN or bilirubin ≥ 3 ULN: stop all TB drugs and perform LFTs weekly. Restart TB treatment when LFTs return < 3 times ULN.
  b) AST and ALT < 5 times ULN and bilirubin < 3 ULN: continue TB treatment and perform LFTs weekly.

If LFTs continue to increase after stopping TB treatment, then ongoing progressive drug-induced hepatitis or an unrelated cause of hepatitis should be suspected.

2) Patient on DS-TB treatment

In most cases, the same treatment can be resumed without incident. The objective is to resume the initial regimen or an alternative regimen as rapidly as possible.

If symptoms reappear or LFTs re-increase, try to reintroduce the TB drugs one by one. Start with E and R and reintroduce H three to 7 days later. If E, R and H have been introduced and the LFT abnormalities have not recurred, do not introduce Z as it is most likely the causative agent.

The alternative regimen depends on the drug causing hepatotoxicity:
- Z is involved: 2 (HR)E/7 (HR)
- H is involved: 6RZE-Lfx
- R is involved: treat as MDR/RR-TB

3) Patient on DR-TB treatment

When restarting TB treatment, start with the drugs least hepatotoxic (E, Lfx or Mfx, Cs or Trd, Dlm, Am or S, Ipm/Cln or Mpm), then drugs moderately hepatotoxic (Bdq, Cfx, Amx/Clav), then give the most hepatotoxic (Z, H, R, Eto or Pto, PAS). Add drugs one at a time every 5 to 7 days, and check LFTs.

The causative agent can generally be identified in this manner. It can be discontinued if not essential and replaced with another less hepatotoxic TB drug.

**Note:** hepatotoxicity may occur in patients receiving regimens containing pretomanid (Pa-Mfx-Z and Bdq-Pa-Lzd). However, the responsible drug has not been determined.

**Metallic taste**

Eto or Pto, FQs
Encourage the patient to tolerate this adverse effect. Normal taste returns when TB treatment is stopped.

# Nausea and vomiting

**Eto or Pto, PAS, Z, Amx/Clv, Cfz, Lzd, IpM/Cln or Mpm, Bdq**

Nausea and vomiting are frequent, especially with Eto or Pto and PAS during the first few weeks of treatment. To avoid nausea and vomiting, these drugs can be initiated at low dose with gradual increase over one to 2 weeks.

- **Always look for:**
  - Signs of dehydration (thirst, dry mouth, sunken eyes)
  - Serum electrolytes disorders if vomiting
  - Signs of hepatitis
  - Haematemesis and melena
- Dehydration and electrolyte disorders should be corrected as necessary.
- Treat nausea and vomiting aggressively, using a stepwise approach:

## First phase - Adjust administration of the responsible drug

- Try to identify the drug(s) causing nausea and vomiting. Stop it/them for 2 or 3 days, then gradually reintroduce.
- Administer the drug(s) causing nausea at bedtime.
- Patient on PAS:
  - Take one hour after taking other TB drugs.
  - If PAS is taken once daily, take in 2 divided doses.
- Encourage the patient: nausea and vomiting often improve over the first weeks and may resolve entirely with time.

## Second phase - Administer an antiemetic

**Ondansetron** PO 30 minutes before TB drugs:

- Child 6 months to < 2 years: 2 mg once daily
- Child 2 to < 4 years: 2 mg 2 times daily
- Child 4 to < 12 years: 4 mg 2 times daily
- Child ≥ 12 years and adult: 4 to 8 mg 2 times daily

Ondansetron is a QT prolonging drug and should be avoided in patients on Cfz, Bdq, Mfx, Dlm, Lfx.
In adults, when ondansetron is not available or is to be avoided:

**metoclopramide** PO:

Adult < 60 kg: 5 mg 3 times daily

Adult ≥ 60 kg: 10 mg 3 times daily

The interval between each dose should be at least 6 hours (even in the event of vomiting). Do not use metoclopramide if neurological problems develop.

or

**promethazine** PO 30 minutes before TB drugs:

Adult: 25 mg

**Third phase - Reduce the dose or temporarily stop the responsible drug**

- Patient on Eto or Pto: consider reducing dose by one weight class (e.g. if taking 1000 mg daily, reduce to 750 mg). Avoid giving an adult weighing more than 33 kg less than 500 mg daily of Eto or Pto.
- Patient on Cfz: reduce the dose by half.
- In the event of intractable nausea and vomiting, stop all TB drugs until symptoms resolve.

**Note:** if there is excessive anxiety over the nausea caused by TB drugs, consider adding **diazepam** PO (adult: 5 mg 30 minutes before TB drugs). This can help to avoid “anticipation nausea”. The treatment must be short as benzodiazepines may cause dependence and tolerance. Do not exceed 10 days of treatment.

**Neurotoxicity**

- **Depression**
- **Headache**
- **Optic neuritis**
- **Ototoxicity**
- **Peripheral neuropathy**
- **Psychosis**
- **Seizures**

**Depression**
Cs or Trd, Eto or Pto

The treatment of MDR/RR-TB may contribute to depression. Depressive symptoms may fluctuate during TB treatment. History of depression may increase the risk of developing depression during treatment, but is not a contra-indication to use of any of the above TB drugs.

Consider lowering the dose or discontinuing a suspected TB drug, provided this does not compromise the effectiveness of TB treatment.

Other interventions include psychological support to patient (and family if needed) and, when necessary antidepressant treatment.

Avoid selective serotonin reuptake inhibitors and tricyclic antidepressants with Lzd (risk of serotonin syndrome).

Suicidal ideation is more commonly associated with Cs or Trd. Evidence of suicidal ideation should prompt immediate action:

- Keep the patient in the hospital for surveillance.
- Stop Cs or Trd.
- Lower the dose of Eto or Pto to 500 mg daily until the patient is stable.
- Refer to mental health consultation.

Headache

Cs or Trd, Bdq, Dlm, FQs

Headache is common during the first months of treatment. It can be treated with analgesics. Headache due to Cs or Trd can be prevented by starting at low dose (250 to 500 mg daily), with gradual increase over 1 to 2 weeks.

Optic neuritis

Lzd, E; rarely Eto or Pto

This adverse effect is typically due to Lzd and E.

Symptoms include loss of red-green colour distinction, reduced visual acuity and central scotoma. Loss of red-green colour distinction is the first sign. In this case, stop the suspect drug immediately and permanently.
Symptoms are usually reversible after discontinuation of the drug, but optic neuritis due to Lzd may be irreversible.

**Ototoxicity**

**Aminoglycosides; rarely: Cs or Trd, FQs, Eto or Pto, H, Lzd**

Hearing loss, tinnitus and/or vestibular disorders (vertigo, dizziness, imbalance) are signs of ototoxicity. Ototoxicity is most commonly observed in patients receiving large cumulative doses of aminoglycosides. Concomitant use of loop diuretics (furosemide), particularly in patients with renal insufficiency, may exacerbate ototoxicity.

