Chapter II

Review of Literature
Historical Aspect of Diq (Tuberculosis)

Tuberculosis is one of the oldest diseases known to human beings. It is a chronic specific infectious disease caused by bacillus known as *Mycobacterium tuberculosis*. The bacilli predominantly attacks lungs and cause pulmonary tuberculosis, which constitutes about 70% of active TB cases. The remaining 30% of active TB is extra pulmonary, which can affect lymph nodes, tissue surrounding the lungs and heart, meninges, kidneys, fallopian tubes, bones and joints, ears, throat and skin. Although TB can infect other organs in the body, the lungs are the organs, frequently attacked by the bacteria, which is characterized by a chronic cough, significant weight loss, loss of appetite, evening rise of temperature, night sweat, chest pain and shortness of breath.

Evidence that *M. tuberculosis* and humans have long coexisted comes primarily from studies of bone samples collected from a Neolithic human settlement in the eastern Mediterranean. Genetic evidence gathered from these studies indicates that roughly 9,000 years ago there existed a strain of *M. tuberculosis* similar to strains present in the 21st century. Evidence of mycobacterial infection has also been found in the mummified remains of ancient Egyptians, and references to *phthisis*, or “wasting,” occur in the writings of the Greek physician Hippocrates. In the medical writings of Europe through the Middle Ages and well into the industrial age, tuberculosis was referred to as phthisis, the “white plague,” or consumption—all in reference to the progressive wasting of the victim’s health and vitality as the disease took its inexorable course. The cause was assumed to be mainly constitutional, either the result of an inherited disposition or of unhealthy or dissolute living.

This historical disease has casted deep imprints on different cultures and has been named differently like *Shosa* (cough) or *Raja Yaksama* (wasting) in Vedic, *Phthisis* (to waste) in Greek, *Consumption* in Latin, *Loaping* in Chinese, *Tabes* in Roman, *White plague* in Europe and *Diq* in Arabic literature.

Although, the causative agent of TB was discovered by Robert Koch in 1882, but this disease has been detected as long as 5000 BC. The various skulls and other bones, which have been recovered from different parts of the world, show that
tuberculosis was present in Neolithic man. The Egyptians of antiquity recorded some
descriptions about tuberculosis. The mummified bodies have recorded definite evidence
of tuberculosis of bones and joints. In a mummy of 21st dynasty of Egypt, Pott’s disease
was proved which is an evidence of its age.\textsuperscript{7}

The Eber’s Papyrus, an important medical treatise was written about 1553-1550 BC by a
physician named Hesy Ra in the 3rd Egyptian dynasty, described TB as a pulmonary
consumption with enlarged cervical lymph nodes.\textsuperscript{12} The old testament mentioned a
consumptive illness that affected the Jewish people during their stay in Egypt, the region
known for a high prevalence of the disease.\textsuperscript{12}

The reference of disease called phthisis is found in ancient Greek literature by Buqrat
(Hippocrates).\textsuperscript{12} He is called the father of medicine as well as of epidemiology. He wrote
a book Kitabul Taqaddamatil Ma’rifa, on symptoms of disease, Kitabul Wafida, a book
on infectious disease and a book Kitabu fi Istakhrajin Nusos on diagnosis.\textsuperscript{13,14,15} He
described the characteristics of disease phthisis as fever, colourless urine, cough with
thick sputa, loss of thirst and appetite. He mentioned that delirious persons are prone to
disease.\textsuperscript{12} Buqrat (Hippocrates) and many others at that time believed the phthisis to be
hereditary in nature.\textsuperscript{19} But one legendary person that disagreed with the hereditary nature
of phthisis was Arastoo (Aristotle) (384-322 BC), who believed that it was in fact
contagious.\textsuperscript{12}

A prominent figure of Roman medicine was Jalinoos (Galen) (129-200 AD), who
described signs and symptoms, etiology and pathogenesis of tuberculosis in great
detail\textsuperscript{19} He wrote a book Kitabul Zabool on tuberculosis.\textsuperscript{16}

\textbf{Tuberculosis in core Age of Unani Medicine:}

During the medieval period, Arabs pioneers such as Raban Tabri (780-950 AD), Razi
(Rhazes) (850-923 AD), Majoozi (930-994 AD), Ibn Sina (Avicenna) (980-1037 AD),
Ahmad Tabri (985 AD), Masiil (970-1010 AD), Ismail Jurjani (1140 AD),
Najeebuddin Samarqandi (1222 AD), Abul Qasim Zahrawi (936-1036 AD) etc. were
searching for the causes of human ailments and devised various diagnostic tools.
Abul Hasan Ali bin Sahal Raban Tabri (210-295 AD): mentioned elevation of body temperature after meal as a method of diagnosis for TB. He described the signs of first, second and third grade of tuberculosis separately.\textsuperscript{[20]}

Hunain bin Ishaq (809-879 AD) wrote a book ‘Kitabul Hummiyat’ on fevers, a book ‘Kitabul Zabool’ on Diq and a book “Kitabul Tagaddamatil Ma’rifa” on signs and symptoms for diagnosis and treatment also reveal in this book.\textsuperscript{[16]}

Abu Bakr Muhammad bin Zakariya Razi (850-923 AD) one of the brilliant physicians of his time, also known as father of clinical medicine and a pioneer in experimental medicine, has described in detail about diagnosis of Diq in his books Al Hawi, Al Mansoor\textsuperscript{[21]} and Al Fakhir. He described that elevation in body temperature after meals is a reliable and confirm sign of diq.\textsuperscript{[22]} He said that on palpation, Miraqe Batan (skin over abdomen) becomes thin in second stage of Diq.\textsuperscript{[23]} He wrote a book “Kitabu fil Furoq bainal Amraz” on differential diagnosis and treatment of tuberculosis.\textsuperscript{[16]}

Ali bin Abbas Majoozi (930-994 AD) has given details about this wasting disease. He differentiated this disease from Humma Ufooni.\textsuperscript{[24]} Ibn Sina (980-1037 AD) has mentioned Diq in same manner as his precede. In addition to this, he said it a fatal disease.\textsuperscript{[25]}

Ahmad bin Muhammad Tabri (985 AD) in his book Moalajat Bugratia has mentioned difference between Sil and Diq although spelt synonymously. He also mentioned about the factors responsible for susceptibility and diagnostic tools of Tuberculosis.\textsuperscript{[26]}

Abu Sahal Maslihi (1010 AD) has solely devoted one chapter named Babul Diq in his book “Kitabul Miyah” in which he has described the diagnostic tool and treatment of tuberculosis.\textsuperscript{[21,27]}

Najeebuddin Samarqandi (1232 AD) has also mentioned the sign and symptom and treatment of tuberculosis.\textsuperscript{[30]}

Ghulam Hasnain Kantoori mentioned the presence of Raakh (ashes) on body in 3\textsuperscript{rd} stage of Diq.\textsuperscript{[24,30]}
Milestones of TB in Renaissance and After:

Giralamo Fracastro (1483-1533 AD) said it an infectious disease.\(^{[33]}\)

Paracelsus (1493-1541 AD) believed that tuberculosis was caused by failure of internal organ and called it Tartaric process.\(^{[34]}\)

Franciscus Sylvius (1614-1672 AD) differentiated between different forms of tuberculosis (pulmonary, ganglion)\(^{[35]}\) and first employed the term tuberculosis.\(^{[7]}\)

Richard Morton (1637-1698 AD) described tubercle as a true cause.\(^{[36]}\)

