Ministry of Higher Education and Scientific Research
Al-Hilla University College
Department of Medical Laboratories Techniques

Tuberculosis (TB)

A Project Research

Submitted to the Department of Medical Laboratories Techniques/ Al-Hilla University College in Partial Fulfillment of the Requirements for the Degree of Bachelor of Medical Laboratories Techniques

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(مثل الذين ينفقون أموالهم في سبيل الله كمثل حبة

أنبتت سبع سنابل في كل سنبلة مائة حبة والله

يضاعف لمن يشاء)

صدق الله العلي العظيم

سورة البقرة – الآية 261

Dedication

T0 the great person Who I missed and wished he is with me now;

My Father

To my First teacher who gives me encouragement, happiness and inspiring me with hope;

My Mother

To the Candles Which Light My Life;

My Sister & Brothers

To My Colleagues in various Knowledge Fields;

My Friends

Acknowledgment

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My special and sincere thanks to patients who gave me the samples from and may Allah heal them and have mercy on those who died because of this epidemic.

My sincere thanks are also to my family, friends and to anyone who helped and supported me by his pray for success in my work.

Introduction

Tuberculosis (TB) is an ancient human disease caused by Mycobacterium tuberculosis which mainly affects the lungs, making pulmonary disease the most common presentation (K Zaman, 2010) [1]. However, TB is a multi-systemic disease with a protean presentation. The organ system most commonly affected includes the respiratory system, the gastrointestinal (GI) system, the lymphoreticular system, the skin, the central nervous system, the musculoskeletal system, the reproductive system, and the liver [2][3].

Evidence of TB has been reported in human remains dated thousands of years (Hershkovitz et al., 2017, K Zaman, 2010). For a human pathogen with no known environmental reservoir, Mycobacterium tuberculosis has honed the art of survival and has persisted in human communities from antiquity through modern times.

In the past few decades, there has been a concerted global effort to eradicate TB. These efforts had yielded some positive dividends, especially since 2000 when the World Health Organization (WHO, 2017) estimated that the global incidence rate for tuberculosis has fallen by 1.5% every year. Furthermore, mortality arising from tuberculosis has significantly and steadily declined. The World Health Organization (WHO, 2016) reports a 22% drop in global TB mortality from 2000 through 2015.

Despite the gains in tuberculosis control and the decline in both new cases and mortality, TB still accounts for a huge burden of morbidity and mortality worldwide. The bulk of the global burden of new infection and tuberculosis death is borne by developing countries, with 6 countries, India, Indonesia, China, Nigeria, Pakistan, and South Africa, accounting for 60% of TB death in 2015 (WHO, 2017) [4].

Tuberculosis remains a significant cause of both illness and death in developed countries, especially among individuals with a suppressed immune system[5][6]. People with HIV are particularly vulnerable to death due to tuberculosis. Tuberculosis accounted for 35% of global mortality in individuals with HIV/AIDS in 2015. (W.H.O, 2017). Children are also vulnerable, and tuberculosis was responsible for one million illnesses in children in 2015, according to the WHO.

