Review Article

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The Next Pandemic - Tuberculosis: The Oldest Disease of Mankind Rising One More Time

Amer Saleem and Mohammed Azher

Overview Of History

Mycobacterium tuberculosis was first isolated on 24th March 1882 by a German Physician Robert Koch, who received a Nobel Prize for this discovery in 1905 [1]. Tuberculosis is one of the oldest diseases in the history of mankind with evidence of tubercular decay found in some Egyptian mummies from 3000-2400 BC [2]. The study of tuberculosis was also known as phthisiatry from phthisis, the Greek term for tuberculosis. Hippocrates identified phthisis as the most widespread disease of the time which involved the coughing up of blood, fever and was almost always fatal [3]. Avicenna first identified that pulmonary TB was an infectious disease and developed the method of quarantine in order to limit the spread of disease [4 & 5]. The disease was given the name of tuberculosis in 1839 by JL Schonlein [6].

Burden Of Disease

Tuberculosis (TB) is an infectious disease caused by various strains of mycobacteria; of which the commonest cause is Mycobacterium tuberculosis [7]. The disease can affect any part of human body but commonly attacks the lungs. One third of the world's current population has been infected by Mycobacterium tuberculosis and new infections occur at a rate of 1 per second [8]. About 5-10% of these infections leads to active disease which, if left untreated, kills about 50% of its victims. TB affects approximately 8 million people worldwide and about 2 million people die of this disease annually. In the 19th century pandemic tuberculosis killed about 1/4th of the adult population of Europe [9]. Nevertheless, these figures may be only the tip of the iceberg. Tuberculosis is again on the rise and main cause for the resurgence of TB is immunodeficiency as a result of HIV co-infection or, less commonly, immunosuppressive treatment such as chemotherapy or corticosteroids.

Introduction To Mycobacteria

Mycobacteria are aerobic and non-motile bacteria (with the exception of Mycobacterium marinum which is motile within macrophages) which are characteristically alcohol-acid fast [10]. They are present in the environment widely in water and various food sources. They are usually considered to be Gram-positive bacteria, but they do not generally retain the crystal violet stain and are thus called Gram-positive acid-fast bacteria. These acid-fast bacilli (AFB) are straight or slightly curved rods 0.2-0.6 mm wide and 1-10 mm long. Mycobacteria are classified on the basis of growth & their ability to produce pigment.

On the basis of growth:

- Rapid growing: Mycobacteria that forms colonies clearly visible to naked eye within 7 days on sub-cultures
- Slowly growing: Mycobacteria that do not form colonies clearly visible to naked eye within 7 days on sub-culture

On the basis of pigmentation mycobacteria are divided into 3 groups:

- Photochromogens (Group I): Produce non-pigmented colonies in dark and pigmented colonies when exposed to light and re-incubation e.g., M. kansasii, M. marinum etc
- Scotochromogens (Group II): Produce deep yellow to orange colonies when grown in the presence of either light or darkness e.g., M. scrofulaceum, M. xenopi etc
- Non-chromogens (Group III & IV): Non-pigmented in light and dark or only a pale yellow, buff or tan pigment that does not intensify after exposure to light e.g., M. tuberculosis, M. avium-intra-cellulare, M. ulcerans etc

For Clinical Purposes mycobacteria are divided into 3 main classes:

- Mycobacterium tuberculosis complex: These are the mycobacteria which can cause TB and include M. tuberculosis, M. bovis, M. pinnipedii, M. africanum, M. microti and M. canetti.
- Mycobacterium leprae causes leprosy, also known as Hansen's disease.
- Non-tuberculous mycobacteria (NTM) or environmental mycobacteria, atypical mycobacteria and mycobacteria other than tuberculosis (MOTT). These include all other mycobacteria which can cause pulmonary disease resembling tuberculosis, lymphadenitis, skin disease or disseminated disease. These include: Mycobacterium avium complex,

Mycobacterium abscessus, Mycobacterium fortuitum and M. Kansasii which can cause both tuberculosis and leprosy in mammals.

