An Overview of Tuberculosis: What You Need to Know

38

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Abbreviations

AIDS	Acquired immunodeficiency syndrome
BAL	Bronchoalveolar lavage
CNS	Central nervous system
CXR	Chest X-ray
DOTS	Directly observed therapy short course
DST	Drug susceptibility testing
EMB	Ethambutol
FDC	Fixed drug combination
HIV	Human immunodeficiency virus
ICD	International Classification of Diseases
IFN-γ	Interferon gamma
INH	Isoniazid
LJ	Löwenstein Jensen
MDG	Millenium Development Goals
MDR-TB	Multidrug resistant-tuberculosis
MGIT	Mycobacterial growth inhibitor tubes
PCR	Polymerase chain reaction
RIF	Rifampicin
RR-TB	Rifampicin resistant-tuberculosis
STAG-TB	The Strategy Technical Advisory Group Tuberculosis
STR	Streptomycin
TB	Tuberculosis
TBB	Transbronchial biopsy
TDR-TB	Total drug resistant-tuberculosis

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TNF	Tumor necrosis factor
VR	Vital registration
WHA	World Health Assembly
WHO	World Health Organization
XDR-TB	Extensively drug resistant-tuberculosis
ZN	Ziehl-Neelsen

38.1 Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. It can affect any organs, usually the lungs. Other strains of *Mycobacterium*, such as *M. bovis* and *M. africanum*, are exceptionally appearing as pathogens in Europe.

TB is transmitted among people through the air. The source of infection is human, from persons who have pulmonary TB or TB of the larynx. Other clinical forms of TB are not contagious. Patients with pulmonary TB are contagious if, when they cough, there are up to 10,000 bacilli in 1 ml of sputum. When patients with pulmonary TB cough, sneeze or spit, they expel germs into the air. For infection to occur, only a few of these germs need to be inhaled.

The risk of infection in a person living in close contact with a diseased person is 30%. Health care professionals who work with patients with TB and employees of microbiological laboratories that diagnose TB are at greater risk. The incubation period lasts 4–12 weeks, from infection to the presence of radiopaque lesions on the lung. Infection usually remains latent and can persist for a lifetime. Only about 3% of infected people develop the disease within 3 years. Progression of infection to the disease is significantly higher in immunocompromised patients, such as those with acquired immunodeficiency syndrome (AIDS), cancers and diabetes mellitus. One-third of the world's population has latent TB; that is, people who have been infected by *M. tuberculosis* but do not yet have the disease and cannot transmit it.

In active TB disease, the symptoms (e.g., fever, night sweats, cough, weight loss) may be mild for a long time. This can lead to failure in seeking care and results in further transmission of *M. tuberculosis*. Without adequate therapy, more than two-thirds of people with TB disease will die.

38.2 Epidemiology

TB was mentioned thousands of years ago as the most common infective disease. Hippocrates called TB "phthisis" and concluded that it is was the most widespread fatal disease of his time [1]. The period of greatest TB infection was in the nineteenth century, when it took the largest number of lives, often young.

Robert Koch, in 1882, discovered the cause of TB, a rod-shaped bacterium, *M. tuberculosis*. The major step in the fight against TB in the modern age was his lecture on Friday, March 24, 1882, in Berlin, where he described *M. tuberculosis*. His work was published on April 10, 1882, in the journal *Berliner Klinische Wochenschrift* and was translated into many world languages [2]. From that time, he began research on drugs to combat the disease. In the second half of the twentieth century TB treatment became successful, with several drugs used in combination, the control of patients' treatment, and long enough therapy. However, since the last two decades of the twentieth century, the incidence of TB cases has been growing again, and the disease has now returned, associated with the new disease, AIDS.

The big problem in TB treatment is a new form of the disease, multidrug resistant-tuberculosis (MDR-TB). TB is also more commonly associated with diseases such as diabetes, malignant disease, renal disease and congenital and acquired immunodeficiencies. The highest rates of TB are in Africa, Southeast Asia, and parts of South America. Developing countries, in contrast to industrialized countries, have a higher rate of the disease. Rising numbers of MDR-TB represent a major threat that is going out of control. Despite the measures taken by the World Health Organization (WHO), the infection is spreading rapidly. In 1993, the WHO declared TB a global emergency, concerned because of the extent of

TB as a problem in most developing countries [3, 4]. In the last two decades of the twentieth century, global strategies for TB control have been recommended for acceptance and adaptation in all countries. The phenomenon of MDR-TB forms of the disease led to the introduction of new measures in the therapy of TB; namely the directly observed therapy short course (DOTS) strategy [5].