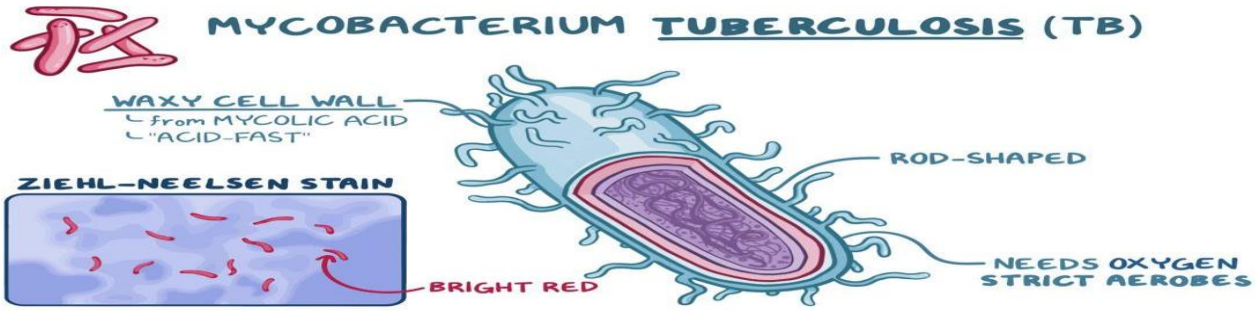

Figure 1: Mycobacterium tuberculosis Bacteria

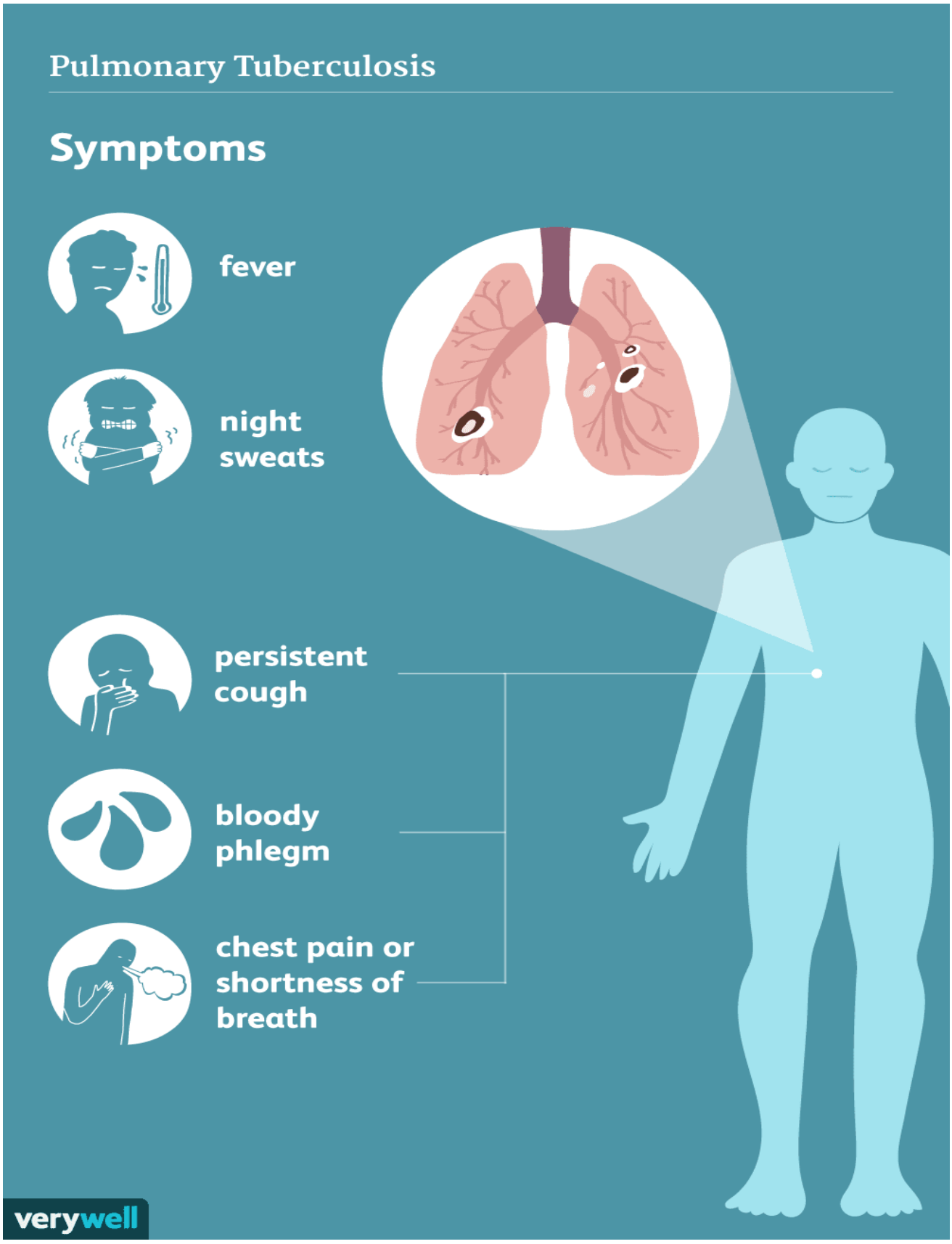

Figure 2: Tuberculosis: Signs, Symptoms, and Complications

Etiology

M. tuberculosis causes tuberculosis. M. tuberculosis is an alcohol and acid-fast bacillus. It is part of a group of organisms classified as the M. tuberculosis complex. Other members of this group are Mycobacterium africanus, Mycobacterium bovis, and Mycobacterium microti[1]. Most other mycobacteria organisms are classified as non-tuberculous or atypical mycobacterial organisms.

M. tuberculosis is a non-spore-forming, non-motile, obligate-aerobic, facultative, catalase-negative, intracellular bacteria. The organism is neither gram-positive nor gram-negative because of a very poor reaction with the Gram stain. Weakly positive cells can sometimes be demonstrated on Gram stain, a phenomenon known as "ghost cells."

The organism has several unique features compared to other bacteria, such as the presence of several lipids in the cell wall, including mycolic acid, cord factor, and Wax-D. The high lipid content of the cell wall is thought to contribute to the following properties of M. tuberculosis infection:

- Resistance to several antibiotics
- Difficulty staining with Gram stain and several other stains
- Ability to survive under extreme conditions such as extreme acidity or alkalinity, low oxygen situation, and intracellular survival (within the macrophage).

The Ziehl-Neelsen stain is one of the most commonly used stains to diagnose T.B. The sample is initially stained with carbol fuchsin (pink color stain), decolorized with acid-alcohol, and then counter-stained with another stain (usually, blue-colored methylene blue). A positive sample would retain the pink color of the original carbol fuchsin, hence the designation, alcohol, and acid-fast bacillus (AAFB).