Baseline and follow-up audiometry is required to detect early hearing loss. Hearing loss in high frequencies (> 4000 Hz) is often the first sign of auditory toxicity due to aminoglycosides and can be unnoticed by the patient.

In case of hearing loss, tinnitus or vestibular disorders, discontinue the suspected drug if this does not compromise the effectiveness of TB treatment.

If no alternative is available, reduce the dose of aminoglycoside (3 times weekly rather than daily, e.g. on Monday, Wednesday and Friday). Continuation of aminoglycoside therapy despite hearing loss almost always results in deafness.

Tinnitus and vestibular disorders can rarely be due to the following drugs: Cs or Trd, FQs, Eto or Pto, H and Lzd. If stopping the aminoglycoside does not improve symptoms, other drugs can be discontinued to see if the symptoms improve, then reintroduced one by one to see if symptoms return. Drug-induced tinnitus and vestibular disorders can be irreversible.

**Peripheral neuropathy**

**Lzd, Cs or Trd, H, Eto or Pto; rarely E, FQs**

Peripheral neuropathy refers to damage to the nerves located outside of the central nervous system. This adverse effect is associated to several TB drugs but is commonly due to Lzd, Cs or Trd and H.
Peripheral neuropathy occurs most commonly in the lower extremities. Signs and symptoms include sensory disturbances (e.g. numbness, tingling, burning, pain, loss of temperature sensation), difficulty walking, weakness and decreased or absent deep tendon reflexes. At times, sensory changes may occur in upper extremities.

Linezolid-induced neuropathy is extremely painful and may be non-reversible.

1) Patient on DS-TB treatment

- To prevent isoniazid-induced peripheral neuropathy:
  Administer pyridoxine PO to patients at risk (pregnant and breastfeeding women, neonates and breastfed infants, and patients with HIV infection, alcohol dependency, malnutrition, diabetes, chronic hepatic disease, and renal impairment) along with their TB treatment:
  Neonate, infant and child < 5 kg: 5 mg once daily
  Child ≥ 5 kg and adult: 10 mg once daily

- If peripheral neuropathy develops:
  Administer pyridoxine PO
  Child < 12 years: 10 to 20 mg 2 times daily
  Child ≥ 12 years: 50 mg 2 times daily
  Adult: 50 mg 3 times daily
  For pain management: ibuprofen or paracetamol.

2) Patient on DR-TB treatment

- To prevent peripheral neuropathy:
  Administer pyridoxine PO:
  ▪ Patient on H: all patients at risk, as for DS-TB.
  ▪ Patient on Cs or Trd, Lzd, H\(^{h}\) and Eto or Pto:
    Neonate, infant, child: 1 to 2 mg/kg (usual range in child: 10 to 50 mg) once daily
    Adult: 100 mg once daily

- If peripheral neuropathy develops:
  ▪ Patient on Lzd: stop Lzd immediately. For mild symptoms not requiring analgesics, Lzd can be restarted at a lower dose once symptoms subside. For moderate or severe symptoms, stop Lzd permanently. Consider additional TB drugs to reinforce the therapeutic regimen.
  ▪ Patient on Cs or Trd or H\(^{h}\): stop these drugs. If they are essential to the regimen, they may be re-introduced once symptoms subside.

Other contributing causes should be addressed (e.g., diabetes or malnutrition).

Administer pyridoxine PO: 100 mg daily in adults until symptoms resolve.

For pain management: ibuprofen or paracetamol.

Physiotherapy may be of benefit.

If these measures are insufficient, treat as chronic neuropathic pain.

Do not use tricyclic antidepressants in patients on Lzd (risk of serotonin syndrome).

Do not use carbamazepine (strong CYP450 inducer) in patients on Bdq or Dlm.
Psychosis

Cs or Trd, FQs, H, Eto or Pto

Visual or auditory hallucinations, delusions, paranoia and bizarre behaviour are hallmarks of psychosis. Health personnel should be familiar with these symptoms to allow early detection.

The most likely TB drug involved is Cs or Trd, but psychotic symptoms may occur with FQs, H, Eto or Pto.

History of psychosis is not a contra-indication to the use of the above-mentioned drugs, though psychiatric symptoms are more likely to occur in such circumstances.

Some patients may need antipsychotic treatment throughout the duration of TB treatment. Psychosis is generally reversible upon discontinuation of TB treatment.

For acute psychosis:
- If patients are at risk of harming themselves or others: urgent hospitalisation.
- Stop Cs or Trd.
- Treat the acute psychosis.

Once psychotic symptoms have resolved, antipsychotic treatment can be tapered most of the time. Cs or Trd can be resumed, generally at lower dose. Antipsychotic treatment should be continued until the end of Cs or Trd treatment and then can usually be stopped gradually (do not stop it abruptly).

If the patient does not tolerate the reintroduction of Cs or Trd, another TB drug should be considered. Whenever psychosis occurs in a patient on Cs or Trd, check the serum creatinine. Cs or Trd is 100% renally excreted and a decrease in renal function can result in toxic levels of Cs or Trd. In this case, a temporary suspension of Cs or Trd and re-introduction at an adjusted dose may be needed (Appendix 12).

Seizures

Cs or Trd, H, FQs, Eto or Pto, Ipm/Cln or Mpm

All the above-mentioned drugs may cause seizures. However, rule out or treat other possible causes (e.g., epilepsy, meningitis, encephalitis, alcohol withdrawal, hypoglycaemia, stroke, cancer, or toxoplasmosis in HIV-infected patients).
In the event of seizures, measure blood glucose level and blood electrolytes. Measure also serum creatinine. With impaired renal function, TB drugs can reach toxic levels, causing seizures. Dosage adjustment may be necessary (Appendix 12).

A history of seizures is not an absolute contra-indication to the use of the above-mentioned drugs. However, do not use Cs or Trd if there is an alternative. In patients with epilepsy, seizures should be controlled with anti-epileptic therapy before starting TB treatment.

The use of TB drugs (especially H and R) in patients on antiepileptics may lead to decreased blood levels of antiepileptics and seizures.

In patients without history of seizures, a first episode of seizures on TB treatment is likely due to the TB drugs. However, none of the above drugs leave permanent damage.

If a patient has a seizure for the first time:

- Stop suspected TB drugs for a short period.
- Start antiepileptic treatment, especially in the event of repeated seizures after stopping suspected drugs. Do not use carbamazepine or phenytoin in patients receiving Bdq or Dlm (strong CYP450 inducers).
- Reintroduce TB drugs that are essential to TB treatment. Usually, they can be resumed at a lower dose, but the effective dose should be reached as soon as possible.

Antiepileptic treatment may be necessary until the end of the TB treatment.

### Endocrine disorders

- **Gynecomastia**
- **Hypothyroidism**

### Gynecomastia

**Eto or Pto**

Eto or Pto may cause breast enlargement in men and women. Galactorrhoea has been reported. Encourage the patient to tolerate this adverse effect. Symptoms resolve when Eto or Pto is stopped.