38.2.1 Risk Factors for Developing Diseases

TB is a disease related to poverty, and this could explain its appearance in different population groups. Risk factors such as poverty, lack of food, financial problems, and difficult psychosocial circumstances are the major determinants of TB [6, 7]. Also, there are vulnerable groups, which include those with human immunodeficiency virus (HIV) infection, homeless people, migrants and refugees, alcohol abusers, and prisoners. Because of their increased risk these groups are more likely to develop active disease. In these patients TB may not be diagnosed, representing a danger for spreading infection in the community [8]. A common aggravating factor is the fear of stigmatization, which is an important reason for poor compliance with treatment. The most sensitive groups have to be identified in every region so that intervention aimed at the needs of difficult to reach groups can be implemented [9]. HIV/AIDS-positive patients have an extremely high risk of contracting TB. So, the HIV status of every newly diagnosed TB patient has to be checked, according to current recommendations. The percentage of TB patients who know their HIV status has increased in the past 10 years, reaching a peak of 46% in 2012 [10].

The world prison population is currently about 8–10 million people. The median incidence rate ratio for TB in inmates versus the general population was reported to be 23. Treatment that was not sufficiently long, and interrupted treatment, significantly increased the development and spread of MDR-TB, thus creating TB reservoirs, a factor that threatens the whole community, through prison officials, visitors, and former prisoners [11–13].

38.3 Directly Observed Therapy Short Course

Directly observed therapy short course (DOTS) was launched in 1994–1995. It was based on five crucial components: (1) political commitment with increased and continual financing, (2) case detection among people presenting with symptoms in clinics through quality-assured bacteriology, (3) standardized and supervised treatment along with patient support, (4) an effective drug supply and management system, and (5) a standard monitoring and evaluation system ("Framework-WHO, 1994, IUATLD, 1996") [14, 15].

To accelerate efforts and reach the international targets set in the context of the Millenium Development Goals (MDG), in 2006 the WHO launched an enhanced global strategy named the Stop TB Strategy. This new strategy aimed to ensure universal access to high-quality health services and patient-centered care for all individuals with TB, through additional efforts addressing the challenges emerging in the new century [16, 17].

The principles of DOTS were incorporated as the first component of the 2006 Stop TB Strategy, together with five additional components: (1) address TB/HIV, MDR-TB, and the needs of vulnerable populations, (2) contribute to health system strengthening based on primary health care, (3) engage all care providers, (4) empower TB patients and encourage community engagement and (5) enable and promote research [16].

The WHO extended the DOTS program in 1998 to include the treatment of MDR-TB (called "DOTS-Plus"). The scope of this plan was to address the MDG challenge and pursue the other international targets in order to halve the 1990 TB prevalence and mortality rate by 2015 and eliminate TB as a public health problem by 2050 (<1 case per 1 million population) [18]. Despite all

these efforts and the resulting achievements described above, including the reaching of the TB-relevant target in the MDG, global control is progressing slowly, with a decline in incidence of 2% per year on average.

The new post-2015 Global TB Strategy approved by the 67th World Health Assembly in May 2014, aims at "ending the global TB epidemic" by 2035 This implies a reduction of mortality for 95% by decreasing incidence for 90% (<10 TB cases/100,000 population) to 2035 in comparison with 2015, and the suppression of any "catastrophic cost" for TB-affected families [19].

The most important aspect of treatment was the introduction and the routine use of new technologies for the quick detection of resistant strains and the development of special diagnostic algorithms, which were particularly useful for high-risk patients. Despite the implementation of these all measures, TB is still one of the world's biggest health problems.

38.4 TB Mortality

TB mortality among HIV-negative patients can be directly measured by using data from national Vital registration (VR) systems. VR systems have high coverage, and causes of death are accurately coded according to the newest revision of the International Classification of Diseases (ICD-10). For estimating TB deaths, mortality surveys can be used**.** Most countries with a high incidence of TB lacked national or sample VR systems in 2014, and few mortality surveys were done. In the absence of VR systems or mortality surveys, TB mortality can be estimated as a product of TB incidence and the case fatality rate, or it can be based on mortality data from countries with VR systems. TB deaths in HIV-positive people are difficult to estimate even when VR systems exist, because deaths among HIV-positive people are coded as HIV deaths, and contributory causes (such as TB) are mostly not recorded. Africa is the part of the world, where is the greatest need to introduce or implement VR systems where causes of death are classified according to the ICD system.