Epidemiology

1- Geographic Distribution

Tuberculosis is present globally[1]. However, developing countries account for a disproportionate share of tuberculosis disease burden. In addition to the six countries listed above, several countries in Asia, Africa, Eastern Europe, and Latin and Central America continue to have an unacceptably high burden of tuberculosis.

In more advanced countries, high-burden tuberculosis is seen among recent arrivals from tuberculosis-endemic zones, healthcare workers, and HIV-positive individuals. The use of immunosuppressive agents such as long-term corticosteroid therapy has also been associated with an increased risk.

More recently, the use of a monoclonal antibody targeting the inflammatory cytokine, tumor necrotic factor alpha (TNF-alpha), has been associated with an increased risk. Antagonists of this cytokine include several monoclonal antibodies (biologics) used for the treatment of inflammatory disorders. Drugs in this category include infliximab, adalimumab, etanercept, and golimumab. Patients using any of these medications should be monitored for tuberculosis before and during the period of drug treatment.

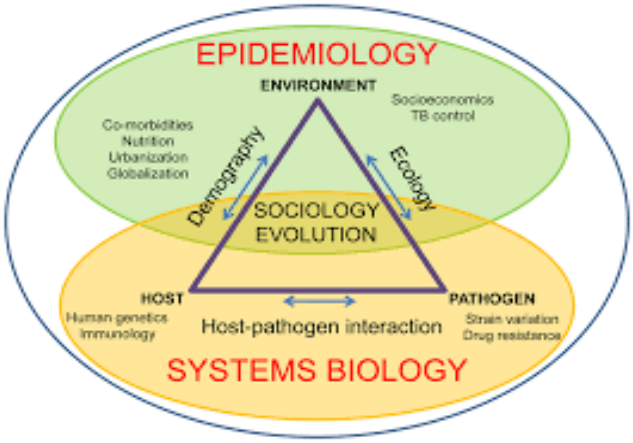

Figure 3: Epidemiology of Tuberculosis

2- Other Major Risk Factors

- Socioeconomic factors: Poverty, malnutrition, wars
- Immunosuppression: HIV/AIDS, chronic immunosuppressive therapy (steroids, monoclonal antibodies against tumor necrotic factor), a poorly developed immune system (children, primary immunodeficiency disorders)
- Occupational: Mining, construction workers, pneumoconiosis (silicosis)

