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A RETROSPECTIVE ANALYSIS OF THE CO-MORBIDITIES AND TREATMENT SCHEDULE OF PULMONARY TUBERCULOSIS REPORTING AT ANANTA INSTITUTE OF MEDICAL SCIENCES AND RESEARCH CENTRE, RAJSAMAND, RAJASTHAN

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ABSTRACT

The bacillus that causes TB, a chronic granulomatous infectious disease, is called Mycobacterium tuberculosis. While TB can affect any organ or tissue, the most common form is pulmonary tuberculosis. According to the World TB Report 2021, India has an eradication incidence of all forms of tuberculosis for the year 2020 of 188 per lakh people and a prevalence of 312 per lakh people the following year. The WHO predicts that 10 million people will get TB disease globally in 2020, and 1.5 million people will die from it, including more than 2 lakh people who are HIV positive. Fever, anorexia, weight loss, coughing, and other symptoms may be signs of pulmonary TB. Extra-pulmonary or EPTB can occur, albeit being less common in any organ or tissue Even worse, it could spread and result in miliary TB, which is more common in old and immunocompromised individuals. Each form of TB has the potential to be fatal if left untreated. The typical treatment plan consists of a two-month intensive phase and a four-month continuous phase.

The four drugs used in the intensive phase are isoniazid, rifampicin, pyrazinamide, and ethambutol, and they are all taken in a single dosage in the early morning. As pyrazinamide loses its effectiveness after two months, it is not administered during the continuous phase. Extra-pulmonary TB treatment duration varies by case and is frequently longer. The problem that the world is currently facing is drug resistance. When a FQ is present and there is drug

resistance to Isoniazid, Rifampicin, and any additional two drugs from second line, the condition is referred to as multidrug resistance (MDR-TB).

In the reserve category, it is referred to as Extended Resistance (XDR-TB). The failure of treatments and the challenges in controlling or eradicating the disease have been profoundly impacted by these two forms of TB.

KEYWORDS:- TB, Pulmonary tuberculosis, Incidence, Prevalence, Extrapulmonary tuberculosis, Miliary tuberculosis, Treatment, ATT, MDR-TB, XDR-TB.

INTRODUCTION

Mycobacterium tuberculosis, an acid-fast bacilli, is the causative agent of TB, a chronic granulomatous infectious illness. While TB may infect any organ or tissue, pulmonary tuberculosis is the most prevalent kind. Extra- pulmonary tuberculosis may damage intestines, meninges, bones and joints, lymph glands, skin, eyes, reproductive tract etc. When a person with active lung illness coughs or sneezes and inhales the contaminated droplets, the disease is transmitted.

The elimination incidence of all kinds of tuberculosis in India for the year 2020 was 188 per lakh people, and the prevalence was 312 per lakh people in the following year, according to the Global TB Report 2021. According to the WHO, 10 million people are expected to get TB illness worldwide in 2020, and 1.5 million people will pass away from it, including more than 2 lakh HIV-positive individuals. After COVID-19, TB is the second most common infectious killer in the world and the thirteenth largest cause of death overall. Sadly, India has the highest TB prevalence rate in the world.

Treatment for TB comes with a number of significant issues. First, the lengthy duration and intricacy of the therapy cause non-compliance, which results in a worse than ideal outcome, such as failure or relapse and, more concerningly, a drug resistance emergency. Second, anti-tubercular medication side effects are frequent and exacerbate the non-adherence issue.

The major causes of TB persistence in underdeveloped nations include low socioeconomic position, filthy living circumstances, ignorance, and a careless attitude. Moreover, TB as an opportunistic illness has increased internationally due to HIV, Diabetes, other immune weakened diseases, and the use of high doses of immunosuppressants.

One of the unfavourable consequences for patients in a DOTS programme is defaulters to treatment, which continues to be a significant barrier for control programmes.

The symptoms of pulmonary TB might include fever, anorexia, weight loss, coughing, and other symptoms. Extra-pulmonary or EPTB, however less prevalent, can arise in any organ or tissue. It may even spread, causing miliary TB, which is more frequent in elderly and immunocompromised people. If untreated, TB in any form has the potential to be lethal. Complications brought on by poorly treated patients may aggravate indications and symptoms, cause organ damage, and ultimately cause the organ to stop functioning.