Spread Of Tuberculosis

Today we know that TB is an airborne and highly infectious disease. A person becomes infected when he or she inhales Mycobacterium tuberculosis suspended in air as micro-droplets. Patients suffering from pulmonary TB who have detectable Mycobacterium tuberculosis in their sputum are known as smear positive cases of pulmonary TB. The bacterial load in sputum can be as high as 10,000,000 bacilli/mL. When such smear positive patients of pulmonary TB cough, sneeze or expectorate they produce micro-droplets of phlegm containing Mycobacterium tuberculosis (MTB). The size of these micro-droplets varies from 0.5 to 5mm in diameter. These micro-droplets can remain suspended in air up to 8 hours or even more (depending upon droplet size and environmental conditions including air flow). A single sneeze can produce up to 40,000 of these droplets [11]. MTB cannot invade the mucous membranes of the respiratory tree and must reach the alveoli where it replicates. The size of the MTB-containing micro-droplet must be <1mm to be carried to the end of the bronchial tree otherwise it will be deposited on the walls of bronchial tree and cleared away by mucociliary action. Current knowledge asserts that even less than 10 bacteria may cause pulmonary infection [12 & 13]. A sputum smear positive patient of TB, if left untreated, can cause infection in 10-15 new people each year.

Definition of TB contacts: People exposed to someone with infectious TB, generally including family members, roommates or housemates, close friends, coworkers, classmates, and others. They are a high priority group for latent-TB infection (LTBI) treatment as they are at high risk of being infected with TB.

Definition of close TB contacts: A person who had prolonged, frequent, or intense contact (i.e. >8 hours/day) with a person with sputum positive TB while he or she was infectious. They are more likely to become infected with TB than the contacts those who see the patient less often.

Pathogenesis

Once in the distal end of bronchial tree, MTB is engulfed by a macrophage in order to start replication within this host cell. Depending upon genetic factors, these macrophages can provide a variable environment for the replication of MTB. If this primary infection starts with a single mycobacteria and the initial host response is incapable of halting this process, within weeks or months there will be millions of tubercle bacilli within the body. MTB spreads in sequence from this primary site to the hilar-mediastinal lymph node initially. When seen on the X-ray, this primary focus of pulmonary infection is called a Gohn focus. It is generally located in the upper lobe or the apical segment of the lower lobe [7]. The Gohn focus plus enlarged hilar-mediastinal node is called a Gohn complex. Tubercle bacilli enter the thoracic duct from the hilar-mediastinal lymph nodes, then by passing via the subclavian vein and right atrium, gain access to pulmonary and systemic circulation. As a result MTB can access, and subsequently infect, any organ of the body. Immunocompetent hosts can normally generate an effective immune response within 3-8 weeks, which tackles the primary Gohn focus and can cause involution of the lesions throughout the body. This immune response is a delayed type hypersensitivity reaction to the cell wall protein of bacilli and this is also responsible for positive tuberculin skin test, which appears 4-12 weeks after infection. The primary immune response is not however sufficient to sterilize the tissues and MTB can remain dormant in these foci. Latent foci may persist in the lungs or other organs of the body and are capable of producing disease reactivation which may be pulmonary or extra-pulmonary. In some cases where the initial host response is not capable of causing involution of the primary disease (such as infancy or an immunocompromised state) the infection proliferates and spreads, causing so-called “progressive primary disease”.

Mycobacterium bovis is a mycobacterium that causes tuberculosis in cattle but which can also infect humans. It can be transmitted from cattle to human by ingestion of infected milk and very rarely by inhalation of animal aerosol micro-droplets and by eating infected raw meat. The process of pasteurisation kills M. bovis and other bacteria in milk, meaning that infections in human are rare [14].

When To Suspect Tuberculosis

Primary Tuberculosis: Tuberculosis caused by infection with tubercle bacilli and characterized by the formation of a primary complex in the lungs consisting of a small peripheral pulmonary focus and hilar or para-tracheal lymph node involvement; it may cavitate and heal with scarring or progress. It is mainly seen in children but 10% cases of adults suffering from pulmonary TB have primary infection.