The fight against TB has resulted in a yearly death rate in 2013 of approximately half that in comparison with the rate in 1990. In 2014 1,510,000 people were killed by TB (1.1 million HIV-negative and 0.4 million HIV-positive), among them 890,000 men, 480,000 women, and 140,000 children [19]. Worldwide, TB ranks alongside HIV as a one of the leading causes of death. In 2014 there were 1.2 million deaths from HIV, including 0.4 million TB deaths among HIV-positive people.

38.5 Immunopathogenesis of TB Disease

The development of an infection by *M. tuberculosis* depends on the initial relationship between the pathogen and the host cell, most often the macrophage. The surface characteristics of both entities will strongly affect the outcome. Mycobacteria are gram-positive, but their wax-rich cell walls confer on them unique features. Because of this, they are classified as acid-fast bacilli. *M. tuberculosis* is capable of binding to a variety of host cell receptors, including Fc receptors and complement receptors (both with or without prior opsonization), the macrophage mannose receptor, surfactant protein receptors, and CD14. Having gained entry into the macrophage with its variety of its surface molecules, *M. tuberculosis* faces the problem of establishing residence inside a primary host effector cell. The manipulation of the nutritional requirements of *M. tuberculosis*, coupled with the immune status of the host, dramatically alters the course of infection and could open up potential avenues for therapeutic intervention [20].

Although interferon-gamma (IFN-γ) is a major cytokine involved in the control of *M. tuberculosis* infection, many others cytokines, such as interleukin 12 (IL-12) and tumor necrosis factor (TNF), participate in the activation of the immunological system. TNF can synergize with IFN-γ to activate macrophages. TNF is also the cytokine most responsible for organizing granulomas. However, as with many infections, the

synthesis of TNF must be precise, as too much synthesis leads to increased cellular accumulation, and to compromised lung function and damaged tissue.

CD4+ T cells are important in the host defence. The importance of this T-cell subset in controlling acute mycobacterial infections has long been proposed. Despite the intraphagosomal location of mycobacteria, it is known that CD8+ T cells have an important role in the successful immune response to the organism**.** A better understanding of the relationship between *M. tuberculosis* and its host will ensure very important new guidelines for the fight against this disease, which is still of major importance [21].

38.6 Clinical Course

Clinically, TB has a wide range of symptoms. The disease can affect any organ system; however, it usually affects the lungs (60–80%). Extrapulmonary TB is present in 20% of cases, of which 13% are specific pleuritis and 1–4% specific lymphadenitis, while sporadic central nervous system (CNS), genitourinary, osteoarticular, and intestinal TB are also observed. In HIV-positive patients the clinical presentation is atypical and extrapulmonary TB is present in up to two-thirds of patients.

According to sputum positivity, localization of the disease, drug resistance, and recurrence or relapse of the disease, the WHO recommended the following definitions of TB cases [22] (for use since March 2013):

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

Clinically diagnosed case of TB: "*A patient who does not fulfil the criteria for bacteriologically confirmed TB but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment.*"

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

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

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

Retreatment cases of TB: "*A patient who has been treated for 1 month or more with anti-TB drugs in the past. Retreatment cases are further classified by the outcome of their most recent course of treatment into four categories. Relapse patients have previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either treatment).*"

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

Case of multidrug resistant-tuberculosis (MDR-TB): "*TB that is resistant to two first-line drugs: isoniazid (INH) and rifampicin (RIF).*"

Case of RIF resistant-tuberculosis (RR-TB): "*A patient with TB that is resistant to RIF detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs.*"

Treatment after failure: "*The patients have previously been treated for TB and their most*

recent course of treatment failed i.e. they had a positive sputum smear or culture result at month 5 or later during treatment."