Thomas Willis (1624-1709 AD) said that all the diseases of chest must ultimately led to consumption.\(^{[37]}\)

Benjamin Martin (1624-1709 AD) described that cause of TB is some type of animacula.\(^{[38]}\)

Von Leuwenhoek (1632-1723 AD) invented microscope and introduced new discipline in diagnosis.\(^{[10]}\)

Pierre Desalt (1675-1740 AD) observed that sputum spreads the disease.\(^{[7]}\)

Margagui (1682-1771 AD) dissected the body and described the pathological condition of lung.\(^{[7]}\)

Leopold Auebrugger (1761 AD) developed the method of percussion for diagnosis.\(^{[38]}\)

Robert Whyte (1768 AD) described the first clinical manifestation of tubercular meningitis.\(^{[39]}\)

Percivall Pott (1779 AD) described the vertebral lesion, which is latter known as Pott’s disease.\(^{[40]}\)

William Stark (1724-1776 AD) believed that different forms of TB are manifestations of same disease.\(^{[41]}\)
Tuberculosis in Modern Time:
Rene Theodore Laennec (1781-1826 AD) a French scientist, invented stethoscope for auscultation.[10,38]

Gaspard Laurent Bayle (1774-1816 AD) and Laennec (1781-1826 AD) in 1810 AD classified phthisis into six types.[42]

Jean-Antoine Villemin (1869 AD) described the contagious nature.[43]

Robert Koch (1843-1910 AD) in 1882 AD discovered the mycobacterium tuberculosis as a causative agent in the sputum of tuberculous patient[31] and made his report public on 24 March in the same year, since 24 March is known as world tuberculosis day.[12]

Coni in 1884 found chicken tubercle bacillus.[7]

Edward L Trudeau in 1885 AD founded first sanatorium in New York.[44]

Peter Dettweiler in 1886 AD published the finding about sanatorium in which he claimed that 132 was cured out of 1022.[44]

Robert Koch in 1890 AD prepared tuberculin, a purified protein derivative of bacteria.[45]

Theobald Smith in 1898 AD isolated bovine tubercle bacillus.[7]

Rudolf Virchow (1821-1905 AD) began a new discipline of diagnosis i.e. histopathology.[10]

Robert Koch in Dec. 1890 AD introduced tuberculin, a purified protein derivative of bacteria.[45]

Wilhelm Rontgen in 1895 AD discovered the X-rays.[46]

Clemens von Pirquet (1874-1929 AD) in 1907 AD first described diagnostic value of tuberculin.[7]

Charles Mantoux in 1908 AD found tuberculin effective in diagnosing tuberculosis.[42]

Calmette (1863-1983 AD) and Guerin in 1921 AD discovered Bacillus of Calmette and
Guerin (BCG) vaccine.\textsuperscript{[7,31]}

1944- Selman A Waksman discovered Streptomycin.\textsuperscript{[47]}

1946 AD- INH (isoniazid/isonicotinoyl hydrazine) and PAS (Para-amino salicylic acid) was introduced.\textsuperscript{[47]}

1960 AD- National Institute of Tuberculosis (NIT), Bangalore established.\textsuperscript{[31]}

1962 AD- National Tuberculosis Control Programme (NTCP) launched.\textsuperscript{[31]}

1966 AD- Rifampicin proved as an anti-tubercular drug (ATD).\textsuperscript{[31]}

1972 AD- Wallace Fox introduced short course chemotherapy.\textsuperscript{[31]}

Tuberculosis in Pre and Post Independence Era

1930 AD- All India Institute of Hygiene and Public Health, Calcutta was established.\textsuperscript{[31]}

1939 AD- Madras public health passed.\textsuperscript{[31]}

1939 AD - The tuberculosis association of India was established.\textsuperscript{[31]}

1947 AD - Ministry of health was established.\textsuperscript{[31]}

1956 AD - The tuberculosis chemotherapy centre established in Madras.\textsuperscript{[31]}

1962 AD - The District Tuberculosis Programme was formulated.\textsuperscript{[31]}

1985 AD - Universal Immunization Programme (UIP) launched.\textsuperscript{[31]}

1992 AD - NTCP proved fail and revised.\textsuperscript{[31]}

1993- WHO declared TB as global emergency and RNTCP launched with (directly observed treatment, short course chemotherapy) DOTS.\textsuperscript{[31]}

1997- RNTCP expanded to cover entire country.\textsuperscript{[31]}

2005- NRHM launched.\textsuperscript{[31]}
Review of Literature

Tuberculosis is a specific infectious disease caused by *Mycobacterium tuberculosis*. The disease primarily affects lungs and causes pulmonary tuberculosis. It can also affect intestine, meninges, bones, joints, lymph glands, skin and other tissues of the body.\[^{31}\]

In classical Unani literature, disease could be found that no equality in terminology and nomenclature. Different author used different terms at different place while describing the disease like as *Dīq, Sil* (thinness), Phthisis etc.\[^{8, 25, 26, 30}\]

Definition:

According to Abul Hasan Ahmad bin Muhammad Tabri (985 AD), *Sil* means thinness, the thinness, which results due to gradual melting down of organs and consequently the whole body and the disease may be with or without ulcer. Sil with ulcer is also called huma-e-dīq.\[^{8}\]

According to Abul Hassan Ali Ibn Abbas Majusi (930-994 AD) in "Kamil-u-sana", mention that *Hararat Ghair Tabayee* which remains in the body to such an extent that the body fluids are dried up and he also mentioned "Sil is an lungs ulcer which followed by dīq".\[^{24}\]

According to Ibn Hubal Baghdadi (1122-1213 AD), *Dīq* is called *Aqteeqash* (continuous fever) in Greek. *Hararat Ghair Tabayee* reaches the heart and adjoining organs and rest of the body.\[^{53}\]

Abu Marwan Abdul Malik Ibn Zohar (1091-1162 AD) has defined the *Dīq* in same manner as others.\[^{8}\]

Hakeem Azam Khan (1902 AD) has defined *Dīq* in the same way as Majoosi.\[^{54}\]

According to Sahibe Majmaul Bahrain, *Humma Dīq* is called *Tape Dīq* in Persian and *Febris Hectica* in Latin. It is a type of remittent fever that occurs in weak *Mizaj* person.
after putrefaction of any internal organ.\textsuperscript{[55]}

According to Ibn Sina\textsuperscript{[25]} and Ismail Jurjani,\textsuperscript{[28]} Hararat Ghair Tabayee dries up all the body fluids especially of Aazue Aslia in this disease or diq may be due to abnormal heat of the heart, which spread all over the body and destroy the fluids from the organs.

Mulla Nafees Bin Auz Kirmani,\textsuperscript{[56]} Dawood Antaki,\textsuperscript{[57]} Ghulam Jeelani,\textsuperscript{[58]} Abu Mansoor Hassan bin Noohul Qamri,\textsuperscript{[59]} Sadeeddin Gazrooni\textsuperscript{[60]} and Sabit Bin Qurratt\textsuperscript{[61]} have defined the Diq in same way as Ibn Sina.

Another term used recently for pulmonary tuberculosis by different authors is “Tadarran-e-Revi” that’s Tadarran literally means tubercle, and Revi is lungs disease.