Reactivation Tuberculosis: Also known as chronic TB, post-primary disease, recrudescent TB, endogenous reinfection, and adult type progressive TB. It represents 90% of adult cases (in a non-HIV population), and is due to reactivation of dormant AFBs which are seeded at the time of the primary infection. The apical and posterior segments of the upper lobe and superior segment of the lower lobe of the lung are frequently involved.

Clinical Features: Symptoms and signs vary greatly as do radiological signs. A literature review showed that common signs and symptoms seen in TB infection were [15, 16, 17, 18]:

- Cough, which can be either productive or non-productive; it is often initially a dry cough which can later become productive.

- Fever which seen in usually 70% of cases; generally it is low grade but could be as high as 390C, lasting for 14 to 21 days and in 98% cases is resolved completely by 10 weeks.
- Night sweats which is usually seen in 50% of cases
- Weight loss
- Pleural effusion: 50% of the patients with pleuritic chest pain had pleural effusion
- Chest pain: mainly pleuritic with some patients describing retrosternal and inter-scapular dull pain occasionally worsened by swallowing. This pain is believed to be due to enlarged bronchial/ mediastinal lymph nodes
- Dyspnoea can be present in 33% of cases
- Haemoptysis can be seen in 25%of cases
- Fatigue
- Arthralgia
- Pharyngitis

Common radiological findings were as follows:

- Hilar lymphadenopathy: can be seen as early as 1 week after the skin conversion and in almost all of cases within 2 months. It can be associated with right middle lobe collapse
- Pleural effusion: typically within the first 3-4 months but can be seen as late as one year
- Pulmonary infiltrates mainly in the upper zones and peri-hilar areas

How To Investigate [19]

HIV testing should be done in all patients presenting with clinical features of tuberculosis

Active Pulmonary TB

- CXR: Perform an X-ray chest PA view. If the appearance is suggestive of active tuberculosis perform further investigations
- Sputum smear & culture for AFB: send at least 3 sputums for AFB smear and culture including at least one early morning sample. This ideally should be before starting treatment or within 7 days of starting treatment.
- If clinical features and CXR are suggestive of active TB, do not wait for culture and sensitivity results, start the patient on the 4 drug initial treatment. This can be modified according to culture results later on.

Active Non-Respiratory TB

A tissue sample should be taken from the suspected non-respiratory site and sent for histological analysis, AFB smear and culture analysis. Common examples of non-respiratory tuberculosis are tuberculous lymphadenopathy, tuberculous meningitis and disseminated tuberculosis.

Physicians should think about CNS tuberculosis such as TB meningitis if a patient with risk factors (i.e., immigrants from endemic areas, positive history of close contact etc) presents with signs and symptoms such as headache, low grade fever, photophobia and/ or focal neurological signs. Lumbar puncture (LP) after a CT brain to rule out any contra-indication for LP may yield the diagnosis in these scenarios. An MRI brain is also very sensitive for picking up tuberculomas in such cases.

Latent TB

Offer Mantoux testing to the household contacts and close contacts of the person with active TB (aged 5 and older). If the Mantoux is positive or if results are unreliable, as can be the case with BCG-vaccinated persons consider interferon gamma testing (T-spot TB Test). If Mantoux is inconclusive, the patient should be referred to a TB specialist. A similar approach should be used for new entrant TB screening.

QuantiFERON-TB Gold (QFT-G) Test & QuantiFERON-TB Gold in Tube (QFT-GIT) Test

Both of these tests have replaced the QuantiFERON-TB (QFT) Test. It is an interferon gamma release assay (IGRA) and measures a component of cell-mediated immune reactivity to mycobacterium tuberculosis. In QFT-G test a blood sample is mixed with antigens (2 Mycobacterium TB protein) and a control. Mixtures are incubated for 16 to 24 hours and then the amount of interferon gamma is measured. If the patient is infected with mycobacterium TB, white blood cells will release interferon gamma when they come in contact with TB antigens. Clinical features, chest X-ray and sputum/ tissue smear and culture for AFB are needed to differentiate between active and latent TB.