38.7 Diagnostic Tests in Tuberculosis

38.7.1 Screening Test

The WHO has developed guidelines on TB screening, according to The Strategic and Technical Advisory Group TB (STAG-TB) [23]. Screening is defined as: "*the presumptive identification of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly.*" Screening tests distinguish well persons who probably have a disease from persons who have not. Screening tests are not diagnostic. Persons with a positive or suspected positive result must visit their doctors for diagnosis and, eventually, therapy [24].

There are two key goals of systematic screening for active disease: (1) thorough early detection and therapy achieve a better outcome for patients suffering from TB and (2) by shortening the duration of TB infectiousness, the incidence and transmission of TB is significantly decreased [25].

Persons whose are positive at screening should be subjected to confirmatory testing to establish a TB diagnosis, with any reference tests or new tests that are available. Persons whose are negative at screening would not be tested with any confirmatory tests.

38.7.2 Index Tests

Chest X-ray (CXR) as a screening test means one posterior-anterior CXR recording. There are three different types of recording: conventional CXR (producing a 36 × 43 cm film), digital, and mass miniature radiography [26]. CXR classification systems can distinguish any abnormality versus a normal recording. Among abnormal CXRs only abnormalities suspicious of TB would qualify as a positive screening result [27]. Sequential (or serial) screening has two steps. In the first step persons are screened for symptoms, and CXR screening, as a second step, is performed only for symptom positive persons. Parallel screening means both screening steps are available, and persons having symptoms and/or abnormalities on chest X-ray have conditions that suggest a further diagnostic test. For example, this is practiced in TB prevalence studies, in order to ensure that the sensitivity is as high as possible. Parallel screening also avoids the need for laboratory diagnostics to be performed in all respondents [28].

38.7.3 Reference Tests

Tests with high specificity, considering mycobacterial culture and mycobacterium speciation, are the reference tests for bacteriologically confirmed TB. Cultures on liquid medium are the most sensitive. Before the automated reading of mycobacterial growth inhibitor tubes (MGIT) culture was available, culture on solid medium Löwenstein Jensen (LJ) was the basis of culture tests, and can still be the only available test in settings with limited resources. MGIT culture increases the recovery of mycobacteria by 11–18% compared with LJ culture, but MGIT culture can have lower specificity because of higher contamination rates [29, 30]. The Ziehl-Neelsen (ZN) method shows a wide variation of sensitivity, between 50% and 70% in most studies [31]. Direct ZN microscopy has a specificity of 98%. In comparison with culture, the sensitivity of the nucleic acid amplification test Xpert MTB/RIF test is 92%, and specificity is 99% in smear-positive and smear-negative patients [32]. Serological tests are not recommended as diagnostic tests in TB [33]. Before choosing the best diagnostic algorithm, the TB prevalence, test availability, and logistic conditions should be considered (e.g., X-ray or Xpert *Mycobacterium tuberculosis*/RIF availability). A systematic review to determine screening tests in HIV-infected persons has been published recently. Due to the increase in the prevalence of TB and its close association with

AIDS, there has been research into new methods for quickly discovering TB in clinical samples, new systems for culture and sensitivity testing TB, and amplification methods, polymerase chain reaction (PCR). Rapid tests such as PCR confirmed the diagnosis of TB in 1–2 days, while current substrates AST-streptomycin (STR), INH, RIF, etambutol (EMB) (SIRE) confirmed the diagnosis in 7–10 days [34].

38.8 Radiological Diagnosis of TB

Given the most common sites of pulmonary TB, X-ray and computed tomography of the heart and lungs is a basic diagnostic method for the detection of pulmonary TB. The primary infection shows infiltrative lesions in the parenchyma of the middle and lower lung fields, with regional lymphadenitis (which occurs most commonly 3 months after infection) and calcified-primary complex or Ghon's complex.

38.8.1 Postprimary Infection

There are three basic radiological signs of postprimary pulmonary TB: ulcers, caverns, and fibrosis. Radiologically, these signs manifest as multiple infiltrates with areas of destruction in the typical radiological images of caverns (Fig. 38.1).

Hematogenous dispersion of TB leads to radiological signs of miliary TB and hematogenous dissemination to other organ systems (e.g., CNS, bones and kidneys) (Fig. 38.2).

Radiologically visible pleural effusion, with or without signs of destruction of lung parenchyma, is the second most common radiological sign of TB. A special entity is tuberculoma a solitary peripheral nodule that is usually peripherally linked to a pleura.