Multi-Drug Resistant Tuberculosis (MDR-TB) and Extremely Multi-Drug Resistant Tuberculosis (XDR-TB)

3- MDR-TB

- This refers to tuberculosis with strains of Mycobacterium which have developed resistance to the classic anti-tuberculosis medications. TB is especially a problem

among patients with HIV/AIDS. Resistance to multiple anti-tuberculosis medications, including at least the two standard anti-tuberculous medications, Rifampicin or Isoniazid, is required to make a diagnosis of MDR-TB.

- Seventy-five percent of MDR-TB is considered primary MDR-TB, caused by infection with MDR-TB pathogens. The remaining 25% are acquired and occur when a patient develops resistance to treatment for tuberculosis. Inappropriate treatment for tuberculosis because of several factors such as antibiotic abuse; inadequate dosage; incomplete treatment, is the number one cause of acquired MDR-TB.

4- XDR-TB

- This is a more severe type of MDR-TB. Diagnosis requires resistance to at least four anti-tuberculous medications, including resistance to Rifampicin, Isoniazid, and resistance to any two of the newer anti-tuberculous medications. The newer medications implicated in XDR-TB are the fluoroquinolones (Levofloxacin and moxifloxacin) and the injectable second-line aminoglycosides, Kanamycin, Capreomycin, and amikacin.
- The mechanism of developing XDR-TB is similar to the mechanism for developing MDR-TB.
- XDR -TB is an uncommon occurrence.

Pathophysiology

Although usually a lung infection, tuberculosis is a multi-system disease with protean manifestation. The principal mode of spread is through the inhalation of infected aerosolized droplets.

The body's ability to effectively limit or eliminate the infective inoculum is determined by the immune status of the individual, genetic factors, and whether it is a primary or secondary exposure to the organism. Additionally, M. tuberculosis possesses several virulence factors that make it difficult for alveolar macrophages to eliminate the organism from an infected individual. The virulence factors include the high mycolic acid content of the bacteria's outer capsule, which makes phagocytosis to be more difficult for alveolar macrophages. Furthermore, some of the other constituents of the cell wall, such as the cord factor, may directly damage alveolar macrophages. Several studies have shown that mycobacteria tuberculosis prevents the formation of an effective phagolysosome, hence, preventing or limiting the elimination of the organisms.

The first contact of the Mycobacterium organism with a host leads to manifestations known as primary tuberculosis. This primary TB is usually localized to the middle portion of the lungs, and this is known as the Ghon focus of primary TB. In most infected individuals, the Ghon focus enters a state of latency. This state is known as latent tuberculosis.

Latent tuberculosis is capable of being reactivated after immunosuppression in the host. A small proportion of people would develop an active disease following first exposure. Such cases are referred to as primary progressive tuberculosis. Primary progressive tuberculosis is seen in children, malnourished people, people with immunosuppression, and individuals on long-term steroid use.

Most people who develop tuberculosis do so after a long period of latency (usually several years after the initial primary infection). This is known as secondary tuberculosis. Secondary tuberculosis usually occurs because of the reactivation of latent tuberculosis infection. The lesions of secondary tuberculosis are in the lung apices. A smaller proportion of people who develop secondary tuberculosis do so after getting infected a second time (re-infection).

The lesions of secondary tuberculosis are similar for both reactivation and reinfection in terms of location (at the lung apices), and the presence of cavitation enables a distinction from primary progressive tuberculosis which tends to be in the middle lung zones and lacks marked tissue damage or cavitation.

Type-IV Hypersensitivity and Caseating Granuloma

Tuberculosis is a classic example of a cell-mediated delayed type IV hypersensitivity reaction.