Its advantages over tuberculous skin testing are:

- This test requires a single patient visit to draw a sample
- Results are available within 24 hours
- Results are not dependent on reader
- It is not affected by prior BCG vaccination

Its limitations/ disadvantages include:

- The blood sample must be processed within 12 hours of collection (while white cells are still viable)
- There is limited data for use of QFT-G in immune-compromised patients, children under 17 years of age and persons recently exposed to MTB
- False positive results may occur with Mycobacterium szulgai, kansasii and marinum infection

QFT-GIT is a modification of QFT-G test. It consists of 3 blood collection tubes containing: 1) no antigen, 2) TB antigen, 3) mitogen. These tubes must be transferred to an incubator within 16 hours of blood collection. Interferon gamma detection is then carried out via ELISA. Its specificity varies from 96-99% and sensitivity is as high as 92% in individuals with active disease.

T-Spot TB Test

It is a type of ELISPOT assay, developed by the researchers at the University of Oxford in England. It counts the number of effector T-cells in the blood that produce gamma interferon so gives an overall measurement of antigen load on immune system. As it does not depend upon production of antibody or recoverable pathogen, it can be used to detect latent TB and it is much faster. In one study it was found that its sensitivity is 97.2% [20].

Treatment Of Tuberculosis (Caused By Mycobacterium Tuberculosis)

Active TB will kill 2 of every 3 people affected, if left untreated. Disseminated TB is 100% fatal if untreated. For the treatment of TB, drugs are used in combination and never singly. Patients require regular supervision of their therapy during treatment to monitor compliance and side effects of medications. Treatment of atypical mycobacterial infections should be under the care of specialized units as this needs special care and drug regimens are complicated. Drugs for treatment of TB are divided into 3 categories:

1st Line Drugs: 1stline anti-TB drugs are very effective against TB. There are 5 first line drugs. All have 3 letter and 1 letter standard abbreviations.

- Rifampicin is RMP or R
- Isoniazid is INH or H
- Ethambutol is EMB or E
- Pyrazinamide is PZA or Z
- Streptomycin is STM or S

Using a single drug usually results in treatment failure and drug resistant strains [21]. The frequency of Mycobacterium tuberculosis developing spontaneous mutations conferring resistance to an individual drug is well known: 1 in $10^7$for EMB, 1 in 10^8 for STM & INH, 1 in 10^{10} for RMP [22]. A patient with extensive pulmonary TB usually has 10^{12}bacteria in his body and hence will have about 10^5 EMB-resistant bacteria, 10^4 STM-resistant bacteria, 10^4 INH resistant bacteria and 10^2 RMP resistant bacteria. Drug-resistant tuberculosis occurs when drug-resistant bacilli outgrow drug-susceptible bacilli. Mutations can produce bacilli resistant to any of the anti-tuberculosis drugs, although they occur more frequently for some drugs than others. The average mutation rate in M. tuberculosis for resistance to isoniazid is 2.56 x 10^{-8}mutations per bacterium per generation; for rifampicin, 2.25 x 10^{-10}; for ethambutol, 1.0 x 10^{-7}; and for streptomycin, 2.95 x 10^{-8}. The mutation rate for resistance to more than one drug is calculated by multiplying the rates for the individual drugs. For example, the mutation rate for resistance to both isoniazid and rifampicin is approximately 2.56 x 10^{-8} times 2.25 x 10^{-10}, or 5.76 x 10^{-18}. The expected ratio of resistant bacilli to susceptible bacilli in an unselected population of M. tuberculosis is about 1:10^6 each for isoniazid and streptomycin and 1:10^8 for rifampicin. Mutants resistant to both isoniazid and rifampicin should occur less than once in a population of 10^{14} bacilli. Pulmonary cavities contain about 10^7 to 10^9 bacilli; thus, they are likely to contain a small number of bacilli resistant to each of the anti-tuberculosis drugs but unlikely to contain bacilli resistant to two drugs simultaneously [23].