Late radiological manifestations of TB in the lung generally represent its complications, and they include aspergilloma, arterial pseudoaneurysms, bronchiectasis, bronchial artery pseudoaneurysm, bronchopleural fistula, pulmonary artery pseudoaneurysm/Rasmussen aneurysm, empyema and fibrothorax.

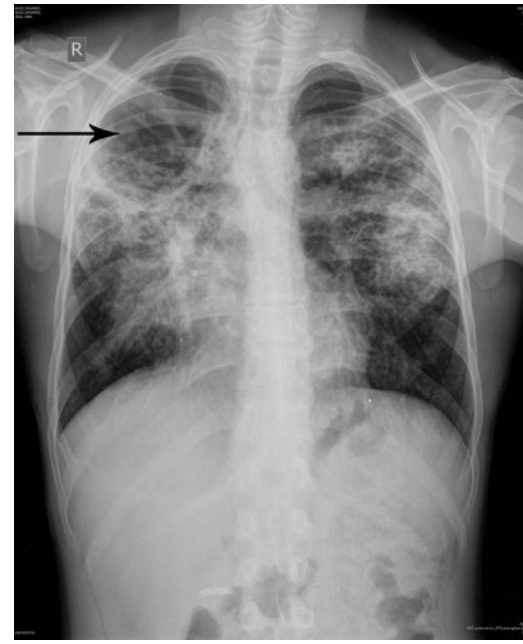

Fig. 38.1 Massive pulmonary tuberculosis (TB) with bronchogenic dissemination shows multiple infiltrates with areas of destruction in the typical radiological images of caverns on both sides of the lung

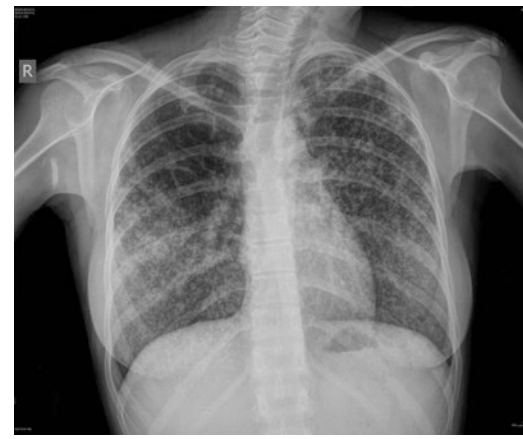

Fig. 38.2 Miliary pulmonary TB shows diffuse micronodular lesions (like grains of millet in the lung parenchyma)

38.8.2 Bronchoscopy as a Diagnostic Test for Tuberculosis

Bronchosopy is a very important diagnostic method in patients with clinical or radiological suspicion of TB who are not able to produce

sputum, or those patients with negative sputum smear microscopy results. In some studies, bronchoalveolar lavage (BAL) showed a sensitivity of 60% and a specificity of 100%. Bronchoscopy is a credible method for the diagnosis of pulmonary TB, with a low incidence of complications. The combination of transbronchial biopsy (TBB) and BAL increases the sensitivity of this method and clarifies the differential diagnosis with other diseases [35].

38.9 Anti-Tuberculosis Drugs

Global TB control has achieved the greatest success with the implementation of the DOTS strategy worldwide. The essential first-line anti-TB drugs include INH, RIF, EMB, pyrazinamide and STR. Second-line anti-TB drugs include aminoglycosides (kanamycin, amikacin), quinolones (ciprofloxacin, ofloxacin, levofloxacin), ethionamide or prothionamide, cycloserine, para-aminosalicylic acid and a polypeptide (capreomycin).

The WHO recommends the use of a fixed dose combination of anti-TB drugs, although these combinations have not been systematically evaluated [35]. The doses of the first and second-line anti-TB drugs are presented in Tables 38.1a and 38.1b.

The second-line anti-TB drugs are useful for treating disease that is resistant to first-line treatment (i.e., MDR–TB).

An initial phase treatment with a combination of several first-line anti-TB drugs serves to take care of the drug-resistant organisms and to provide "a quick kill" to decrease the bacillary load. As the final, that results in decreased the number of "persisters" in the focus.

For those TB patients with known positive HIV status and for all TB patients living in HIV prevalent settings, daily TB treatment, at least during the intensive phase and also during the continuation phase, is recommended.