The typical methods used to diagnose TB include sputum analysis, x-rays, CBNAT, bronchoscopy, sonography, CT scans, etc.

The normal treatment programme includes a two month intense phase following by four months of continuous phase.

Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol are the four medications used in the intense phase, and they are all administered in one early morning dose. Pyrazinamide is not used in the continuous phase since it ceases to be beneficial after two months. The length of treatment for extra-pulmonary TB varies by case and is often longer.

In immune-compromised individuals, longer treatment periods and more medications are required to treat TB, particularly in HIV+ patients where the infection may be opportunistic. Drug resistance is the issue the world is now experiencing. When there is a FQ and resistance to Isoniazid, Rifampicin, and any two more medications from second line, the condition is referred to as multidrug resistance (MDR-TB).

It is referred to as Extended Resistance in the reserve category (XDR-TB). These two types of TB have significantly contributed to treatment failure and the difficulties in containing or eliminating the illness.

Over the years, our nation has launched a number of programmes to combat this disease. The Directly Observed Treatment Short-Course (DOTS) philosophy and the World Health Organization's global TB control plan are both incorporated into the RNTCP (Revised National Tuberculosis Control Program). With assistance from the World Bank and other development organisations, this was started in 1997.

It was changed to NTEP in 2020. (National Tuberculosis Elimination Program). The goal of this initiative is to create a "TB free India," with a strategic focus on the "Prevent, Detect, Treat, and Build" pill are for social protection and universal coverage. Via the public health care system, it offers a range of high-quality, no-cost TB diagnostic and treatment services across the nation.

The "NIKSHAY" site has been introduced as part of the NTEP, which stands for the elimination of tuberculosis (TB). In addition to the National Informatics Center (NIC) and the WHO country office of India, it is created and maintained by the Central TB Division (CTD), Ministry of Health and Family Welfare. It serves as the country's national TB monitoring system and allows for the submission of all patient data to the Indian government.

I decided to undertake this study to gather data on co-morbidities and treatment plans of patients with pulmonary tuberculosis who reported to Ananta Institute of Medical Sciences and Research Centre, Rajsamand, Rajasthan, between March 2021 and February 2022 after considering the aforementioned status of tuberculosis cases, reporting, treatment, and management challenges.

Tuberculosis is a chronic granulomatous disease and a major health problem in developing countries, about one-third of the world's population is infected with Microbactericun tuberculosis. As per WHO estimate, I million people globally develop active tuberculosis and 1.7 million die of it annually. In India, it is estimated that nearly 2 million people develop active disease every year and about 0.5 million die from it. A new dimension got added in the 1980s due to spread of HIV with high prevalence of tuber-culosis and mycobacterium avium complex (MAC) infection among these patients. India has a large load of HIV infected subjects and these patients are especially vulnerable to severe forms of tubercular/MAC infection. While lately, the increase in TB case rate associated with HIV infection has been halted in the USA, no such trend is apparent in India. Energence of "multidrug resistant (MDR) TB of which over 0.4 million case are occurring globally every year, is threatening the whole further of current antitubercular chemotherapy.[1]

The "Mycobacterium" species of pathogenic bacteria, which belongs to the Mycobacteriacease family, is the causal organism of TB M. Tuberculosis, which Roberts Koch first identified in 1882, has a unique, waxy coating on its cell surface that is principally

caused by the presence of mycolic acid M. tuberculosis might look faintly Gram positive.(2) Those who have active TB in their lungs cough, spit, talk, or sneeze can transmit the disease to others through the air. Latent TB carriers do not disseminate the illness. Active infection is more prevalent in smokers and HIV/AIDS patients.[3]

Coughing, sputum production, hemoptysis, shortness of breath, weight loss, anorexia, fever, and malaise are all indications of pulmonary TB. Nowadays, people with pulmonary TB who exhibit the complete range of symptoms and indications are uncommon in industrialised nations, but such patients are often seen by doctors and other healthcare professionals in poor nations. In industrialised nations, lung cancer has become a more frequent cause of some or all of these symptoms; if cigarette smoking rises, this may also become the case in developing nations.[4]