There are different regimens available for the treatment of TB. The initial 2 months of treatment (usually rifampicin based) is called Initial Phase or Intensive Phase Treatment which later leads to Continuation Phase Treatment. Initial intensive phase treatment is designed to kill actively growing bacteria. Drugs are listed using their single letter abbreviation and a prefix denotes the number of months a treatment has to be given and a subscript denotes intermittent dosage. For example; $2RHEZ/4RH_3$ = 2 months of initial phase treatment with Rifampicin, Isoniazid, Ethambutol, Pyrazinamide and 4 months continuation phase treatment with Rifampicin and Isoniazid given 3 times per week. If there is no subscript, it means the drugs are given daily.

Usual anti-TB regimens are:

- 2RHEZ/4RH3 (in less endemic areas)
- 2RHEZ/4RH (mostly practised, especially in non-endemic areas including UK); standard recommended regimen 24
- 2RHEZ/7RH (in most endemic areas)
- 2RHEZ/10RHE (in cases of disseminated, bone and CNS tuberculosis)

2nd Line Drugs 25 & 26: These are less effective than 1st line drugs, have more toxic side effects and are usually not available in most of the developing countries of the world. There are 6 classes of 2ndline anti-TB drugs:

- Aminoglycosides: e.g., Amikacin (AMK) & Kanamycin (KM)
- Polypeptides: e.g., Capreomycin, Viomycin
- Fluoroquinolones: e.g., Ofloxacin, Ciprofloxacin (CIP), Levofloxacin, Moxifloxacin (MXF)
- Thioamides: e.g., Ethionamide, Prothionamide
- Cycloserine:
- p-Aminosalicylic acid: (PAS or P)

3rd Line Drugs: These are drugs which may be useful, but are not on the WHO list of second line drugs. These are not as effective. 3rdline drugs include:

- Rifabutin (this is an effective drug but is very expensive for developing countries, so it not included in WHO list). Occasionally this can be used for patients who are intolerant to or have bacterial resistance to Rifampicin.
- Macrolides: Clarithromycin (CLR), Azithromycin
- Linezolid: (LZD) not of proven efficacy
- Thioacetazone (T)
- Thioridazine
- Arginine
- Vitamin D
- R207910: efficacy not proven

Indications of Steroids in the treatment of TB

Steroids should be used along with anti-TB drugs in following situations:

- CNS TB (proven benefit)
- TB pericarditis (proven benefit)
- TB involving eye (definitely beneficial)
- TB pleuritis (beneficial – 20-40mg tapered over 4-8 weeks)
- Extremely advanced TB (beneficial)
- TB in children (may be beneficial)
- Miliary TB (beneficial)
- Genitourinary TB (beneficial)
- Laryngeal TB (may be beneficial – scanty evidence)
- TB peritonitis (may be beneficial – scanty evidence)

Important Definitions / Terms [25, 27, 28, 29]

New Case: A patient diagnosed as having TB who has never had anti-TB treatment before or had taken anti-TB treatment for less than 4 weeks.

Sputum Smear Positive Case of Pulmonary TB: A patient who has 2 out of 3 consecutive sputum samples positive for AFB.

Sputum Smear Negative Case of Pulmonary TB: A patient clinically and radiologically suspected to have pulmonary TB but with 3 consecutive sputum samples which are negative for AFB and is also culture negative for AFB.

Culture Positive Case of Pulmonary TB: A patient with 3 consecutive sputum smear samples which are negative for AFB but with at least 1 specimen positive for AFB in culture.

Short Course Therapy for TB: The short course therapy for treatment of TB includes 2RHEZ/4RH and also known as standard regimen. If PZA is not included in the regimen for treating TB, the course should be extended from 6 months to 9 months. If rifampicin is not included in treatment regimen then the length of course should be 18 months in total.

Treatment Failure: A TB patient is said to have treatment failure if they remain smear or culture positive while on treatment at the 5th month or if they were initially smear positive, became negative but then reverted to positive at the end of 5months of treatment. Another scenario is that of a patient who was initially smear negative but then becomes smear positive after 2 months of treatment. Important things to note are:

- Never add a single drug to a failing anti-TB regimen
- Most cases are due to non-compliance
- There is a high chance of Mycobacterium developing resistance to anti-TB drugs

Relapse of TB: A patient is said to have a relapse of TB if they were treated and declared cured but is again smear or culture positive; with the same organism. If the patient gets an infection with a new MTB then they are deemed to be a new case. Because genetic analysis of the infecting MTB is required to determine if re-infection is with the same organism or a new one, it is difficult to accurately diagnose TB relapse.