While standard anti-TB therapy needs to be used for all new TB cases, when retreatment is required for relapse, starting with first-line therapy and drug susceptibility testing (DST) is recommended. If DST is not applicable and the patient has had a good clinical and radiological response for 2–3 months of therapy, or if DST confirms that there is no resistant disease, first-line therapy could be continued and given for 7 months [36]. When fully supervised first-line therapy fails, or if DST shows that a patient has MDR-TB, then second-line drugs have to be included for this patient. If patients do not respond on MDR treatment or they show extensively drug resistant tuberculosis (XDR-TB) on DST, they need to be treated with salvage regimens.

Third-line drugs may be useful, but they have doubtful or non-proven efficacy. The third line anti-TB drugs are rifabutin, macrolides, linezolid, thioacetazone, thioridazine, arginine, vitamin D and bedaquiline. These drugs, apart from

Table 38.1a Anti-TB drugs (first line) and their recommended doses for adults

	Recommended dose			
	Daily		3 times per week	
Drug	Dose and drug (mg/kg body weight)	Maximum (mg)	Dose and drug (mg/kg body weight)	Daily maximum (mg)
Isoniazid	5 (4–6)	300	10 (8–12)	900
Rifampicin	10 (8–12)	600	10 (8–12)	600
Pyrazinamide	25 (20–30)	–	35 (30–40)	–
Ethambutol	15 (15–20)	–	30 (25–35)	–
Streptomycin	15 (12–18)		15 (12–18)	1000

Notes: (1) Patients over 60 years old may not be able to tolerate more than 500–750 mg daily, so some guidelines recommend reduction of the dose to 10 mg/kg per day in these patients. (2) Patients weighing less than 50 kg may not tolerate doses above 500–750 mg daily (*WHO Model Formulary 2008*, www.who.int/selection_medicines/list/en/)

Table 38.1b Second-line anti-TB drugs and their recommended doses for adults

Drugs	Daily dose (mg/kg)	Route	Maximum daily dose
Kanamycin	15	IM	Up to 1 g
Amikacin	15	IM	Up to 1 g
Ethionamide	10–15	Oral	Up to 1 g
Cycloserine	10	Oral	Up to 1 g
Para-aminosalicylic acid	250	Oral	Up to 1 g
Ofloxacin	15–20	Oral	800–10,000 mg
Levofloxacin	7.5–10	Oral	750–1000 mg
Moxifloxacin	7.5–10	Oral	400 mg

IM intramuscular

rifabutin, are not very effective. Rifabutin is effective, but because of its high price, it is not on the WHO list for most developing regions.

38.10 Challenges in the Prevention and Treatment of Tuberculosis Today

Patients with MDR-TB are often unsuccessfully treated, with approximately 50% of MDR-TB patients worldwide being treated successfully. In 2015 the treatment success target of ≥75% with MDR-TB patients was achieved by 43 of the 127 countries and regions that investigated outcomes for the 2012 cohort, including three high-MDR-TB-burden countries (Estonia, Ethiopia, and Myanmar). Extensively drug resistant-tuberculosis (XDR-TB) was reported by 105 countries in 2015, representing about 9.7% of all reported TB cases in those countries [37].

After the development of RIF in the 1960s, no new anti-TB drugs were registered until 2012 and 2013. A new drug, bedaquiline, which was approved by the US Food and Drug Administration in 2012, is recommended by the WHO for the therapy of selected MDR-TB cases [37]. The European Medicines Agency approved bedaquiline in 2013 and this drug is now available for use in MDR-TB therapy in Europe [38]. Early diagnosis, motivation of patients to comply with treatment, and the implementation of the DOTS strategy are crucial for preserving the efficacy of anti-TB therapy and disease control.

Conclusion

TB has, for centuries, represented a major health problem. Since 1882, when Robert Koch discovered *M. tuberculosis*, there has been research on drugs for TB. During the 20th century the WHO implemented a number of guidelines for preventive measures and for the therapy of this disease, including the DOTS strategy, which led to a fall in the incidence of TB. However, in the last two decades of the 20th century, the number of TB cases again grew, associated with the new disease, AIDS. In some parts of the world, such as Africa, TB associated with AIDS is one of the leading causes of death. Also, a new form of the disease, MDR-TB, has become a big problem. Additional measures by the WHO, implemented in the health care systems of the relevant countries, as well as research on new drugs, will be necessary, in the future, for better control of the disease.

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