According to \textit{Taber’s medical dictionary}, tuberculosis is defined as:

“Relating to or affected with tuberculosis or condition marked by infiltration of a specific tubercle as opposed to the term tubercular, regarding a non specific tubercle”.\textsuperscript{[62]}

According to \textit{Dorland’s pocket medical dictionary}, tuberculosis is defined as:

“Any of the infectious disease of human and other animals due to species of Mycobacterium and marked by formation of tubercle and caseous necrosis in tissue of any organ”.\textsuperscript{[63]}

WHO has defined the case as a patient whose sputum is positive for tubercle bacilli, and such cases are the target of case finding.\textsuperscript{[31]}

WHO has defined suspect as whose sputum is negative but who shows suggestive opacities in chest X-ray.\textsuperscript{[31]}

\textbf{Epidemiology of disease:}

Roughly a third of the world’s population has been infected with \textit{M. tuberculosis}, and new infections occur at a rate of one per second.\textsuperscript{[64]} TB is the leading cause of death that can be attributed to single infectious disease agent. It is one of the top 10 causes of death.\textsuperscript{[64, 65]} The vast majority of tuberculosis cases are found in developing worlds and the disease occurs predominantly in people aged 15-59 years.\textsuperscript{[1]} It is estimated that about one third of
current global population is infected asymptotically with tuberculosis, of whom 5-10% will develop clinical disease during their life time.[31]

It is estimated that TB affects 1.7 billion individual worldwide with 8-10 million new cases in which 1.7 million deaths occur each year.[66] 80% of TB patients live in Asia and sub Sahara Africa.[67,68,70] India, China, Indonesia, Bangladesh and Pakistan account for more than half of global estimate of active TB.[71]

India is the highest burden country in the world, about one-fifth (20%) of the global burden of TB. Every year approximately 1.8 million persons develop tuberculosis, of which about 0.8 million are new smear positive cases. Two out of every five Indians are infected with TB bacilli. Every day about 5 thousand people develop the disease. Patients with this infectious disease can infect 10-15 persons in a year.[31]

However the biggest challenge of all, as per the WHO, estimated in 2009 that 4.4 lakh multi-drug resistant (MDR) stains of TB a year, which are both hard to detect and treat.

“The main issue is in Russia, China and India, where most of global MDR burden lies,” According to WHO, The global detection rate for MDR-TB was about 5% in 2009.[64]

WHO estimation that the largest number of new TB cases in 2008 occurred in south east Asia region, which accounted for 34% of incident cases globally. However, the estimated incident rate in sub-Saharan Africa is nearly twice of Southeast Asia Region, which has recorded over 350 cases per 100,000. Among TB patients notified in 2009, an estimated 2.5 lakh had MDR-TB. Of these, slightly more than 30,000(12%) were diagnosed with MDR-TB and notified.

The four countries that had the largest number of estimated cases of MDR-TB in absolute turn in 2008 were china (100,000), India (99000), Russia (38000) and South Africa (13000).By July 2010, 58 countries had reported at least lease of extensively drug-resistant TB (XDR-TB).

In India, 2 persons die by TB every 3 minutes, more than one thousand people die every day and almost 0.4 million die every year.[31,2]
In India TB kills more adults in the most productive age group (15-54 years) than any other infectious disease. The disruption caused to society and economy is enormous. Patients take on an average of 3-4 months to recover, losing that much income. The loss is disastrous for those struggling against poverty and financial crisis. The direct cost of disease in India annually is estimated at 300 million US dollar and indirect cost is three billion US dollar.\textsuperscript{[31]}

Tuberculosis kills more women in reproductive age group than all causes of maternal mortality combined and it may create more orphans than any other infectious disease. Nearly one-fifth of female infertility in India is caused by TB. Infected women of India face constraints. They depend on others to get necessary medical attention. It is considered as a stigma in the society. Due to this stigma every year one lakh women are rejected from society.\textsuperscript{[31]}

**Etiology:**

The primary cause of TB is Mycobacterium tuberculosis (MTB).\textsuperscript{[31]}

According to the Unani classical literature, Unani physicians have emphasized to know the causes of diseases and have written separate treatises on this valuable subject. Najeebuddin Samarqandi has written a book *Al Ashab wal Alamat*. Without knowing the etiology, no disease can be uprooted.

According to Raban Tabri, *Humma Diq* is a sequel of that *Humma Yaum* which results due to:

- Aggression
- Insomnia
- Sorrow
- Anxiety
- Stress and depression

He also emphasized that persons suffering from *Sue Mizaj Har* are more susceptible.\textsuperscript{[20]}
According to Abu Bakr Muhammad bin Zakaria Razi with reference to Sabit bin Qurrah Harani, this disease occurs in persons who have following structural peculiarities:

- Narrow chest
- Mejnjain (feather like and less muscular upper arm)
- Long neck
- Protruded larynx
- Head and URT containing morbid matter

He further says that this disease is due to pleurisy, pneumonia and *Warim* (inflammation) of diaphragm and lung. He also says that if *Tanqia* of morbid matter is not done within 40 days then it may convert into *Sil*.[21]

According to Majoosi the causes may be divided into:

- *Asbab Sabiqah*
- *Asbab Badia*

**Asbab Sabiqah** includes

- *Humma Ufoonia*
- *Humma Muharriqa*
- *Shatrub Ghib*
- *Har Warim* of chest
- Syncope treated with hot drugs

**Asbab Badia** includes

- Anxiety and sorrow
- Aggression
- Fatigue
- Wakefulness
- Aphasia
- Apepsia
- *Har yabis* season
He described that on low intensity, these cause *Diq Mutlaq* and on high intensity these causes *Zabool* and *Sil*.\(^{[24]}\)

Ahmad bin Muhammad Tabri mentioned same factors for susceptibility as Razi. In addition to these, he has also mentioned the following factors under the head of susceptibility:

- Emaciated thigh and buttock muscles
- Big and suspended testes
- Yellowish skin.\(^{[26]}\)

He further mentioned six diseases as casual factors, if these are not treated well in time. These diseases are:

1. *Sue Mizaj Meda Har*
2. Diseases of kidneys
3. Stone or wound in urinary bladder
4. *Sue Mizaj Gurda Har*
5. Abscess in the adjoining area of stomach, ureters and kidneys
6. Inflammation of stomach.\(^{[26]}\)

Sharfuddin Ismail and Azam Khan\(^{[28]}\) have described the same causes as mentioned by Majoosi.

**About the causative organism: Mycobacterium tuberculosis.**

Mycobacterium tuberculosis (MTB) is a small aerobic non-motile bacillus. High lipid content of this pathogen accounts for many of its unique clinical characteristics\(^{[26]}\). It divides every 16 to 20 hours, an extremely slow rate compared with other bacteria, which usually divide in less than an hour\(^{[31]}\) (For example, one of the fastest-growing bacteria is a strain of *E. coli* that can divide roughly every 20 minutes.) Since MTB has a cell wall but lacks phospholipids outer membrane, it is classified as a Gram-positive bacterium. However, if a Gram stain is performed, MTB either stains very weakly Gram-positive or does not retain dye due to the high lipid & mycolic acid content of its cell wall\(^{[70]}\). MTB can withstand weak disinfectants and survive in a dry state for weeks. In nature, the
bacterium can grow only within the cells of a host organism, but *M. tuberculosis* can be cultured *in vitro*.

Using histological stains on expectorate samples from phlegm (also called sputum), scientists can identify MTB under a regular microscope. Since MTB retains certain stains after being treated with acidic solution, it is classified as an acid-fast bacillus (AFB).