Signs of potential extra-pulmonary tuberculosis. Depending on the physical portion that the sickness has damaged. There may be blood in the urine from tuberculosis of the kidney, headaches or disorientation from tuberculosis of the meninges, back discomfort from tuberculosis of the spine, and exhaustion and hoarseness from tuberculosis of the larynx.[5]

Latent tuberculosis infection (LTBI): The germs that cause tuberculosis can reside in the body and cause no symptoms. This is termed latent TB infection. In most people who breathe in TB germs and become sick, the body is able to fight the bacteria and stop them from developing. Those who have latent TB infection:

- Do not exhibit any symptoms
- You don't feel ill
- Can't distribute TB bacterium to others.
- If latent TB infection is not treated, individuals risk developing TB illness.

Many persons with latent TB infection never experience the symptoms of TB illness. Some individuals have TB germs that are inert for the rest of their lives without developing any illness. Yet, in some individuals, particularly those with weakened immune systems, the bacteria become active, grow, and result in TB illness.

If the immune system is unable to prevent the growth of the tuberculosis germs, they become active. TB germs are active when (multiplying in your body). This is called TB disease. People with TB disease are sick. They may also be able to spread the bacteria to people they

spend time with every day.

Many persons with latent TB infection never experience the symptoms of TB illness. Before their immune system can effectively combat the TB germs, some people become ill with TB illness within a few weeks after contracting the infection. Others may get a disease years down the road if their immune system deteriorates for some other cause.

For persons with weakened immune systems, particularly those who have HIV infection. The risk of developing TB disease is much higher than for people with normal immune system.[6]

Miliary TB is a kind of tuberculosis that can be fatal and develops when many germs are circulated widely throughout the body by the bloodstream. Since the many, extremely minute patches that develop in the lungs are the same size as millet, the tiny spherical seeds used as bird food, miliary TB is so named.

Mild TB can affect a single organ, a number of organs, or the entire body. It can affect any organ, including the meninges—tissues that cover the brain and spinal cord—and the two-layered membrane that surrounds the heart, though it most frequently affects the lungs, liver, and bone marrow (pericardium).

Miliary tuberculosis occur most often in the following

- Children under 4 years old
- People with a weakened immune system
- Older people.[7]

*** Comorbidities**

Tuberculosis and HIV coinfection

The primary burden of infectious diseases in resource-limited nations is borne by tuberculosis and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). The two viruses, Mycobacterium TB and HIV, enhance one another in the particular host. increasing the rate of immune function decline. The most significant risk factor for acquiring active TB in high burden settings is HIV coinfection, which substantially raises the likelihood of TB reactivation in individuals with latent TB due to increased vulnerability to primary infection or reinfection. M. tuberculosis infection also has a deleterious influence on the immunological response to HIV, increasing the development from HIV infection to AIDS.

Effective anti-TB treatment, concomitant antiretroviral therapy (ART), preventing HIV-related comorbidities, and managing drug cytotoxicity are all part of the clinical management of HIV-associated TB and prevention/treatment of immune reconstitution inflammatory syndrome (IRIS).[8]

Tuberculosis with diabetes

The epidemiological association between diabetes and TB is widely known, but during the past 50 years, populations with high rates of diabetes (those who are affluent, overfed, and work in more sedentary environments) have been distinguished from those who are still plagued by widespread TB (Poorer, under nourished, persistence of gruelling manual working environment). Growing urbanisation and industrialisation in emerging nations are causing diabetes rates to rise, creating a potentially catastrophic confluence of NCDs (of which diabetes is one of the most common). This is already a reality in some areas of China and India, where large numbers of people from typically rural areas move to congested apartments in metropolitan centres to work for low wages in poorly ventilated mines and factories.