### Hypothyroidism
Eto or Pto, PAS

Symptoms appear slowly, are nonspecific and may include fatigue, muscle weakness, daytime sleepiness, excessive sensitivity to cold, dry skin, coarse hair, constipation, facial puffiness, and depression. Thyroid enlargement and delayed deep tendon reflexes may be seen on examination.

The diagnosis is confirmed by a serum level of thyroid-stimulating hormone (TSH) $\geq 10$ mIU/litre.

Eto or Pto and PAS may cause hypothyroidism, even more frequently when used together. If possible the responsible TB drugs should be replaced but may be continued if there is no alternative.

In both cases, replacement hormone therapy is required:

**levothyroxine** PO

Adult $< 60$ years: initially 75 to 100 micrograms once daily then, adjust in 25 microgram increments every 4 to 12 weeks according to response. Usual maintenance dose is 100 to 200 micrograms daily.

Adult $\geq 60$ years and/or with significant cardiovascular disease: initially 25 micrograms once daily then, adjust in 25 microgram increments every 4 to 12 weeks according to response. Usual maintenance dose is 100 to 125 micrograms daily.

The daily dose should be taken at the same time each day, 30 to 60 minutes before a meal or a caffeine-containing drink (e.g. coffee, tea) or other drugs to improve absorption.

Monitor TSH until it normalizes below 5 mIU/litre.

Thyroid dysfunction resolves upon discontinuation of TB treatment. Hormone replacement may be discontinued several months after TB treatment completion.

**Dermatological disorders**

- Alopecia
- Fungal infection
- Photosensitivity
- Skin reactions

**Alopecia**
H, Eto or Pto

Temporary and mild hair loss may (rarely) occur in the first months of treatment. Encourage the patient to tolerate this adverse effect. Symptoms resolve when TB treatment is stopped.

Fungal infection

FQs

Vaginal, penile, skin fold and oral candidiasis may occur in patients taking FQs. Topical antifungals or short-course oral antifungals are usually effective.

Photosensitivity

Cfz, FQs; rarely Z

Advise patient to avoid direct exposure to the sun, wear protecting clothes (e.g. long sleeves) and use sunscreen.

Skin reactions

All TB drugs

Skin reactions such as itch and skin rash may be hypersensitivity reactions due to any TB drug. General signs of hypersensitivity such as fever, dizziness, vomiting and headache may also occur. Skin reactions usually appear early during treatment, often in the first month, but rarely during the first week. Most skin reactions are mild or moderate. Severe – even lethal – exfoliative dermatitis (Stevens Johnson’s syndrome) may occasionally occur, particularly if administration of the TB drug continues after first signs of hypersensitivity appear.

Minor skin reactions
Major skin reactions

- Simple itching: symptomatic treatment (e.g. antihistamine) without interrupting or modifying the TB treatment.
- Localised, mild skin rash, with or without itching:
  - Rule out other possible causes unrelated to TB drugs (i.e. scabies, contact dermatitis).
  - If no obvious other cause, stop all TB drugs.
  - Give symptomatic treatment (an antihistamine, no corticosteroids except in emergencies) and wait for disappearance of symptoms.
  - Once the reaction has resolved, try to determine which drug caused the reaction (see rechallenge of TB drugs below).

Rechallenge of TB drugs

Each TB drug can be reinstated as a “challenge” (a test-dose). Introduce one drug at a time, starting with the drugs least likely to have caused the reaction.

Give the drugs in a setting where a health care provider can respond to any severe allergic reaction.

If a test-dose of any drug causes a reaction, discontinue this drug, unless it is deemed essential to the regimen (in this case, desensitisation can be considered).

- First-line TB drugs
  - Start with isoniazid over 3 days then add rifampicin over 3 days, etc.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Likelihood</th>
<th>Trial dose 1</th>
<th>Trial dose 2</th>
<th>Trial dose 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Least likely</td>
<td>50 mg</td>
<td>Full dose</td>
<td>Full dose</td>
</tr>
<tr>
<td>R</td>
<td>Least likely</td>
<td>75 mg</td>
<td>300 mg</td>
<td>Full dose</td>
</tr>
<tr>
<td>Z</td>
<td>Likely</td>
<td>250 mg</td>
<td>1000 mg</td>
<td>Full dose</td>
</tr>
<tr>
<td>E</td>
<td>Likely</td>
<td>100 mg</td>
<td>500 mg</td>
<td>Full dose</td>
</tr>
</tbody>
</table>

Note: if the initial reaction to treatment is severe, a weaker trial dose should be used (approximately 1/10th of the dose indicated for trial dose 1).

- Second-line TB drugs
  - Start with the most important drug in a regimen unless there is suspicion that it is the cause of the
reaction. Restart each TB drug one after the other, starting at about 1/10 of the dose on Day 1, half-dose on Day 2 and full dose on Day 3.

Musculoskeletal disorders

- Arthralgias
- Tendinitis/tendon rupture

Arthralgias

Z, Rfb, H, Bdq, FQs

Arthralgias generally diminish over time. Serum uric acid levels are frequently elevated, but this is of little clinical relevance. Anti-hyperuricaemic therapy is of no proven benefit in these patients.

Begin therapy with an anti-inflammatory agent, e.g. ibuprofen PO (adult: 400 to 800 mg 3 times daily). Paracetamol PO (adult: 500 to 1000 mg 3 times daily) may also help bring relief when given together with an anti-inflammatory drug.

If symptoms fail to resolve, consider lowering the dose of the suspected agent (most often Z), if this does not compromise the effectiveness of TB treatment.

Tendinitis/tendon rupture

FQs

In the acute phase, the main symptom of tendinitis is pain when moving the affected joint or palpating the tendon.

In later phase, continuous pain and tendon thickening or nodularity may be present.

The Achilles tendon is involved in most cases, but other joints may be affected (shoulder, hand, etc.). New and intense physical activities are not recommended during a treatment with a FQ.

Tendinitis is more common in older patients, patients with renal insufficiency or under corticosteroids.
Tendon rupture is a complication of tendinitis. Signs and symptoms include a snap or pop sound at the time of rupture, bruising, inability to move the joint and a lack of continuity of the tendon on palpation.

Early detection of tendinitis, symptomatic treatment, and discontinuation of FQ can prevent tendon rupture. If the TB treatment is likely to fail without the FQ, try to continue the FQ. Inform the patient that tendon rupture may occur, but that FQ is essential to prevent TB treatment failure.

Symptomatic treatment:
- Rest the joint involved.
- Pain management: application of ice, and ibuprofen PO:
  - Adult: 400 to 600 mg every 4 to 6 hours when required, maximum dose: 2400 mg daily.

Miscellaneous

- Electrolyte disorders
- Haematologic disorders
- Lactic acidosis
- Nephrotoxicity
- QT prolongation

Electrolyte disorders

Aminoglycosides

Electrolyte disorders can occur with the aminoglycosides and are typically reversible with discontinuation of therapy.

Other potential causes (vomiting and diarrhoea) should be treated if present.