The most common acid-fast staining technique, the Ziehl-Neelsen stain, dyes AFBs a bright red that stands out clearly against a blue background. Other ways to visualize AFBs include an auramine-rhodamine stain and fluorescent microscopy.

The *M. tuberculosis* complex includes four other TB-causing mycobacteria: *M. bovis*, *M. africanum*, *M. canettii* and *M. microti*. *M. africanum* is not widespread, but in parts of Africa it is a significant cause of tuberculosis. *M. bovis* was once a common cause of tuberculosis, but the introduction of pasteurized milk has largely eliminated this as a public health problem in developed countries. *M. canettii* is rare and seems to be limited to Africa, although a few cases have been seen in African emigrants. *M. microti* is mostly seen in immunodeficient people, although it is possible that the prevalence of this pathogen has been underestimated.

**Common risk factors of Tuberculosis:**

Those persons who are in pollution with silicosis have an approximately 30-fold greater risk for developing TB because Silica particles irritate the respiratory system, causing immunogenic responses such as phagocytosis, which, as a consequence, results in high lymphatic vessel deposits. It is this interference and blockage of macrophage function that increases the risk of tuberculosis. Some possible indoor sources of silica include paint, concrete and Portland cement. Crystalline silica is found in concrete, masonry, sandstone, rock, paint, and other abrasives. The cutting, breaking, crushing, drilling, grinding, or abrasive blasting of these materials may produce fine silica dust. It can also be in soil, mortar, plaster, shingles, and wearing dusty clothes.

Those persons with chronic renal failure and also on hemodialysis have an increased risk: 10–25 times greater than the general population. Persons with diabetes mellitus have
a risk for developing active TB that is two to four times greater than persons without diabetes mellitus, and this risk is likely greater in persons with insulin-dependent or poorly controlled diabetes. Other clinical conditions that have been associated with active TB include gastrectomy with attendant weight loss and malabsorption, jejunoileal bypass, renal and cardiac transplantation, carcinoma of the head or neck, and other neoplasms (e.g., lung cancer, lymphoma, and leukemia).\[82\]

Low body weight is associated with risk of tuberculosis as well. A body mass index (BMI) below 18.5 increases the risk by 2-3 times. On the other hand, an increase in body weight lowers the risk. Patients with diabetes mellitus are at increased risk of contracting tuberculosis,\[83\] and they have a poorer response to treatment, possibly due to poorer drug absorption.\[83\]

Other conditions that increase risk include the sharing of needles among I.V. drug users; recent TB infection or a history of inadequately treated TB; chest X-ray suggestive of previous TB, showing fibrotic lesions and nodules; prolonged corticosteroid therapy and other immunosuppressive therapy; Immunocompromised patients (30-40% of AIDS patients in the world also have TB) hematologic and reticuloendothelial diseases, such as leukemia and Hodgkin's disease; end-stage kidney disease; intestinal bypass; chronic malabsorption syndromes; vitamin D deficiency\[84\] and low body weight.

Twin studies in the 1940s showed that susceptibility to TB was heritable. If one of a pair of twins got TB, then the other was more likely to get TB if he was identical than if he was not. These findings were more recently confirmed by a series of studies in South Africa. Specific gene polymorphisms in \textit{IL12B} have been linked to tuberculosis susceptibility.\[85\]

Some drugs, including rheumatoid arthritis drugs that work by blocking tumor necrosis factor-alpha (an inflammation-causing cytokine), raise the risk of activating a latent infection due to the importance of this cytokine in the immune defense against TB.\[86\]
Transmission of disease:

Transmission can only occur from people with active—TB, not latent—TB. The probability of transmission from one person to another depends upon the number of infectious droplets expelled by a carrier, the effectiveness of ventilation, the duration of exposure, and the virulence of the *M. tuberculosis* strain.[79] When people suffering from active pulmonary TB cough, sneeze, speak, or spit, they expel infectious aerosol droplets 0.5 to 5 μm in diameter. A single sneeze can release up to 40,000 droplets. Each one of these droplets may transmit the disease, since the infectious dose of tuberculosis is very low and inhaling less than ten bacteria may cause an infection.[87] People with prolonged, frequent, or intense contact are at particularly high risk of becoming infected, with an estimated 22% infection rate. A person with active but untreated tuberculosis can infect 10–15 other people per year. Others at risk include people in areas where TB is common, people who inject drugs using unsanitary needles, residents and employees of high-risk congregate settings, medically under-served and low-income populations, high-risk racial or ethnic minority populations, children exposed to adults in high-risk categories, patients immunocompromised by conditions such as HIV/AIDS, people who take immunosuppressant drugs, and health care workers serving these high-risk clients.[88] TB can also be transmitted by eating meat infected with TB. *Mycobacterium bovis* causes TB in cattle.[89]

Pathogenesis:

The primary site of mycobacterium infection is lungs, TB infection begins when the mycobacteria reach the pulmonary alveoli and form Ghon focus that is primary site of infection, where they invade and replicate within the endosomes of alveolar macrophages.[79] the Ghon focus generally located in either the upper part of the lower lobe, or the lower part of the upper lobe of lungs.[79] Bacteria are picked up by dendritic cells, which do not allow replication, although these cells can transport the bacilli to local (mediastinal) lymph nodes. Further spread is through the bloodstream to other tissues and organs where secondary TB lesions can develop in other parts of the lung (particularly
The apex of the upper lobes), peripheral lymph nodes, kidneys, brain, and bone. All parts of the body can be affected by the disease, though it rarely affects the heart, skeletal muscles, pancreas and thyroid.

Tuberculosis is classified as one of the granulomatous inflammatory conditions. Macrophages, T lymphocytes, B lymphocytes and fibroblasts are among the cells that aggregate to form a granuloma, with lymphocytes surrounding the infected macrophages. The granuloma functions not only to prevent dissemination of the mycobacteria, but also provides a local environment for communication of cells of the immune system. Within the granuloma, T lymphocytes secrete cytokines such as interferon gamma, which activates macrophages to destroy the bacteria with which they are infected. Cytotoxic T cells can also directly kill infected cells, by secreting perforin and granulysin.

Importantly, bacteria are not always eliminated within the granuloma, but can become dormant, resulting in a latent infection. Another feature of the granulomas of human tuberculosis is the development of abnormal cell death, also called necrosis, in the center of tubercles. To the naked eye this has the texture of soft white cheese and was termed caseous necrosis.

If TB bacteria gain entry to the bloodstream from an area of damaged tissue they spread through the body and set up many foci of infection, all appearing as tiny white tubercles in the tissues. This severe form of TB disease is most common in infants and the elderly and is called military tuberculosis. Patients with this disseminated TB have a fatality rate near 100% if untreated. However, if treated early, the fatality rate is reduced to near 10%.

Affected tissue is replaced by scarring and cavities filled with cheese-like white necrotic material. During active disease, some of these cavities are joined to the air passages bronchi and this material can be coughed up. It contains living bacteria and can therefore pass on infection. Treatment with appropriate antibiotics kills bacteria and allows healing to take place. Upon cure, affected areas are eventually replaced by scar tissue.
In 85-90% of cases, the primary complex heals spontaneously in 1-2 months and the tuberculin skin test becomes positive. In 10-15%, multiplication of M. tuberculosis is not contained and lymph node enlargement results in either local pressure effects, lymphatic spread to pleura or pericardium, or rupture into an adjacent bronchus or pulmonary blood vessel.[2,4,10,90]

According to Unani medicine, Tuberculosis develops when the Hararat Ghariba destroys the Rutoobat Tabayee of human body and vital organs become Har Yabis. Initially the Hararat Ghariba is ignited into the heart from where it is distributed all over the body and dry up the body fluids.