Tuberculosis with malnutrition

All infections and diseases are at danger due to malnutrition's impact on immunity. Micronutrient deficits as well as protein calorie malnutrition (PCM) can inhibit the immune system in a number of ways. Chronic malnutrition significantly affects chronic infectious diseases like HIV and TB, which need ongoing immunological monitoring and management. Between 42% and 80% of adult pulmonary TB patients have malnutrition, which is often indicated by a BMI of less than 18.5 kg/m2.

Tuberculosis with malaria

Although there is a large body of work on HIV/tuberculosis and HIV/malaria coinfections and comorbidity, TB and malaria-related clinical and immunological interactions have received noticeably less attention. Unlike HIV, both mycobacterium tuberculosis (Mtb) and plasmodium species are ancient infections that have coevolved in the same human populations over millennia, with genetic evidence for, coinfection demonstrated in 2000-3000 Year old mummified mummies from lower Egypt. Studies using animal models show that malaria infection triggers immune reactions that reduce the host's resistance to long-term tuberculosis infection. These immune responses include exacerbated leukocyte infiltrates, tissue pathology, and hypercytokinamia, which are accompanied by altered T-cell responses

and suggest that malaria causes a dysregulation of the innate and adaptive antimycobacterial defence.

Tuberculosis with influenza

Results from the 1918 influenza outbreak revealed a clear relationship with higher risk for TB associated sickness and mortality during this time period. According to studies using mouse models, prior exposure to influenza A impairs immune responses to Mtb infection and decreases survival, possibly as a result of dendritic cell expression of the MHC (major histocompatibility complex) being downregulated and decreased CD4 and CD8 T cell activation to eradicate mycobacteria.

Tuberculosis with helminths:

There is growing understanding that disadvantaged groups living in tropical and subtropical climates are more likely to have immune profiles with varying responses to TB infection. In a U.S. study of immigrants from countries with a TB epidemic, individuals who were latently infected with the disease and concurrently infected with helminth or Helicobacter pylori had elevated levels of IFN- and cytokines (despite having no acute sickness or recent treatment history). H. pylori was linked to improved IFN-TB responses.[9]

Tuberculosis in pregnancy

The vast majority of medical professionals just disagree with the importance of TB in pregnancy to public health. It is best described as a doubled-edged sword, one blade being the influence of TB on pregnancy and the pattern of growth of the infant, while the other being the effect of pregnancy on the advancement of tuberculosis.

In addition to contributing significantly to the global disease burden, tuberculosis also has a major impact on maternal mortality, ranking among the top three killers of women between the ages of 15 and 45.

Effect of TB on pregnancy

The severity of the illness, the stage of the pregnancy at the time of diagnosis, the existence of extra-pulmonary spread and HIV coinfection, as well as the course of treatment, may all have an impact on how TB affects pregnancy.

The prognosis is documented as being poorest in women whose severe condition is diagnosed during puerperium as well as in those who additionally have HIV infection. Non-

compliance with therapy further affects the prognosis. In addition to premature labour, low birth weight, and increased neonatal mortality, these women have also been found to have a higher risk of spontaneous abortion, small-for-date fetuse size, and poor weight growth during pregnancy.

Tuberculosis and The newborn

The probability of postnatal transmission is substantially higher of haematogenous spread from the umbilical vein to the foetal liver than through swallowing and aspiration of contaminated amniotic fluid. Congenital TB is an uncommon consequence of in utero tuberculosis infection. After that, the liver becomes the major focus, and the peri-portal lymph nodes are also involved. Unlike in adults, when the lungs account for more than 80% of the original infection, the tubercle bacilli only secondarily infect the lungs in children.[10]

First-line antituberculosis drugs

The following discussion of individual anti-TB agents focuses on treatment of TB in adults, unless otherwise noted. Several agents are being actively investigated during the current remarkable period of drug development for TB treatment.

(1) Isoniazid: Isoniazid is a crucial medication for the treatment of both LTBI and TB illness. Both intracellular and extracellular, actively dividing M. tuberculosis are effectively bacteriostatically inhibited by isoniazid. This medication is bacteriostatic to germs that divide slowly. Isoniazid is regarded as the first-line therapy for LTBI because it is often well tolerated, has a proven track record of effectiveness, and is reasonably priced.