Delayed Hypersensitivity Reaction: By stimulating the immune cells (the helper T-Lymphocyte, CD4+ cells), Mycobacterium tuberculosis induces the recruitment and activation of tissue macrophages. This process is enhanced and sustained by the production of cytokines, especially interferon-gamma.

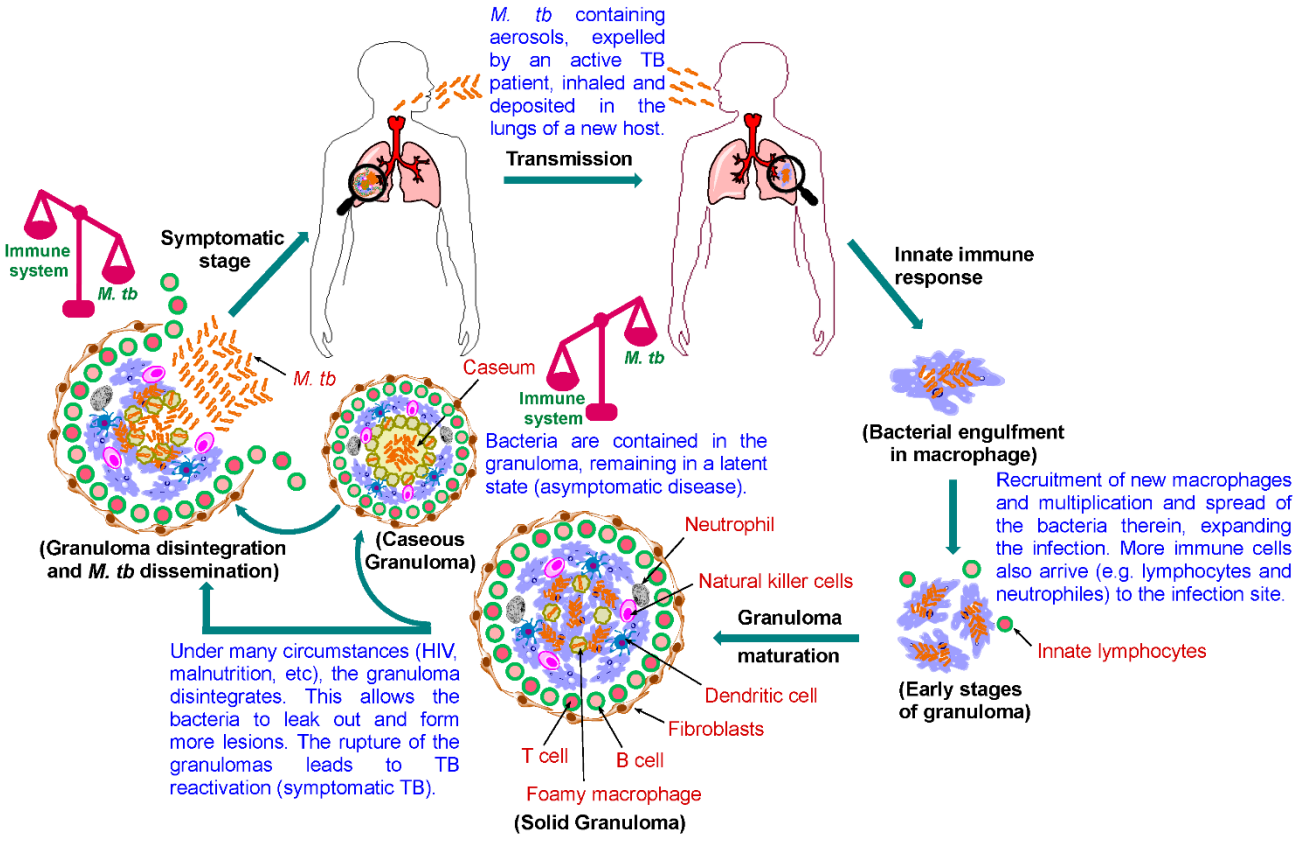

Figure 4: Pathophysiology of Tuberculosis

Two main changes involving macrophages occur during this process, namely, the formation of multinucleated giant cells and the formation of epithelioid cells. Giant cells are aggregates of macrophages that are fused together and function to optimize phagocytosis. The aggregation of giant cells surrounding the Mycobacterium particle and the surrounding lymphocytes and other cells is known as a granuloma.