TB Default Case: A TB patient who completed 1 month of anti-TB treatment, stopped the treatment, and then returns for TB treatment over 2 months after treatment was first initiated. If the patient returns within 2 months of initial treatment, then his/ her initial regimen should be continued.

Re-treatment Regimen: A patient should be a given re-treatment regimen when they relapse or are a TB default case. In highly endemic areas for TB, most authorities prefer an initial intensive phase with 5 drugs for 3 months (2 months RHEZS and 1 month RHEZ).

Chronic Case of TB: A patient is said to be a chronic case of TB, who remains sputum smear positive after 1 re-treatment course. Such patients invariably have drug resistant TB.

Extra-pulmonary TB: TB involving organs other than lungs is called extra-pulmonary TB. For the purpose of treatment and understanding, TB of the central nervous system is excluded from this classification.

Pulmonary TB: Tuberculosis involving lungs is called pulmonary TB.

Respiratory TB: TB involving lungs, pleural cavity, mediastinal lymph nodes or larynx.

CNS Tuberculosis: TB can involve the meninges, brain & spinal cord. It is called TB-meningitis, cerebritis & myelitis respectively. Standard treatment is for 12 months and steroids are mandatory. INH & PZA have 100% penetration into CSF.

Miliary Tuberculosis: This a complication of 1–3% of all TB cases. Tuberculosis involving 2 or more organs/ systems of the body is called disseminated TB or miliary TB. It is also called tuberculosis cutis acuta generalisata and tuberculosis cutis disseminate. It is a form of tuberculosis that is characterized by the wide dissemination and by the tiny size of the TB lesions (1–5 mm). Its name comes from a distinctive pattern seen on a chest X-ray of many tiny spots distributed throughout the lung fields with the appearance similar to millet seeds—thus the term "miliary" tuberculosis. Miliary TB may infect any number of organs, including the lungs, liver, and spleen.

MDR-TB: Multi-drug Resistant TB (MDR-TB) is defined as TB caused by mycobacterium tuberculosis resistant to isoniazid and rifampicin. The diagnosis and appropriate treatment of MDR-TB is still a major challenge.

XDR-TB: Extensively-drug Resistant TB (XDR-TB) is defined as TB caused by mycobacterium tuberculosis resistant to

isoniazid, rifampicin, quinolones and any 1 of 3 injectables: kanamycin, capreomycin or amikacin.

Treatment Categories of TB Patients:

There are four treatment categories of TB patients for details see table 1.

Table 1

Treatment Category	Type of TB Patient
Category I	New sputum smear +ve or Smear –ve pulmonary TB cases with extensive parenchymal involvement New severe extra-pulmonary TB cases
Category II	TB relapse cases TB treatment failure cases
Category III	Non-severe sputum smear –ve pulmonary TB Non-severe extra-pulmonary TB
Category IV	Chronic TB case

Directly Observed Treatment Short-course (DOTS):

In this programme a trained person observes the patient swallowing tablets for preferably the whole course of treatment or at least the initial 2 months of treatment. Daily or thrice weekly dosages are recommended but twice weekly dosages are not recommended because of the risk of omitting (by mistake or by chance) one dose. This would result in once weekly dose and it is not acceptable. WHO recommends the DOTS strategy in an attempt to control tuberculosis. There are 5 main points of action:

- Government commitment to control TB
- Diagnosis based on sputum smear microscopy tests done on patients who actively report TB symptoms
- Direct observation short course chemotherapy treatment
- Definite supply of drugs
- Standardized reporting and recording of cases and treatment outcomes

DOTS-Plus:

WHO extended the DOTS programme in 1998 to include treatment of MDR-TB and this is called DOTS-Plus. It requires the capacity for drug susceptibility testing and provision of 2nd line anti-TB drugs with facilities for identification and drug sensitivities.