If clinical signs of mild to moderate hypokalaemia develop (i.e. muscle cramps, spasms or weakness) or if serum potassium level is between 2.5-3.4 mmol/litre, potassium replacement is required:

**Potassium chloride** PO

Child under 45 kg: 2 mmol/kg (2 ml/kg) daily in divided doses
Child 45 kg and over and adult: 30 mmol (30 ml) 3 times daily

If clinical signs of severe hypokalaemia develop (i.e. marked muscle weakness, cardiac arrhythmias) or if serum potassium level is < 2.5 mmol/litre, hospitalise and urgently administer potassium chloride by slow IV infusion.

For a patient with hypokalaemia:
Most TB drugs can cause hematological disorders that may involve any blood cells (red cells, white cells, platelets). However, the TB drugs most involved are Lzd, R and H.

### Severity grade in adults

<table>
<thead>
<tr>
<th>Severity grade in adults</th>
<th>Anaemia</th>
<th>Neutropenia</th>
<th>Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>10.5 - 9.5 g/dl</td>
<td>1500 - 1000/mm³</td>
<td>100,000 - 75,000/mm³</td>
</tr>
<tr>
<td>Moderate</td>
<td>&lt; 9.5 - 8.0 g/dl</td>
<td>&lt; 1000 - 750/mm³</td>
<td>&lt; 75,000 - 50,000/mm³</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 8.0 - 6.5 g/dl</td>
<td>&lt; 750 - 500/mm³</td>
<td>&lt; 50,000 - 20,000/mm³</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>&lt; 6.5 g/dl</td>
<td>&lt; 500/mm³</td>
<td>&lt; 20,000/mm³</td>
</tr>
</tbody>
</table>

(a) Adapted from NIAID Division of Microbiology and Infectious Diseases, severity scale, Nov-2007.

1) **Patient on DS-TB treatment**

R can cause potentially life-threatening thrombocytopenia. This is more common when R is used intermittently.
Clinical features may include minor haemorrhage (e.g. epistaxis) or severe haemorrhage and thrombocytopenic purpura.

Measure platelets when thrombocytopenia is suspected:
- Moderate thrombocytopenia: stop R and monitor platelets weekly until > 75,000/mm³.
- Severe thrombocytopenia: stop all TB drugs. Hospitalise. Treat shock or severe haemorrhage.

In any event R should not be reintroduced.

2) **Patient on DR-TB treatment**

Lzd may cause anemia, neutropenia and/or thrombocytopenia.
Lactic acidosis

**Lzd**

Lactic acidosis is a rare but potentially life-threatening increase of lactic acid in the bloodstream, that can be due to mitochondrial toxicity of certain TB drugs, usually Lzd. Signs and symptoms include nausea and vomiting, abdominal pain, extreme fatigue, muscle cramps and increased respiratory rate.

If lactic acidosis is suspected, measure blood lactate and pH. Blood lactate ≥ 4 mmol/litre and pH < 7.35 confirm the diagnosis. Stop Lzd and hospitalise for adequate management.

Note that lactic acidosis may also be due to ART (NRTIs).
Nephrotoxicity

Aminoglycosides

Nephrotoxicity is diagnosed by a rise in serum creatinine above baseline. In its early form it is usually asymptomatic, which means it is very important to monitor serum creatinine while on aminoglycosides. Symptomatic cases may present with decreased urine output, evidence of volume overload (edema, anasarca or shortness of breath) or uremic symptoms such as mental status changes (confusion, somnolence).

Comorbidities such as diabetes or chronic renal failure are not a contra-indication to treatment with aminoglycosides, though caution must be exercised in such circumstances.

- If renal failure occurs:
  - Stop the aminoglycoside.
  - Rule out other causes of renal failure (e.g., diabetes, dehydration, other drugs, congestive heart failure, urinary obstruction, urinary tract infection, prostate hypertrophy).
  - Adjust doses of other TB drugs to creatinine clearance (Appendix 12).
  - Monitor serum creatinine and electrolytes every 1 to 2 weeks until stable.
- If renal function stabilises or improves and if the drug is essential, resume the aminoglycoside adjusted to creatinine clearance (Appendix 12).

QT prolongation

Cfz, Mfx\(^h\), Bdq, Mfx, Dlm, Lfx

Some TB drugs may cause QT prolongation and predispose to torsades de pointes, arrhythmias, and sudden death. ECG should be performed before starting TB treatment then monitored throughout the course of treatment in patients taking these drugs. Possible other causes include other QT prolonging drugs (Appendix 19), hypothyroidism and genetic causes such as long QT syndrome.

Mild or moderate QT prolongation (QTcF > 470 in women and > 450 ms in men and ≤ 500 ms) is common. Severe QT prolongation (QTcF > 500 ms or increase > 60 ms from baseline) is relatively rare.

- In all cases:
  - Measure serum electrolytes and correct electrolyte disorders if necessary.
  - Measure thyroid stimulating hormone (TSH) and, if necessary, treat hypothyroidism.
Appendix 17. Air change per hour (ACH) measurement recommendations

The ACH in a mechanically ventilated room should remain more or less constant, whereas natural ventilation will vary according to:

- Whether the doors/windows/vents in that room are open or not;
- Wind speed and direction;
- Temperature and humidity differential between inside and outside.

The ACH rate is one tool among others to assess if:

- The efficiency of the system in delivering the outdoor air and in removing the pollutants to each location in the room;
- The overall airflow direction is from clean to dirty zones.

To calculate the ACH in a given room:

- Start by drawing a sketch of the room;
- Measure the dimensions of the room and calculate the volume (in m$^3$);
- Measure the surface (in m$^2$) of all the openings/vents in the room and air direction across the openings/vents;
- Measure the air speed (in meters per second) using an anemometer.

$$ \text{ACH} = \frac{0.65 \times \text{air speed (m/s)} \times \text{opening area (m}^2\text{)} \times 3600}{\text{Room volume (m}^3\text{)}} $$

Summary of proposed specifications:

- For mild and moderate QT prolongation: monitor ECG at least weekly.
- For severe QT prolongation: stop QT prolonging drugs, hospitalise, perform continuous ECG monitoring until QT returns to normal. Once the patient is stable (normal QT CF and no electrolyte disorders), critical QT prolonging TB drugs can be reintroduced:
  - Patient on Bdq: consider resuming while suspending all other QT prolonging drugs.
  - Patient on Mfx: use Lfx instead.
  - Patient on Cfz or Dlm: consider stopping if alternatives are available.
  - Patient on QT prolonging non-TB drug: consider stopping it.
There are two main techniques to measure the ventilation. The most commonly used is the anemometer that measures the velocity (speed) of air (see manufacturer’s recommendations for various types of anemometers). The technique using the gas analyser is difficult and should only be used by trained staff.