Epithelioid cells are macrophages that have undergone a change in shape and have developed the ability for cytokine synthesis. Epithelioid cells are modified macrophages and have a flattened (spindle-like shape) as opposed to the globular shape characteristic of normal macrophages. Epithelioid cells often coalesce together to form giant cells in a tuberculoid granuloma.

In addition to interferon-gamma (IFN-gamma), the following cytokines play important roles in the formation of a tuberculosis granuloma, Interleukin-4 (IL-4), Interleukin-6 (IL-6), and tumor necrotic factor-alpha (TNF-alpha).

The appearance of the granuloma in tuberculosis has been described as caseous or cheese-like on gross examination. This is principally explained by the rich mycolic acid content of the mycobacterium cell wall. Because of this unique quality, the term caseous or caseating necrosis has been used to describe granulomatous necrosis caused by mycobacteria tuberculosis.

Histologically, caseous necrosis would present as a central area of uniform eosinophilia on routine hematoxylin and eosin stain

Differential Diagnosis

Tuberculosis is a great mimic and should be considered in the differential diagnosis of several systemic disorders. The following is a non-exhaustive list of conditions to be strongly considered when evaluating the possibility of pulmonary tuberculosis.

- Pneumonia
- Malignancy
- Non-tuberculous mycobacterium
- Fungal infection
- Histoplasmosis
- Sarcoidosis

Toxicity and Adverse Effect Management

Side Effect associated with most commonly used anti-TB drugs [7]

1) Isoniazid- Asymptomatic elevation of aminotransferases (10-20%), clinical hepatitis (0.6%), peripheral neurotoxicity, hypersensitivity.[8]

2) Rifampin- Pruritis, nausea & vomiting, flulike symptoms, hepatotoxicity, orange discoloration of bodily fluid.

3) Rifabutin- Neutropenia, uveitis (0.01%), polyarthralgia’s, hepatotoxicity (1%))

4) Rifapentine- Similar to rifampin

5) Pyrazinamide- Hepatotoxicity (1%), nausea & vomiting, polyarthralgia’s (40%), acute gouty arthritis, rash, and photosensitive dermatitis

6) Ethambutol- Retrobulbar neuritis (18%)

One of the most important aspects of tuberculosis treatment is close follow-up and monitoring for these side effects. Most of these side effects can be managed by either close monitoring or adjusting the dose. In some cases, the medication needs to be discontinued, and second-line therapy should be considered if other alternatives are not available.

Conclusion and Data

What is tuberculosis?

Tuberculosis o(TB)A disease resulting from an infection caused by bacteria (germs) known as Mycobacterium tuberculosis. The ancestors can lead to the damage of my heads or other members and cause a serious disease.

How does this disease spread?

1. the disease is spread through the air when a person with TB coughs into the lungs. When someone sneezes or talks, they spread germs into the air.
2. When others breathe in these germs, they can become infected.
3. Most people who become infected with tuberculosis are caused by contracting the virus. A sound from an infected person they spend a long time with, such as a family member or friend. Third.
4. But tuberculosis is transmitted from the domestic things) such as the tools of the medication, the imitators, the correspondence, the archive, the clothes, or the philosophers (, so it is not necessary that the injured people use things that are absent.

What are the symptoms?

TB can attack any part of the body, but the lungs are the site where it spreads its infection. People infected with TB may exhibit some or all of the following symptoms:

1. A cough that lasts more than three weeks
2. Fever infections
3. Losing weight without any reason
4. Sweat at night
5. Always feeling tired
6. Loss of appetite
7. Spit with some blood in it
8. Pain and/or swelling in the area affected by TB if the TB is outside the lungs.

How is it diagnosed?

With regard to pulmonary tuberculosis: an x-ray can show whether TB has affected the lungs.