According to Ibn Sina, there are two types of Rutoobaat in human body.

1. Rutoobaate Oola
2. Rutoobaate Sania.[74,75]

**Rutoobaate Oola:** These include all four types of Akhlat i.e. Dam, Belgham, Safra and Sauda.

**Rutoobaate Sania:** These are further of two types.

1. Rutoobaate Fuzlia
2. Rutoobaate Ghair Fuzlia

**Rutoobaate Fuzlia:** which are excreted from the body i.e. sweats, tears, semen, mucous, milk and menses.[75]

**Rutoobaate Ghair Fuzlia:** these are that have changed its primary condition to secondary but still these are not incorporated into Aazae Baseet (simple organ). These are classified into four types according to their sites.

1. Rutoobaate Mahsoora
2. Rutoobaate Talliya
3. Rutoobaat Qareeb ba Iniqaad
4. Rutoobaate Manviya[73]

**Rutoobaate Mahsoora:** These Rutoobaat remain in the capillaries of the vital organs by which they are nourished.

**Rutoobaate Talliya:** These are the Rutoobaat that are dispersed inside vital organs. These Rutoobaat are ready to nourish the body when there is depletion in nutrition and also keep the organ moist when it becomes dry due to strenuous work.
Rutoobaat Qareeb ba Iniqaad: These Rutoobaat are near to incorporate (going to form an organ). In fact these Rutoobaat are the food which have been changed into the Jauhare Aaza, according to its Mizaj, viscosity and colour but it has not turned completely according to consistency.

Rutoobaate Manviya: The Rutoobaat, which are present in the organs since birth by which Aazae Aslia are interconnected.[73]

But according to Ismail Jurjani,[28] there are three types of Rutoobaate Tabayee in the human body i.e.

1. Rutoobaate Awwal
2. Rutoobaate Saani
3. Rutoobaate Saalis

Rutoobaate Awwal: The Rutoobaat which are dispersed in vessels and in all vital organs. During starvation and fasting when there is delayed or cut off in food and water then Tabiyat pays attention towards these Rutoobaat and digest them.

Rutoobaate Saani: The Rutoobaat which are present in organs just similar to organ, but not completely solidified.

Rutoobaate Saalis: The Rutoobaat by which vital organs are made up and all parts of the organs are connected. Therefore, when these Rutoobaat are consumed then connections between parts of the organs become discontinued. Diq is established when Aazae Aslia become Har and one of the mentioned body fluids is dried.[28]

According to Raban Tabri, Humma Yaum may convert into Humma Diq, particularly in those persons who are temperamentally Har Yabts. Sometimes chronic fever may change into Diq because the fever dries up the body fluid. Humma Diq may also be caused by those factors which stimulate the body Hararat.[20]

According to Ibn Sina, Diq develops as a consequence of other Humma. Sometimes it occurs after Humma Yaum or Humma Ufoonia, and sometimes after Humma Waramia. It is impossible that Diq develops from the beginning because Ishtea‘al (ignition) in the
vital organs is not possible without prior ignition of the Khilt and Rooh. Humma Ufoonia and Humma Waramia may convert into Diq due to the following reasons:

- High grade fever of Humma Ufoonia
- Extreme Talteef in meal
- Avoidance of cold water
- Application of Tila and Zimad on cardiac and adjoining area
- Uses of Har Advia

According to Ibn Rushd when organ suffers from Sue Mizaj Har then food reaching here shows Mizaji resemblance. The organ gets Hararat Ghariba from the food even if the food is cold. That is why temperature rises after every meal.

According to Ismail Jurjani, the origin of Diq is from Qalb (heart) but sometime Hararat of liver, stomach and lungs reaches to Qalb and causes Diq.

Classification of Tuberculosis:

According to Unani medicine, the grading (classification) of tuberculosis depends upon Tahallul Rutoobate Badania.

Majoosi described that there are three grade of Diq i.e.

1. Diq Mutlaq
2. Zabool/Sil
3. Mufattit/Mukhashshif

1. **Diq Mutlaq**: When the fluids of capillaries become dry and fluids of soft organ like fat are heated then this condition is called Diq Mutlaq. This is the first grade of Diq.

2. **Zabool/Sil**: When the Hararat Ghariba destroys the fluids of soft organs and begins to dry the fluids by which vital organs are connected then this is known as Zabool.

3. **Mufattit**: If the fluids of vital organs are dried by Hararat Ghariba, then this condition is known as Mufattit.

According to Ibn Sina, Diq is divided into the three grades:
**First grade**

When the Hararat Ghariba dries the first Rutoobaat (Rutoobaate Talliya) of vital organs especially fluids of Qalb (heart), then it is first grade of Diq, also known as Diq Mulaq. Its Greek equivalent is Aqteeqash.

**Second grade**

When the Hararat Ghariba destroys Rutoobaat Qareeb ba Iniqaad then it is the 2nd grade of Diq, known as Zabool. Zabool has been further divided into three stages according to appearance of signs and symptoms like Ibtida (mild), Wast (moderate) and Intiha (severe). In Greek, it is also called Farleemoos.

**Third grade**

If the Hararat Ghariba destroys Rutoobaate Manviya then it is the 3rd grade of Diq i.e. Mufattit. Its Greek equivalent is Ranjbas.

Ibn Sina further exemplified the grades with burning of oil, Batti (ribbon) and material of Batti sequentially.

He also described that if the Diq is associated with Rutoobaat Qareeb ba Iniqaad then it is first grade of Diq, when it is associated with the muscles then it is second grade of Diq and when it is associated with Aazae Aslia then it is third grade of Diq.

According to site, Diq may divided into:

- Pulmonary (lungs)
- Extra-pulmonary (lymph node, pleura, upper airway, genitourinary, bone, meninges, gastrointestinal, pericardium etc.)

Lungs are the main organs affected in tuberculosis. Depending upon type of tissue response and age, it is divided into 2 types:

1. Primary tuberculosis
2. Secondary tuberculosis
Primary Tuberculosis: The infection in an individual that has not been previously infected or sensitized or immunized is known as primary tuberculosis or Ghon's complex or childhood tuberculosis. The elderly and immune suppressed peoples may develop primary tuberculosis more than once. In the primary tuberculosis the source of organism is always exogenous.

Secondary Tuberculosis: The infection in the previously infected or sensitized individual is called secondary tuberculosis or post primary or re-infection or chronic tuberculosis. It may follow shortly after primary tuberculosis, but most commonly arises from re-activation of dormant bacilli of primary lesions many decades after primary infection, often when resistance is weakened. It may result from exogenous re-infection because of decline of immunity afforded by primary. disease.\textsuperscript{[10,91]}
Clinical Classification of Pulmonary Tuberculosis: [105]

Clinical Classification of Pulmonary Tuberculosis is based on the pathogenesis of the disease:

<table>
<thead>
<tr>
<th>Class</th>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No TB exposure not infected</td>
<td>No history of exposure negative reaction to tuberculin skin test</td>
</tr>
<tr>
<td>1</td>
<td>TB exposure no evidence of infection</td>
<td>History of exposure negative reaction to tuberculin skin test</td>
</tr>
<tr>
<td>2</td>
<td>TB infection no disease</td>
<td>Positive reaction to tuberculin skin test, Negative bacteriologic studies (if done), No clinical, bacteriologic, radiographic evidence of TB</td>
</tr>
<tr>
<td></td>
<td>TB clinically active</td>
<td>( M. \text{ tuberculosis} ) cultured (if done), clinical, bacteriologic, radiographic evidence of current disease</td>
</tr>
<tr>
<td>4</td>
<td>TB not clinically active</td>
<td>History of episode(s) of TB or abnormal but stable radiographic findings Positive reaction to the tuberculin skin test Negative bacteriologic studies (if done) and No clinical or radiographic evidence of current disease</td>
</tr>
<tr>
<td>5</td>
<td>TB suspect</td>
<td>Diagnosis pending TB disease should be ruled in or out within 3 months.</td>
</tr>
</tbody>
</table>
Clinical Features of Tuberculosis:

When the disease becomes active, 75% of the cases are pulmonary TB, that is, TB in the lungs.