Latent TB Infection (LTBI):

A patient is said to have LTBI when he is infected with MTB but does not have any symptoms and signs suggestive of active TB and has a normal chest X-ray. Such patients are non-infectious but 10% of these persons go on to develop active TB in their life at a later stage. They have positive tuberculin skin test and positive Interferon Gamma Release Assay (IGRA) tests (e.g. T-SPOT.TB test, QuantiFERON-TB Gold &QuantiFERON-TB Gold-in tube tests). There are different regimens for treatment of LTBI, commonly used are the following:

- 9H; 9 months INH (gold standard – only practised in USA)
- 6H; 6 months INH
- 3RH; 3 months INH + RMP (recommended in UK)

Common Causes Of Rising Burden Of Tuberculosis

- The following are a few causes of rising burden of TB globally:
- Non-compliance with medication
- Presence of drug resistant strains of mycobacteria
- Faulty regimens
- Un-diagnosed cases
- Under-diagnosed cases
- Lack of newer, more effective anti TB medication.

Role Of Pcr In The Diagnosis Of Tuberculosis

There have been a number of studies regarding the role of PCR in the diagnosis of TB. They show that it has a high sensitivity and specificity but gold standard is still tissue smear and culture for AFB. In certain scenarios PCR of different tissue samples (pulmonary or extra-pulmonary) urine, CSF, sputum and blood can be useful and can also tell us about mycobacterial rifampicin resistance.

Role Of Physicians In Prevention & Control Of Tuberculosis In Relation To Airtravel [30]

- Inform all patients with infectious TB that they must not travel by air on a flight exceeding 8 hours until they have completed at least 2 weeks of adequate therapy.
- Inform all patients with MDR-TB and XDR-TB that they must not travel by air until they are culture-negative.
- Advise patients with TB who undertake unavoidable air travel of less than 8 hours' duration to wear a surgical mask or to otherwise keep the nose and mouth covered when speaking or coughing during the flight. This recommendation should be applied on a case-by-case basis and only with the agreement of the airline(s) involved and the public health authorities at departure and arrival.
- Inform relevant health authorities of the intention of a patient with infectious TB to travel against medical advice.
- Inform relevant health authorities when a patient with infectious TB has a recent history of air travel (travel within 3 months).

Side Effects Of Medications Used For Treatment Of Tuberculosis [31, 32, 33, 34]

Patients who are on treatment for TB should be monitored regularly for any signs of medication toxicity. This may include

blood tests in addition to clinical examination. Common side effects of the routinely used 4 anti-TB medications (INH, rifampicin, Ethambutol & PZA) are as follows:

Hepatotoxicity: INH, PZA and rifampicin are known to cause liver toxicity. Ethambutol is a safer medication in patients with known liver problems. INH is contraindicated in patients with active hepatitis and end stage liver diseases. 20% patients can have an asymptomatic rise in AST concentration in the first 3 months of therapy. Symptoms of liver toxicity include anorexia, nausea, vomiting, dark urine, jaundice, fever, persistent fatigue, abdominal pain especially in the right upper quadrant. Routine base line LFTs are recommended prior to starting treatment. After that they should be repeated at least once a month and more frequently in those who are at risk of developing hepatotoxicity. Patients at increased risk of hepatotoxicity include:

- HIV positive
- Pregnant or post-partum (3 months after delivery)
- History of or at risk of chronic liver disease (daily use of alcohol, IV drug users, hepatitis, liver cirrhosis)
- Patients taking any other medication which have potential hepatotoxic side effects
- The risk of hepatotoxicity increases with age (> 35 years old)

Suspect drug induced liver injury if there is AST/ ALT rise > 3 times base line with symptoms or > 5 times in the absence of symptoms, or disproportionate rise in ALP and total bilirubin. In such a situation:

- Stop hepatotoxic anti-TB medications (INH, rifampicin and PZA) immediately
- Admit the patient to hospital
- Carry out serological tests for Hepatitis A, B, and C (particularly in those who are at risk for hepatitis)
- Look for other causes (hepatotoxic medications, high alcohol consumption)
- In acutely ill smear or culture positive patients start liver friendly medications i.e. Ethambutol Quinolones, and Streptomycin, until the cause for hepatotoxicity is identified.
- Re-challenge: Once LFTs are normal (or < two times the upper normal limit) start with Ethambutol and add INH 1st. If LFTs do not rise after 1 week add Rifampicin. Next add PZA if there is no rise in LFTs after 1 week of adding Rifampicin. If at any point LFTs increase or symptoms recur, stop the last added drug – as this is the culprit drug.