- A sputum test shows whether TB germs are present in the sputum that comes out with a cough.
- If the person cannot cough up spit, other tests may need to be done.

With regard to tuberculosis outside the lungs:

- Some tests can help with the diagnosis, such as a fine-needle biopsy or biopsy. A swab from a wound, a sample taken during a surgical procedure, or a morning urine sample.

لؤي حسن	ذكر	40	سجين	ردهة السجن	طوارئ	سجن بابل المركزي	تدرن رئوي + فقر الدم الحاد
نضال عباس سرور	اثني	60	ربة بيت	2نساء	عيادة	بابل / الحمزة الغربي	تدرن رئوي
سعد عبد العزيز	ذكر	25	سجين	ردهة السجن	طوارئ	سجن بابل المركزي	ارتفاع حموضة الدم + داء السكري النوع الاول + تدرن رئوي
علوان عايد صالح	ذكر	60	سجين	ردهة السجن	طوارئ	الموصل	اشتباه تدرن في اغشية الدماغ / احيل الى الطب العدلي لمعرفة سبب الوفاة
حسن خفيف حسن	ذكر	50	كاسب	الحميات	طوارئ	بابل / جبلة	تدرن رئوي
محمود احمد حميد	ذكر	23	سجين	ردهة السجن	طوارئ	سجن بابل المركزي	تدرن رئوي مقاوم للعلاج + تليف الرئوي الثانوي المزمن
سعد عبد العزيز عبد المجيد	ذكر	32	سجين	ردهة السجن	طوارئ	سجن بابل المركزي	تدرن + داء السكري و مضاعفاته
احمد غازي فيصل	ذكر	32	سجين	ردهة السجن	طوارئ	سجن بابل المركزي	تدرن معد للعلاج
سرحان كميل رحمن	ذكر	55	سجين	ردهة السجن	استشارية	سجن بابل المركزي	ورم الخصية + اشتباه تدرن رئوي
ياسر جاسم محمد	ذكر	26	سجين	ردهة السجن	طوارئ	سجن بابل المركزي	تدرن مقاوم للعلاج + التهاب القولون المزمن
محمد عدنان جاسم	ذكر	35	سجين	ردهة السجن	طوارئ	سجن بابل المركزي	تدرن رئوي
اكرم علي شعيب	ذكر	25	سجين	ردهة السجن	طوارئ	سجن بابل المركزي	سعال دموي + فطريات اللثة عقابيل تدرن
محمود احمد حميد	ذكر	35	سجين	ردهة السجن	طوارئ	سجن بابل المركزي	تليف رئوي عقابيل تدرن رئوي
حسن فاضل كاظم	ذكر	25	سجين	ردهة السجن	طوارئ	سجن بابل المركزي	تدرن رئوي
اكرم علي شعيب	ذكر	35	سجين	ردهة السجن	طوارئ	سجن بابل المركزي	تدرن رئوي
عبد عاشور عبد	ذكر	60	كاسب	الحميات	طوارئ	حلة / عنانة	تدرن فعال
علي ناهي فرحان	ذكر	50	موظف	2رجال	عيادة	حلة / ابي غرق	داء السكري غير المسيطر عليه + توسع القصبات الهوائية المزمن + تدرن رئوي
صهيب غانم شنين	ذكر	55	سجين	ردهة السجن	استشارية	سجن بابل المركزي	تدرن رئوي + تليف رئوي + التهاب الكبد الناتج عن علاج التدرن
عمر فيصل علي	ذكر	22	سجين	ردهة السجن	طوارئ	سجن بابل المركزي	نوبة ربو قصبي + تدرن رئوي
سرحان كميل رحمان	ذكر	55	سجين	ردهة السجن	طوارئ	سجن بابل المركزي	تدرن رئوي
هيثم عدنان كنوش	ذكر	30	سجين	ردهة السجن	طوارئ	سجن بابل المركزي	تدرن رئوي
منهل ناصر جاسم	ذكر	30	سجين	ردهة السجن	طوارئ	سجن بابل المركزي	تحسس القصبات عقابيل تدرن رئوي

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