### Appendix 18. Advantages and disadvantages of ventilation techniques

<table>
<thead>
<tr>
<th>Surface (m²)</th>
<th>Height (m)</th>
<th>ACH</th>
<th>Opening window surface area (m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single rooms</strong></td>
<td>&gt; 7.5 (2.5 x 3)</td>
<td>&gt; 3</td>
<td>&gt; 12</td>
</tr>
<tr>
<td><strong>Wards</strong></td>
<td>4.5 m²/patient</td>
<td>&gt; 3.5</td>
<td>&gt; 12</td>
</tr>
<tr>
<td><strong>Waiting rooms (preferably outside)</strong></td>
<td>3 m²/patient</td>
<td>&gt; 3.5</td>
<td>&gt; 12</td>
</tr>
<tr>
<td><strong>Sputum collection areas (preferably outside)</strong></td>
<td>&gt; 1.5</td>
<td>&gt; 2.5</td>
<td>&gt; 20</td>
</tr>
<tr>
<td><strong>Toilets</strong></td>
<td>&gt; 1.2</td>
<td>&gt; 2.5</td>
<td>&gt; 12</td>
</tr>
<tr>
<td><strong>Consultation rooms</strong></td>
<td>&gt; 7.5 (2.5 x 3)</td>
<td>&gt; 3</td>
<td>&gt; 12</td>
</tr>
<tr>
<td><strong>Central corridors (avoid in new buildings)</strong></td>
<td>&gt; 2</td>
<td>&gt; 3</td>
<td>&gt; 12</td>
</tr>
<tr>
<td>Installation/equipment</td>
<td>Climate</td>
<td>Technical considerations</td>
<td>Cost</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------</td>
<td>--------------------------</td>
<td>------</td>
</tr>
<tr>
<td></td>
<td>Cold</td>
<td>Hot</td>
<td></td>
</tr>
<tr>
<td>Windows and doors</td>
<td>no</td>
<td>yes</td>
<td>simple</td>
</tr>
<tr>
<td>Whirly birds</td>
<td>no</td>
<td>yes</td>
<td>very simple</td>
</tr>
<tr>
<td>Chimney</td>
<td>no</td>
<td>yes</td>
<td>very simple</td>
</tr>
<tr>
<td>Assisted natural ventilation</td>
<td>Ceiling, wall and desk fans</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Extractors/extractor exhaust fans</td>
<td>no</td>
<td>yes</td>
<td>simple</td>
</tr>
</tbody>
</table>
## Appendix 19. Potential overlapping toxicities of ARVs and anti-TB drugs

Drugs that are more strongly associated with the listed toxicities appear in bold lettering.

<table>
<thead>
<tr>
<th>Mechanical ventilation and air conditioning</th>
<th>Heating and air conditioning</th>
<th>Relative pressure between rooms</th>
<th>High consumption of energy</th>
<th>Could need heat exchange, heat filter, HEPA filter, ventilation system</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>Ideal</td>
<td>High</td>
<td>difficult</td>
<td>difficult</td>
</tr>
<tr>
<td>ideal</td>
<td>Difficult</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>difficult</td>
<td>High</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(R&D), solar power
<table>
<thead>
<tr>
<th>Toxicity</th>
<th>ARV agent</th>
<th>Anti-TB agent</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal pain</td>
<td>All ARVs</td>
<td>Eto/Pto, PAS, Cfz, FQs, H, Lzd, E, Z</td>
<td>Abdominal pain is common and often benign; however, it may be an early symptom of severe adverse effects such as pancreatitis, hepatitis or lactic acidosis.</td>
</tr>
<tr>
<td>Central nervous system (CNS) toxicity</td>
<td>EFV</td>
<td>Cs, H, Eto/Pto, FQs</td>
<td>EFV has a high rate of CNS adverse effects (dizziness, impaired concentration, depersonalization, abnormal dreams, insomnia and confusion) in the first 2-3 weeks of use, but they typically resolve on their own. If they do not resolve, consider substitution of the agent. There are limited data on the use of EFV with Cs; concurrent use is accepted practice as long as there is frequent monitoring for CNS toxicity.</td>
</tr>
<tr>
<td>Depression</td>
<td>EFV</td>
<td>Cs, FQ, Eto/Pto</td>
<td>Severe depression can be seen in 2.4% of patients receiving EFV. Consider substitution of EFV if severe depression develops.</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>All protease inhibitors, ddI (buffered formulation)</td>
<td>Eto/Pto, PAS, FQs Amx/Clv, Ipm/Cln</td>
<td>Diarrhoea is common. Also consider opportunistic infections as a cause of diarrhoea, or <em>Clostridium difficile</em> (pseudomembranous colitis).</td>
</tr>
<tr>
<td>Dysglycaemia (disturbed blood sugar regulation)</td>
<td>Protease inhibitors</td>
<td>Eto/Pto</td>
<td>PI tend to cause insulin resistance and hyperglycaemia. Eto/Pto may cause hypoglycaemia and poor glucose regulation in diabetics.</td>
</tr>
<tr>
<td>Electrolyte disturbances</td>
<td>TDF (rare)</td>
<td>Cm, aminoglycosides</td>
<td>Rule out more serious causes of headache such as bacterial or cryptococcal meningitis, toxoplasmosis, etc. Use of analgesics (ibuprofen, paracetamol) and good hydration</td>
</tr>
<tr>
<td>Headache</td>
<td>AZT, EFV</td>
<td>Cs</td>
<td></td>
</tr>
</tbody>
</table>
may help. Headaches secondary to AZT, EFV and Cs are usually self-limited.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Medications</th>
<th>Recommended Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis</td>
<td>NVP, EFV, all protease inhibitors (RTV)</td>
<td>Z, H, R, E, PAS, Eto/Pto When severe, stop both the ART and TB medications, and restart the TB medications first. Also consider CMX as a cause of hepatotoxicity if the patient is receiving this medication.</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>d4T</td>
<td>Eto/Pto, PAS Several studies show subclinical hypothyroidism associated with d4T.</td>
</tr>
<tr>
<td>Lactic acidosis</td>
<td>d4T, ddI, AZT, 3TC</td>
<td>Lzd Early detection and management of hyperlactatemia in order to prevent development of lactic acidosis.</td>
</tr>
<tr>
<td>Myelo-suppression</td>
<td>AZT</td>
<td>Lzd Monitor blood counts regularly. Replace AZT if bone marrow suppression develops. Consider suspension of Lzd. Also consider CMX as a cause if the patient is receiving this medication. Consider adding folinic acid supplements, especially if the patient is receiving CMX.</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>RTV, d4T, NVP, and most others</td>
<td>Eto/Pto, PAS, Z, Amx/Clv, Cft, Lzd, Ipm/Cln Persistent vomiting may be a result of developing lactic acidosis (especially common with long-term d4T use) and/or hepatitis secondary to medications.</td>
</tr>
<tr>
<td>Nephrotoxicity</td>
<td>TDF, IDV</td>
<td>Aminoglycosides, Cm TDF may cause renal injury with the characteristic features of Fanconi syndrome, hypophosphataemia, hypo-uricaemia, proteinuria, normoglycaemic glycosuria and, in some cases, acute renal failure. Avoid TDF in patients receiving aminoglycosides or Cm. If TDF is absolutely necessary, serum creatinine and electrolytes should be monitored at least every 2 weeks.</td>
</tr>
<tr>
<td>Optic neuritis</td>
<td>ddI</td>
<td>E, Eto/Pto, Lzd Suspend agent responsible for optic neuritis permanently and replace with an agent that does not cause optic neuritis.</td>
</tr>
<tr>
<td>Condition</td>
<td>Drugs</td>
<td>Other Drugs</td>
</tr>
<tr>
<td>----------------------------</td>
<td>----------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>d4T, ddl</td>
<td>Lzd</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>d4T, ddl</td>
<td>Lzd, Cs, H, Eto/Pto, S, Km, Amk, Cm, E, FQs</td>
</tr>
<tr>
<td>QT prolongation</td>
<td>RTV boosted PI</td>
<td>Bdq, Cfz, Mfx, other FQs</td>
</tr>
<tr>
<td>Skin rash</td>
<td>ABC, NVP, EFV, d4T and others</td>
<td>All anti-TB drugs</td>
</tr>
</tbody>
</table>