Gastro-intestinal (GI) upset: GI upset is quiet common with anti-TB medications and usually occur in the first few weeks of therapy. Symptoms usually are nausea, vomiting, anorexia, abdominal pain. In such a case recommend good hydration, change the timing of medication (advise to take with a light snack and at bed time) and also check LFTs for possible hepatitis. Aluminium salt containing antacids can reduce bioavailability of INH, so avoid them 1 hour before and 2 hours after INH administration.

Rash: All anti-TB medications can cause a skin rash. Management is based on severity:

- Mild rash or itching: administer anti-histamines 30 minutes prior to anti-TB medications and continue with the therapy. If no improvement, add prednisolone 40mg/day and gradually taper down when the rash clears.
- Petechial rash: Red pinpoint sized dots under the skin due to leakage from capillaries – suspect rifampicin hypersensitivity. Monitor LFTs and full blood count. If platelet count is below normal (base line), stop rifampicin and do not restart it.
- Erythematous rash with fever: and/ or mucous membrane involvement; stop all anti-TB medications immediately and hospitalize the patient. Rule out anaphylaxis (angio-oedema, swollen tongue, throat, stridor, wheezing, flushed face, hypotension) and Stevens-Johnson Syndrome (systemic shedding of mucous membranes and fever). If situation does not permit to stop TB medication then try 3 new drugs i.e. aminoglycoside and 2 oral agents from second line. Once the rash has settled, can re-introduce first line TB medications one by one every 2-3 days, 1st rifampicin, then INH, then PZA and then Ethambutol. While re-introduction, monitor the signs and symptoms of rash, if rash recurs at any point remove the last agent added.

Peripheral neuropathy: signs and symptoms include numbness and tingling in feet and hands, increased sensitivity to touch and stabbing pain. INH can cause peripheral neuropathy. It is more common in malnourished people, diabetes, HIV, renal failure, alcoholism, pregnancy and in breast feeding women. Prevention is the key; prophylaxis is with Pyridoxine (vitamin B6) 10mg/ 100mg INH (normally 25 – 50mg) per week is used in high risk patients.

Optic neuritis: the main agent responsible for this is Ethambutol. It is dose related and gets more intense if treatment is continued. Signs and symptoms are difficulty in reading road signs, decreased red-green colour discrimination, blurring or vision, and colour blindness. These can be unilateral or bilateral. Ethambutol is not recommended in children <5 years of age as visual changes are difficult to monitor. Visual acuity and colour blindness tests are recommended at baseline and also on a monthly basis. Fluctuations of 1 or 2 lines on the Snellen chart is considerable and Ethambutol must be stopped. More than 10% visual loss is considered significant.

Fatigue: INH can cause fatigue and in such situations patients should take the medication at bedtime. If it continues, check LFTs to look for hepatotoxicity.

Flu-like symptoms/joint aches and pains: These are usually seen with Rifampicin and treatment is symptomatic.

Drug-induced lupus: It is seen with INH and blood tests should be done to differentiate it from SLE. It can be managed with steroids while the patient is taking INH.

Competing Interests
None Declared
Author Details
AMER SALEEM, BSc, MBBS, MCPS, FCPS, Specialist Registrar Chest Medicine, Bedford Hospital NHS Trust, Bedford, UK. MOHAMMED AZHER, MBBS, FRCP, Consultant in Chest Medicine, Bedford Hospital NHS Trust, Bedford, UK.
CORRESSPONDENCE: DR MOHAMMED AZHER,Consultant in Chest Medicine, Bedford Hospital NHS Trust, Bedford, UK.
Email: m_azher@gmail.com

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