According to Abul Hasan Ali bin Raban Tabri, the patients present the following signs in

First Stage of tuberculosis:

* Look - discoloured
* Fever - low grade and continuous

Signs in Second and Third Stages:

* Look -
  * dusty look
  * facial cyanosis
  * sleepy and sunken eyes
  * hanging ear lobes
  * forehead skin stretched
  * hard vessels
* Pulse - Zaeef (weak) and Salb (hard)
* Urine - oily
* Temperature - low grade and continuous, elevation after meal.

Razi has described the same as above, in addition to this, he has mentioned following

Signs in Second Stage:

* Look -like the state of Subat (coma)
* Stool - oily
* Temporal regions - shrunked
* Voice - weak
* Bones - prominent
* Nails - clubbed and folded
* Blood volume - low
Sings in Third Stage:

- Hair falling
- Diarrhoea

Abul Hasan Ali Ibn Abbas Majooz says that it is difficult to recognize the first stage of tuberculosis because Sue Mizaj Har is equally distributed. In fist stage, low-grade fever is felt. He mentioned the signs as above.\(^{22}\)

Describing the signs of second stage of Diq, Ibn Sina mentions that Nabz Zanbulfar changes into Nabz Misalli due to intake of hot Shraab.\(^{25}\)

He further mentions that diq may be associated with Humma Ufoonaa with following features:

1. After resolution of fever with sweating low grade fever persists
2. Weakness and thinness increased
3. Urine and stool become oily

He also mentioned that if Diq is dominant on other fever, Tazaaut will found too.\(^{25}\)

The clinical manifestations in tuberculosis may be variable, depending upon extent and type of lesion. Usually manifestations appear insidiously, the systemic symptoms, probably related to cytokines released by activated macrophages (TNF and IL-1), often appear early in the course.

Clinical Features:

Usually following clinical features develop during manifestations of TB.

- Malaise
- Headache
- Low grade fever
- Night sweating
- Cough ≥ 3 weeks
- Expectoration
- Haemoptysis (Up to 50% of pulmonary cases)
- Loss of appetite
- Loss of weight
- Dyspnœa
- Orthopœna
- Fatigue

Complications:

- Haemoptysis
- Spontaneous pneumothorax
- Pleural effusion
- Empyema
- Bronchiectasis
- Pulmonary fibrosis
- Corpulmonale
- Lobar tubercular pneumonia
- Tubercular meningitis
- Miliiary tuberculosis

Investigations:

- Sputum for AFB smears.
- *Sputum for AFB Culture*
- Radiological findings
- ESR and Polymerase Chain Reaction (PCR)

Diagnosis:

According to Unani medicine, diagnosis is made by following points:
Physical signs

Nahz (pulse)

Baul (urine)

temperature pattern

According to Raban Tabri, physical signs such as dusty look, facial cyanosis, sleepy and sunken eyes, hanging ear lobes, forehead skin stretched and hard vessels are found.

Nahz (pulse) becomes Sulb, Zaeef, Saroe' and Mutawatir.

Baul (Urine) becomes oily due to wasting of body fats.

Heat is ignited in the body after meal as pouring water on quick lime.\(^{[20]}\)

Razi advocated in Kitabul Mansoori that one of the method of diagnosis is to feed the patient at different times, if patient develops fever after each meal then it is confirm sign of Diq.\(^{[22]}\)

He has further described the diagnosis in detail in Kitabul Hawi that during the process of digestion of food, temperature elevates and the patient seems to be in the state of Subat (coma).\(^{[23]}\) He has described the characteristic of Baul (urine) and Nahz (pulse) same as above.

He further mentioned in Kitabul Fakhir that on putting sputum of Madqooq/Maslool in fire, bad odour comes. According to him, this is the evidence of weak digestion. After some time his belly shrinks and appetite is lost. This is the evidence of dead Quwate Shahwania. Diarrhoea is the evidence of weak Quwate Masika, consequently expectoration stops. Sometimes this condition appears in the initial stage of Khabis and Radi type of Sil. Appearance of this sign in the initial stage indicates that the cause is Maddi Ghair Pukhta (immature matter) and appearance in the last stage indicates nearness to death. Due to weak Quwate Dafita' (eliminative power), respiratory passage is blocked and death occurs as a sequence of suffocation.\(^{[23]}\)

According to Abul Hasan Ali Ibn Abbas Majoosi, despite the presence of Ghair Taboyee Hararat in the body, it is difficult to feel it by the patient as well as Tabib
because Hararat is equally distributed and no organ is devoid of this. But when the patient takes meal, whatever may be the time, temperature rises and it also rises at bed time. It is a reliable sign of Diq. He further mentions that on advancement of first stage skin becomes dry, face becomes thin and eyes become sunken.

He also mentioned that in Zabool (second stage), eyes become muddy and more sunken. He said that in second stage, Miraqe Batan becomes thin and dry. On palpation below Sharaseef, organs felt dry and attached with each other. He said that temperature pattern is such that initially less heat is felt but on keeping hand for longer time, raised temperature is felt. He also said that Salabat (hardness) and Tawatur (continuity) of pulse are like continuously moving stretched string of any musical instrument.[24]

The most prominent physician Ibn Sina stated that temperature of Madqooq (tuberculosed) remains constant and does not vary but on taking meal, temperature elevates and pulse becomes Qawee and Azeem. Observing elevated body temperature, unskilled Tabib advises the avoidance of food and thus kills the patient. The resemblance of elevated temperature is like increase in flame on fueling the lamp or elevated temperature of pot on pouring water. This is the confirm diagnosis of Diq.