Adapted from WHO Guidelines for the programmatic management of drug-resistant tuberculosis[1].

**References**


**Appendix 19. Upper room ultraviolet germicidal irradiation (UVGI) system**

The use of UVGI in the upper part of rooms may be effective in killing or inactivating *M. tuberculosis* generated by infected persons.

**19.1 Mechanism of action**
UV lamps are installed into fixtures suspended from a ceiling or mounted on a wall. Fixtures are shielded with louvers or bafflers in order to block radiation below the horizontal plane of the fixtures. UV lights create in the upper portion of the room a germicidal zone where the bacilli are killed (Figure 1). Patients in the lower portion of the room are not exposed to UVGI lights. Good air mixing is needed to transport the air (and thereby the bacilli) to the upper portion of the room. Disinfection is achieved through the rapid dilution of contaminated lower room air with clean irradiated upper room air.

Figure 1

* 1 feet = 0.3048 m

From the WHO, Implementing the WHO Policy on TB Infection Control in Health-Care Facilities, Congregate Settings and Households

The lamps should irradiate the entire surface of the upper part of the room (Figure 2), in order to disinfect the largest possible volume of air mixed at a low speed between the upper and lower part of the room.

**UVGI Upper-room Irradiation**

Figure 2
Several factors influence the efficiency of UVGI systems:

- **Ventilation rate:** in controlled environment, at rates up to 6 air change per hour (ACH), UVGI systems increase the effect of air cleaning to > 12 ACH. But when ventilation rates are increased above 6 ACH, UVGI system effectiveness could be reduced because the time for bacteria irradiation is shorter.

- **Effective mixing:** within the room may be provided by natural convection currents or fans, preferably, ceiling ones. Low velocity ceiling fans boosted UVGI system’s effectiveness up to 33% when ACH was below 6.

- **Relative humidity:** studies have reported rapidly decreasing air cleaning effectiveness in UVGI systems when the relative humidity goes above 70%.

- **Installation:** the height of the room should be minimum 2.5 m and UVGI fixtures should be installed at the minimum height of 2.1 m. As a thumb rule, a 30W lamp should be sufficient for 18 m² of surface, but room shape and type of fixture should be taken into consideration when calculating the needs. For instance, wall-mounted lamps would have a smaller germicidal area than ceiling-mounted ones. Lamps should be on whenever there is a risk of TB transmission. For example, in rooms with hospitalized patients, the lamps should be turned on 24 hours a day.

- **Maintenance:** see below.

### 19.2 Maintenance

Dust-covered and/or old UVGI lamps are less effective, hence the need for a careful maintenance, including regular cleaning:

- Lamps and fixture surfaces should be wiped at least monthly (more often if necessary) with a cloth dampened with 70% alcohol. Do not use water and soap or any detergent. The cleaning should be performed when lamps and fixtures are cool.

- **Measurement of UVGI level:** must be done at installation and at least once a year. A UV light meter programmed to detect UV light on a wavelength of 254 nm is needed. Measurements should be performed at eye level in the occupied zone (~ 1.6 m) and in upper irradiated portion of the room, at a distance of 1.2 m from the fixture in all possible directions (imitating a circle with measurements in the diagram).
19.3 Disposal

UV lamps contain mercury and quartz and are considered as hazardous waste. Disposal is extremely difficult in many countries; this should be considered before implementing them. If adequate disposal of the lamps by specialized enterprises is not possible in the country, neither their repatriation; UV lamps should be disposed of by encapsulation (sealed in a metal 200 litre drum filled with concrete and then buried away from water sources).

Safety considerations

Reflecting surfaces in the irradiation area of UV lamps must be avoided (i.e. oil painted ceilings, etc.).

At certain wavelengths (including UV-C) UV exposure may be harmful. Skin exposure can produce sunburn (erythema). Exposure of the eyes can produce conjunctivitis (feeling of sand in the eyes, tearing) and/or keratitis (intense pain, sensitivity to light). These symptoms typically commence 6 to 12 hours after exposure.

Despite the fact that these are reversible conditions, health care workers should immediately report them to the IC officer. This could mean that UV irradiation is higher than previously thought at lower room level (lamp poorly positioned? Reflecting surface?).

The USA National Institute for Occupational Safety and Health (NIOSH) states that safe exposure limits are set below those found to initiate eye irritation, the body surface most susceptible to UV. Next table shows the permissible exposure times for given effective irradiances at 254 nm wavelength.

done while moving in circumference spaced of 1 m). Ideally, all upper room measurements should be around 30 μW/cm² to 50 μW/cm². Persons doing these measurements should wear protective equipment (UV-protective glasses, clothing made of tightly woven fabric, soft cotton gloves) and cover exposed skin with opaque creams with solar-protection factors > 15.

- UV lamps last between 5 000 and 10 000 hours of continue use (7 to 14 months). Check manufacturer's information. After this period, UV lamps rapidly lose effectiveness and need to be changed.
Exposures exceeding this limit would require the use of personal protection equipment to protect the skin and eyes.

In order to avoid overexposure of UVGI, education of health care workers should include basic information on UVGI systems and their potential harmful effects of if overexposure occurs.

<table>
<thead>
<tr>
<th>Permissible exposure time&lt;sup&gt;(a)&lt;/sup&gt; (Units given)</th>
<th>Effective irradiance (μW/cm&lt;sup&gt;2&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(Seconds)</strong></td>
<td></td>
</tr>
<tr>
<td>8 h</td>
<td>28,800</td>
</tr>
<tr>
<td>4 h</td>
<td>14,400</td>
</tr>
<tr>
<td>2 h</td>
<td>7,200</td>
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<tr>
<td>1 h</td>
<td>3,600</td>
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<tr>
<td>30 min</td>
<td>1,800</td>
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<tr>
<td>15 min</td>
<td>900</td>
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<td>10 min</td>
<td>600</td>
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<td>5 min</td>
<td>300</td>
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<td>1 min</td>
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<td>0.5 s</td>
<td>0.5</td>
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<tr>
<td>0.1 s</td>
<td>0.1</td>
</tr>
</tbody>
</table>

<sup>(a)</sup> The occupational exposure limit for UV-C at 254 nm is 6,000 μJ/cm<sup>2</sup>. This can be also calculated with the following formula: Dose (in μJ/cm<sup>2</sup>) = Time (in seconds) * Irradiance (in μW/cm).
Appendix 20. Treatment supporters

Update: January 2022

Treatment supporters need specific training to know and understand their role in order to provide the patient with adequate treatment education and support. They should be compensated for their time and services and reimbursed for expenses incurred.


20.1 Selecting a treatment supporter

The treatment supporter\(^a\):

- Is someone from the patient’s community;
- Is preferably a community health worker or a person with a background in health (e.g. pharmacist), but can also be a non health worker (co-worker or neighbour);
- Is chosen by, or is acceptable to, the patient and their family (e.g. supporter and patient of the same sex);
- Is able to observe the patient’s confidentiality;
- Has a stable living situation;
- Has basic literacy skills (can read and write and has basic numeracy skills);
- Is motivated to care for TB patients and committed to supporting them for the full duration of treatment;
- Lives near enough to the patient to be able to make regular visits (daily or weekly) and go to their home immediately in the event of an emergency;
- Is in good physical condition and not immunodepressed\(^b\).

It is usually not recommended to have family members as treatment supporters. The family relationship may interfere with the ability to administer TB treatment, especially if the patient is a child.

20.2 Roles and responsibilities

Role and responsibilities of a treatment supporter may include:

- Supervision of all drug intakes and keeping records on TB treatment card.
- Detection of adverse effects and, when necessary, prompt referral of the patient to a health facility.
- Accompanying the patient to medical consultations.
- Collection and transport of sputum specimens for smear and culture.
- Provision of health education to family members, including the risk of transmission and implementation of infection control measures in the home.
- Detection of signs and symptoms of TB in family members.
- Participation in refresher trainings.

**Notas**


(b) The most common cause of immunosuppression is HIV infection, but chronic illnesses such as diabetes also alter the immune system and are a risk factor for TB infection and active TB.

**Appendix 21. Informing the patient**
21.1 At the start of treatment

Arrange two interviews (allow about 20 minutes for each): one to supply the patients with the information they need to follow the treatment, the second to make sure they have assimilated the information. These interviews should coincide with the first two clinical visits. The first interview should occur before the treatment begins. Depending on how the clinic is organized, the interviews are done either by the prescribing clinician alone at the time of the clinical visit, or with the help of a specially-trained staff member at an interview just for this purpose. Patients may bring someone with them, if they wish.

Outpatients

First interview

- Explain:
  - The disease and how it spreads
    For example: this is a serious, but generally curable, infection that affects the lungs and can be spread if not treated (tailor the information according to the focus of the infection, the resistance pattern).
  - The treatment process:
    Length, intensive/continuation phases, clinical and bacteriological monitoring, visit schedule (tailor the information according to the regimen); how DOT will work and why it is important when relevant.
  - The medications:
    - Management:
      Where, when, and from whom to get medications;
      Number of tablets per day; number of doses per day, etc.;
      Keep tablets in their blister pack until taken, no removing them from their package ahead of time.
    - Main adverse effects and what to do if they occur:
      For example: for rifampicin, point out that it turns the urine, stools, tear, etc. reddish-orange, that this is normal and not a cause for concern. For ethambutol, advise the patient to consult the doctor immediately if s/he notices a decrease in his/her vision or ability to correctly distinguish colours, etc.
    - Special precautions (depending on concomitant treatment):
      For example: take rifampicin in the morning, and fluconazole at night.
  - Any incentives or enablers the patient may qualify for and how the patient can access them.
- Stress the importance of adherence, anticipate problems, and think about possible solutions.
- Answer any questions.
- Give the date of the second interview (one week later).

Second interview (one week later)
Hospitalized patients

First interview

Same as above, plus explain:

- Hospital infection control measures:
- Isolation and why it is indicated; the importance of covering the mouth when coughing or sneezing, the use of sputum containers, visits outside the building, face masks/respirators (who, when, why), airing out the room, etc.
- Timetable for injections and distribution of drugs.

Second interview (when patient is ready for discharge)

- Explain:
  - Where and when to get medications, the visit schedule;
  - DOT and other treatment support as relevant.
- Make sure that the information the patient needs to continue treatment as an outpatient has been assimilated (treatment process, medications, adverse effects and what to do, etc.).
- Stress the importance of adherence, anticipate problems, and think about possible solutions.
- Answer any questions.

21.2 In the course of treatment

Adherence interviews should take place at least monthly (more frequently if needed) throughout the entire course of treatment. Their purpose is to identify/resolve any problems resulting in poor adherence. Assessment is done either by the clinician at the monthly clinical visit, or by the nurse responsible for individual distribution of drugs.

Adherence interviews should be quick (about 5 minutes); on the other hand, devote as much time as necessary to resolving any problems.

The interview at the end of the intensive phase is more specifically devoted to informing the patient, because of the changes in drug regimen for the continuation phase.

Appendix 23. Treatment card for patients on first-line anti-TB therapy

Treatment card for patients on first-line anti-TB therapy.pdf
Appendix 24. Tuberculosis register for patients on first-line anti-TB therapy

Appendix 25. Treatment card for patients on second-line anti-TB therapy

Appendix 26. Tuberculosis register for patients on second-line anti-TB therapy

Appendix 27. Respirators

Update: January 2022

27.1 Introduction
Respirators are masks designed to protect the wearer from inhaling bacilli.

They must be worn by all staff in areas where the risk of TB transmission is high:
- Inpatient department with smear positive or drug-resistant TB patients
- Consultation room for TB diagnosis
- Laboratory (sputum smear preparation and culture/drug susceptibility testing)
- Sputum collection area
- Radiology department
- Waiting areas in high TB prevalence settings

Visitors and attendants must wear a respirator when entering a contagious TB patient’s room.

Recommended respirators include:
- The CE-certified filtering facepiece EN 149 FFP2, filtering efficiency 94% if challenged with 0.4\(\mu\)m particles;
  or
- The United States Centre for Disease Control and Prevention/National Institute for Occupational Safety and Health (NIOSH) certified N95, filtering efficiency > 95% if challenged with 0.3\(\mu\)m particles.

### 27.2 Instructions for use

Respirators are for personal use. The same respirator cannot be shared between staff members or between caregivers.

The respirator should be put on before entering the room and removed after exiting the room.

Respirators must be worn covering the nose, mouth and chin and provide a tight seal around the edge.