He also advocates that due to Sue Mizaj Mustawi, the patient does not feel fever but after meals, the patient feels it.[25]

According to Ibn Rushd, temperature pattern is same as described by Ibn Sina.[75] He also emphasized the time of feeding for the purpose of diagnosis. He advised to feed the patient at that time when pulse is weak and the patient does not feel fever. If temperature elevates after 3 nhours of meal and pulse becomes Sare’e (rapid), Mutwatir (continuous) and Azeem then this fever is definitely Diq. This is because of persistence of Sue Mizaj Har in the organ and thus food reaching there shows Mizaji resemblance and the organ gains Hararat Ghariba from this food, even if it is cold. In contrast to this, it does not happen in Humma Ufoonia (septic fever) because in that case Hararat Ghariba does not persist in the organ where food reaches.[75]

According to Ibn Zohar, the elevated temperature remains 2-3 hours or more than this.[8]
Ibn Hubal Baghdadi has advocated temperature elevation after meal as pathognomic sign.\textsuperscript{53}

Ismail Jurjani has also mentioned the same as Ibn Sina.\textsuperscript{28}

A complete medical evaluation for TB should include:

- Medical history
- Physical examination
- Microbiological examination
- X-ray chest
- Tuberculin test
- Others

Medical History:

Medical history may play an important role. These are:

- Cough \geq 3 weeks
- Expectoration with or without Haemoptysis
- Chest pain
- Low grade fever
- Night sweat
- Loss of appetite
- Loss of weight
- Prior exposure to TB cases
- Past TB treatment
- Demographic risk factors
- Risk factors for TB like HIV etc.\textsuperscript{51}

Physical Examination:

Physical examination is done to assess the patient’s general health and to find other signs to evaluate TB. Usually patients of TB are lean and thin because it usually develops when fluids dry up.\textsuperscript{8, 22}
Other signs may be:

- Sunken eyes
- Prominent bones
- Depressed temporal regions
- Dryness of skin
- Hair loss in advanced cases

Differential Diagnosis:

- Sonokhas
- Humma Ufoonia
- Humma lasiga
- Pneumonia
- Lung abscess
- Lung cancer
- Pulmonary infarction
- Wegener’s granulomas
- Progressive massive fibrosis

**Tahaffuzi wa Moalajati Tadabeer (Prevention and Control):**

*Mizaj* is the key concept in Unani medicine. All the measures revolve around this. Restoration of *mizaj* in healthy and susceptible cases and rectification of *mizaj* in diseased persons are the fundamental principle of prevention and control.

According to **Ahmad bin Muhammad Tabri**, following measures should be applied for prevention:

- Complete avoidance of *Riyazat* (exercise)
- Complete bed rest
- Professional change: If a susceptible person works in hot dry environment e.g. blacksmith, he should abandon it and adopt other profession suitable to his *mizaj.*
- Avoidance of sexual act
• Nutrition with Ratah (wet) meals e.g. chicken (smaller size) soup, testes of cocks and Zardi (yellow part) of half fried egg.

• All the dishes should be prepared with Roghan Badam (almond oil)

• Halwafat (sweets in semisolid/solid form) should be prepared with sugar and Khashkhash.

• Ass milk should be given for three days on every 20 days.

• Person with Hiddat in Mizaj should take Maushshae'er regularly.

• Susceptible person should take nutritive huqna.²⁶

Prevention means reduction in prevalence and incidence of disease in the community.

The preventive measures consist of BCG vaccination. The BCG is a live bacterial vaccine, derived from an attenuated bovine strain of tubercle bacilli.

The aim of BCG vaccination is to induce a benign and artificial primary infection to acquired immunity against Mycobacterium tuberculosis, and to reduce the morbidity and mortality from TB.

In countries where TB is out of control and childhood infection is high like India, the national health policy recommends BCG at time of birth for institutional deliveries and at 6 weeks of age for home delivered infants. BCG administration early in life provides a high level protection, especially against the childhood tuberculosis and tubercular meningitis. Its protection rate is about 80% for 15-20 years of duration, but the duration of protection is under dispute.²¹

Treatment:

In Unani medicine, TB develops when the Aazae Aslia become Har Yabis and body fluids dry up and its treatment is Tabreed and Tarteeb²⁵,⁵⁴ with following regimens:

1. Tadbeere Mubarrida and Murattiba
2. Advia Mubarrida and Murattiba
3. Aghzia Mubarrida and Murattiba²⁵

The best tool to prevent this disease is to diagnose infectious cases rapidly and administer
prompt and appropriate treatment. Additional strategies include BCG vaccination and preventive chemotherapy.[5]

Tuberculosis has been treated with combination therapy for over fifty years. Drugs are not used singly (except in latent TB or chemoprophylaxis), and regimens that use only single drugs result in the rapid development of resistance and treatment failure[106] in combination therapy. The different drugs in the regimen have different modes of action. INH are bactericidal against replicating bacteria. EMB is bacteriostatic at low doses, but is used in TB treatment at higher, bactericidal doses. RMP is bacteriocidal and has a sterilizing effect. PZA is only weakly bactericidal, but is very effective against bacteria located in acidic environments, inside macrophages.

The short course chemotherapy is used for 6 months duration with, Rifampicin (450mg), INH (600mg), PZA (1500mg), Ethambutol (1200mg) and Streptomycin (750mg). These regimens are recommended into two phases:

1. Intensive phase
2. Continuation phase

In intensive phase, active and dormant bacilli are killed using thrice a week drug therapy for a period of 2-3 months (depending upon sputum negativity) with four antitubercular drugs including, INH, R, PZA and Ethambutol or Streptomycin.

In the continuation phase two drugs INH and Rifampicin thrice a week are used for 4 months.[31,96]

All first-line anti-tuberculosis drugs names have a standard three-letter and a single-letter abbreviation:

- Ethambutol is EMB or E,
- Isoniazid is INH or H,
- Pyrazinamid is PZA or Z,
- Rifampicin is RMP or R,
• Streptomycin is STM or S.

we can show the standard regimen as, 2HREZ/4HRj means isoniazid, rifampicin, ethambutol, pyrazinamide daily for two months, followed by four months of isoniazid and rifampicin given three times a week.

Second line anti-tuberculosis drugs:

There are six classes of second-line drugs (SLDs) used for the treatment of TB. A drug may be classed as second-line instead of first-line for one of three possible reasons: it may be less effective than the first-line drugs (e.g., p-aminosalicylic acid); or, it may have toxic side-effects (e.g., cycloserine); or it may be unavailable in many developing countries (e.g., fluoroquinolones):

• aminoglycosides: e.g., amikacin (AMK), kanamycin (KM);
• polypeptides: e.g., capreomycin, viomycin, enviomycin;
• Fluoroquinolones: e.g., ciprofloxacin (CIP), levofloxacin, moxifloxacin (MXF);
• thioamides: e.g. ethionamide, prothionamide
• cycloserine (the only antibiotic in its class);
• p-aminosalicylic acid (PAS or P).

Third line anti-tuberculosis drugs:

Other drugs that may be useful, but are not on the WHO list of SLDs:

• rifabutin
• macrolides: e.g., clarithromycin (CLR);
• linezolid (LZD);
• thioacetazone (T);
• thioridazine;
• arginine;
• vitamin D;
These drugs may be considered "third-line drugs" and are listed here either because they are not very effective (e.g., clarithromycin) or because their efficacy has not been proven (e.g., linezolid, R207910). Rifabutin is effective, but is not included on the WHO list because for most developing countries, it is impractically expensive.

Treatment of MDR-TB

The treatment and prognosis of MDR-TB are much more akin to that for cancer than to that for infection. It has a mortality rate of up to 80%, which depends on a number of factors, including

1. How many drugs the organism is resistant to (the fewer the better),

2. How many drugs the patient is given (Patients treated with five or more drugs do better),

3. Whether an injectable drug is given or not (it should be given for the first three months at least),

4. The expertise and experience of the physician responsible,

5. How co-operative the patient is with treatment (treatment is arduous and long, and requires persistence and determination on the part of the patient),

6. Whether the patient is HIV positive or not (HIV co-infection is associated with an increased mortality).

The treatment of MDR-TB must be undertaken by a physician experienced in the treatment of MDR-TB. Mortality and morbidity in patients treated in non-specialist centres is significantly superior to those patients treated in specialist centres.