Every time that a respirator is put on, a seal check has to be performed:
- Fully open the respirator and slightly bend the nose wire to form a curve.
- Separate the two elastic straps and position the respirator under the chin.
- Stretch the two straps over the head, place the first strap at neck-height and the second strap across the top of the head.
- Model the nose wire around the bridge of the nose and secure the edges until you achieve a perfect
- Check for leaks by covering the respirator with both hands and forcefully inhaling and exhaling several times. The respirator should collapse when inhaling and expand when exhaling and no air leak between the face and the respirator should be Otherwise, straps should be readjusted and/or the respirator repositioned until is sealed properly.

Different factors may not allow proper sealing of respirators to the face: respirator size and/or model; respirator wearer’s facial features, including beard and facial hair; headscarves, etc.
There is limited evidence on the acceptable length of time a respirator can be worn with maintained efficiency. The filter materials remain functional for weeks or months, but with frequent wearing the respirator will become less adjusted.

An extensively used respirator should be discarded after 7 days. However, if for example, it is only used a few hours 2 to 3 times a week, it can be reused for several weeks\(^1\). During this period, staff can reuse their respirator provided it is not wet or damaged and its straps are not loosened. Each staff member should keep their respirator in the pocket of their personal gown without creasing it. If the filter material is damaged or the mask has loose straps, the respirator should be discarded immediately.

**Note:** TB bacillus is trapped in the filter of a mask and will not be released with shaking or other physical movements of the mask.

### 27.3 Storage

Store in a dry, well ventilated place. Respirators should not be crushed during storage.

### 27.4 Disposal

Respirators are disposed of as “soft waste” and do not need to be disinfected before being discarded.

### 27.5 Fit testing

Proper fit of a respirator is critical to ensure respiratory protection. Therefore, all staff members who could be exposed to *M. tuberculosis* should before being required to wear a respirator perform a “fit testing” to determine if the respirators being used fit them properly.

At least two models of respirators should be available. If a worker cannot be fitted with one model, the other one should be used.

Testing is performed using a fit testing kit. The kit contains all the supplies and instructions needed to perform the test.

**Fist testing kit**
Referencias


Appendix 27. Request form for microscopy and Xpert MTB/RIF

Request form for microscopy and Xpert MTB/RIF.pdf

Appendix 28. Surgical masks

Update: January 2022
28.1 Introduction

The purpose of surgical masks is to catch droplet nuclei that patients expel while talking, breathing or coughing.

Surgical masks should be worn by contagious or potentially contagious patients (confirmed or presumed cases) when they leave their rooms to go to another department or any other enclosed area. Wearing a surgical mask is not necessary when patients are alone in their room or outdoors.

The terms “surgical”, “medical” or “procedure” are sometimes used interchangeably to qualify masks. Only masks that conform to the norms EN 14683 or ASTM F2100 should be used.

28.2 Instructions for use

Surgical masks are for personal use. The same mask cannot be shared.
- Open the mask.
- Bend the nasal bar (if included).
- Put the chin into the mask.
- Attach the two straps behind the head or over the ears.

Surgical masks must be replaced at least once a day and when they become wet or damaged.

It is not recommended to wear masks for large portions of the day or while sleeping, as they restrict air movement and are not comfortable.

28.3 Storage

Store in a dry, well ventilated place.

28.4 Disposal

Masks are disposed of as “soft waste” and do not need to be disinfected before being discarded.

Appendix 28. Request form for sputum culture, LPA and DST

[Request form for sputum culture, LPA and DST.pdf]
Appendix 29. BCG vaccine

Update: January 2022

Composition, forms and route of administration

- Live attenuated bacterial vaccine
- Powder for injection, to be dissolved with the entire vial of the specific solvent supplied by the manufacturer, in multidose vial, for intradermal injection

Dosage and vaccination schedule

Refer to national recommendations. In countries with a high incidence of TB (> 40 cases per 100,000), WHO recommends\[1]\:

- Child under 12 months: 0.05 ml single dose as soon as possible after birth
- Child 12 months and over and adult: 0.1 ml single dose

Technique and site of administration

- Clean the injection site with clean water. Do not use antiseptics as risk of inactivation of vaccine). Allow to dry.
- Administer intradermally. If the injection is correctly performed, an “orange-skin” papule measuring 5-8 mm in diameter should appear at the injection site.
- The vaccine is administered in the deltoid region of the arm, about one-third down the upper arm over the insertion of the deltoid muscle.
- The vaccine should be injected in the same place for each child so that the BCG scar is easier to locate.

Contra-indications

- Do not administer to patients with congenital or acquired immunodeficiency (e.g. HIV infection or serologic status unknown, but symptoms consistent with HIV infection, immunosuppressive therapy, malignant haemopathy).
- Postpone vaccination until recovery in the event of acute extensive dermatosis, acute complicated malnutrition or severe acute febrile illness (minor infections are not contra-indications).

Adverse effects

- Local reaction 2-4 weeks after injection: papule that ends up as an ulcer and usually heals spontaneously (dry dressing only) after 2 to 5 months, leaving a permanent
- Complications requiring no specific treatment and which almost always evolve favourably:
  - persistent ulcer with serous discharge for over 4 months after injection;
  - non-suppurated adenitis, most often axillary, sometimes cervical;
• abscess at the injection site due to infection (red, hot and painful abscess) or inadvertent intradermal injection (cold and painless abscess).

• Uncommon complications:
  • suppurative lymphadenitis, mostly observed in neonates, usually due to inadvertent intradermal injection. The lymph node, which can have a diameter of over 3 cm, evolves toward softening and fistulisation with chronic osteomyelitis in exceptional cases.
  • disseminated BCG disease\(^b\), most commonly in immunocompromised children under 2 years old (mortality rate > 70%)\(^2\).

**Precautions**

• If administered simultaneously with other vaccines, use different syringes and injection sites. Do not mix with other vaccines in the same syringe.
• **Pregnancy:** CONTRA-INDICATED
• **Breastfeeding:** no contra-indication

**Storage**

• Reconstituted vaccine: between 2 °C and 8 °C for 6 hours max.
• Powder: between 2 °C and 8 °C.
• Solvent: a cold chain is not required for However, at least 24 hours before reconstitution of the vaccine, the solvent must be refrigerated between 2 °C and 8 °C so that the solvent and lyophilised powder are at the same temperature: a temperature difference during reconstitution may reduce vaccine efficacy. Do not freeze.

**Notas**

(a) BCG vaccine provides high protection for neonates, but only moderate for school age TST negative children.

(b) If disseminated BCG disease is diagnosed, a 6-month TB treatment should be administered.

**Referencias**


Appendix 29. Sputum smear microscopy register

Sputum smear microscopy register.pdf

Appendix 30. Xpert MTB/RIF register

Xpert MTB/RIF register.pdf

Appendix 31. Drug-o-gram

Drug-o-gram.pdf

Appendix 32. Quaterly report

Quaterly report.pdf

Appendix 33. Report on detection and enrolment of TB cases with rifampicin and multidrug-resistance
Appendix 34. Report of final outcomes of drug-resistant tuberculosis

Appendix 35. Check-list for the evaluation of a TB service