Treatment of MDR-TB must be done on the basis of sensitivity testing: it is impossible to treat such patients without this information. If treating a patient with suspected MDR-TB, the patient should be started on SHREZ+MXF+cycloserine pending the result of laboratory sensitivity testing.
A gene probe for *rpoB* is available in some countries and this serves as a useful marker for MDR-TB, because isolated RMP resistance is rare (except when patients have a history of being treated with rifampicin alone). If the results of a gene probe (*rpoB*) are known to be positive, then it is reasonable to omit RMP and to use SHEZ+MXF+cycloserine. The reason for maintaining the patient on INH despite the suspicion of MDR-TB is that INH is so potent in treating TB that it is foolish to omit it until there is microbiological proof that it is ineffective.

There are also probes available for isoniazid-resistance (*katG* and *mabA- inhA*), but these are less widely available.

When sensitivities are known and the isolate is confirmed as resistant to both INH and RMP, five drugs should be chosen in the following order (based on known sensitivities):

- an aminoglycoside (e.g., amikacin, kanamycin) or polypeptide antibiotic (e.g., capreomycin)
- PZA
- EMB
- a fluoroquinolones: moxifloxacin is preferred (ciprofloxacin should no longer be use);
- rifabutin
- cycloserine
- a thioamide: prothionamide or ethionamide
- PAS
- a macrolide: e.g., clarithromycin
- linezolid
- high-dose INH (if low-level resistance)
- interferon-γ
- thioridazine
- meropenem and clavulanic acid

Drugs are placed nearer the top of the list because they are more effective and less toxic; drugs are placed nearer the bottom of the list because they are less effective or more toxic, or more difficult to obtain.

Resistance to one drug within a class generally means resistance to all drugs within that class, but a notable exception is rifabutin: rifampicin-resistance does not always mean rifabutin-resistance and the laboratory should be asked to test for it. It is only possible to use one drug within each drug class. If it is difficult finding five drugs to treat then the clinician can request that high level INH-resistance be looked for. If the strain has only low level INH-resistance (resistance at 1.0 mg/l INH, but sensitive at 0.2 mg/l INH), then high dose INH can be used as part of the regimen. When counting drugs, PZA and interferon count as zero; that is to say, when adding PZA to a four drug regimen, you must still choose another drug to make five. It is not possible to use more than one injectable (STM, capreomycin or amikacin), because the toxic effect of these drugs is additive: if possible, the aminoglycoside should be given daily for a minimum of three months (and perhaps thrice weekly thereafter). Ciprofloxac in should not be used in the treatment of tuberculosis if other fluoroquinolones are available.

There is no intermittent regimen validated for use in MDR-TB, but clinical experience is that giving injectable drugs for five days a week (because there is no-one available to give the drug at weekends) does not seem to result in inferior results. Directly observed therapy certainly helps to improve outcomes in MDR-TB and should be considered an integral part of the treatment of MDR-TB.

Response to treatment must be obtained by repeated sputum cultures (monthly if possible). Treatment for MDR-TB must be given for a minimum of 18 months and cannot be stopped until the patient has been culture-negative for a minimum of nine
months. It is not unusual for patients with MDR-TB to be on treatment for two years or more.

Patients with MDR-TB should be isolated in negative-pressure rooms, if possible. Patients with MDR-TB should not be accommodated on the same ward as immunosuppressed patients (HIV infected patients, or patients on immunosuppressive drugs). Careful monitoring of compliance with treatment is crucial to the management of MDR-TB (and some physicians insist on hospitalisation if only for this reason). Some physicians will insist that these patients are isolated until their sputum is smear negative, or even culture negative (which may take many months, or even years). Keeping these patients in hospital for weeks (or months) on end may be a practical or physical impossibility and the final decision depends on the clinical judgement of the physician treating that patient. The attending physician should make full use of therapeutic drug monitoring (particularly of the aminoglycosides) both to monitor compliance and to avoid toxic effects.

Some supplements may be useful as adjuncts in the treatment of tuberculosis, but the for the purposes of counting drugs for MDR-TB, they count as zero (if you already have four drugs in the regimen, it may be beneficial to add arginine or vitamin D or both, but you still need another drug to make five).

- arginine\textsuperscript{[111]} (peanuts are a good source)
- Vitamin D\textsuperscript{[112]}

**Adverse effects of anti tubercular treatment:**

It can be extremely difficult to identifying which drug is responsible for which side effect, but the relative frequency of each is known\textsuperscript{[113]} The offending drugs are given in decreasing order of frequency:

- Thrombocytopenia: RMP
- Neuropathy: INH
- Vertigo: STM
- Hepatitis: PZA, RMP, INH
- Rash: PZA, RMP, EMB

**Thrombocytopenia:** is only caused by RMP and no test dosing need be done.

**Neuropathy:** The most frequent cause of neuropathy is INH. The peripheral neuropathy of INH is always a pure sensory neuropathy and finding a motor component to the peripheral neuropathy should always prompt a search for an alternative cause. Once a peripheral neuropathy has occurred, INH must be stopped and pyridoxine should be given at a dose of 50 mg thrice daily. Simply adding high dose pyridoxine to the regimen once neuropathy has occurred will not stop the neuropathy from progressing.

**Rashes:** are most frequently due to PZA, but can occur with any of the TB drugs.

**Itching:** RMP commonly causes itching without a rash in the first two weeks of treatment: treatment should not be stopped and the patient should be advised that the itch usually resolves on its own. Short courses of sedative antihistamines such as chlorpheniramine may be useful in alleviating the itch.

**Fever:** during treatment can be due to a number of causes. It can occur as a natural effect of tuberculosis (in which case it should resolve within three weeks of starting treatment). Fever can be a result of drug resistance (but in that case the organism must be resistant to two or more of the drugs). Fever may be due to a superadded infection or additional diagnosis (patients with TB are not exempt from getting influenza and other illnesses during the course of treatment). In a few patients, the fever is due to drug allergy. The clinician must also consider the possibility that the diagnosis of TB is wrong. If the patient has been on treatment for more than two weeks and if the fever had initially settled and then come back, it is reasonable to stop all TB medication for 72 hours. If the fever persists despite stopping all TB medication, then the fever is not due to the drugs. If the fever disappears off treatment, then the drugs need to be tested individually to determine the cause.
Drug-induced hepatitis

The single biggest problem with TB treatment is drug-induced hepatitis, which has a mortality rate of around 5%.[114] Three drugs can induce hepatitis: PZA, INH and RMP (in decreasing order of frequency).[115] It is not possible to distinguish between these three causes based purely on signs and symptoms. Test dosing must be carried out to determine which drug is responsible (this is discussed in detail below).

Liver function tests (LFTs) should be checked at the start of treatment, but, if normal, need not be checked again; the patient need only be warned of the symptoms of hepatitis. Some clinicians insist on regular monitoring of LFT’s while on treatment, and in this instance, tests need only be done two weeks after starting treatment and then every two months thereafter, unless any problems are detected. Elevations in bilirubin must be expected with RMP treatment (RMP blocks bilirubin excretion) and usually resolve after 10 days (liver enzyme production increases to compensate). Isolated elevations in bilirubin can be safely ignored.[115]

If clinically significant hepatitis occurs while on TB treatment, then all the drugs should be stopped until the liver transaminases return to normal. If the patient is so ill that TB treatment cannot be stopped, then STM and EMB should be given until the liver transaminases return to normal (these two drugs are not associated with hepatitis).