Mechanism of action- The mycobacterial enzyme katG catalase-peroxidase activates the prodrug isoniazid, which is combined with decreased nicotinamide adenine dinucleotide (NADH). As a result, fatty acid synthase and eventually mycolic acid production are inhibited by the onicotinic compound known as InhA, which binds to its substrate. The mycobacterial cell wall cannot exist without mycolic acids. Nitric oxide and other free radicals, including those with antimycobacterial action, are released when katG activates isoniazid.

Dosing- In the United States, a daily dosage of 5 mg/kg for adults and 10–20 mg/kg for children is advised for the treatment of tuberculosis (TB). With a combined maximum daily

intake of 300mg. Adults receiving intermittent treatment (often twice weekly) get a dosage of 15 mg/kg, with a daily maximum of 900 mg. When the 12-dose, 3-month weekly LTBI regimen is employed, the dose of isoniazid is 15 mg/kg with a maximum dose of 900 mg. The medicine is also co-administered with rifapentine, therefore there is no dosage modification necessary for patients with renal illness.

(2) Rifampin: A semi-synthetic variant of amycolatopsis refamycinicd is rifmpin (Formerly known as streptomyces mediterranei). Rifampin, the most potent antimycobacterial antibiotic currently on the market, is the cornerstone of first-line TB treatment. The medication was first introduced in 1968 and finally approved. Much shorter TB treatment duration. Both dividing and nondividing M. tuberculosis are susceptible to the sterilising and bactericidal effects of rifampin. The medication is also effective against a wide range of other species, such as legionella, M. Kansasii, certain gram-negative bacteria, and mycobacterium marinum. For the treatment of LTBI, rifampin can be used instead of isoniazid for a period of four months.

Mechanism of action: Both intracellular and extracellular bactericidal action is produced by rifampin. Rifampin, like other rifamycins, binds to and inhibits mycobacterial DNA-dependent RNA polymerase, preventing the production of RNA. Susceptible strains of M. as well as TB. Kanassy and M. Rifampin concentrations of 1 mg/ml block marinum.

Dosing: Rifampin has a maximum daily dose of 600 mg for both adults and children, or 10 mg/kg for adults and 10 mg/kg for children. One dose per day, two doses per week, or three doses per week are administered. Those with renal impairment don't need to change their dose or frequency.

(3) Ethambutol: The bacteriostatic antimycobacterial drug ethambutol was created for the first time in 1961. Ethambutol, a component of the typical first-line treatment, works in concert with the other medications in the regimen and is often well tolerated by susceptible species. The least effective drug against M. tuberculosis is ethambutol. In the later stages of therapy, this medication is also used with additional medications.

Patients who have infections that are resistant to either rifampin or isoniazid are unable to tolerate either of those medications.

Mechanism of action: Bacteriostatic against M. tuberculosis is ethambutol. Its main method

of action is the inhibition of arabinosyltransferases, which are essential for the synthesis of all walls and are likely to prevent the creation of arabinogalactan and lipoarabinomannan. The MIC of ethambutol for M. tuberculosis susceptible strains is 0.5-2 Mg/ml.

Dosing: In just 2-4 administrations after a single dosage of ethambutol, 75-80% of it is absorbed. For intermittent treatment, the dosage is 50mg/kg twice weekly, which is equal to the average adult daily dose of 15kg/mg. For individuals with renal impairment, the dosage must be decreased and the frequency of administration must be decreased to prevent toxicity.

(4) Pyrazinamide: An essential antibacterial medication used in the first stage of tuberculosis treatment is pyrazinamide, a nicotinamide analogue. Its administration for the first 2 months as therapy with Rifampin and isoniazid allows treatment length to be decreased from 9 months to 6 months and lowers rates of recurrence**.**

Mechanism of action: Pyrazinamide, a nicotinamide analogue, is a crucial antibacterial drug used in the initial stage of TB therapy. Its use for the first two months of treatment, together with rifampin and isoniazid, reduces recurrence rates and permits treatment to be cut from nine to six months.

Dosing: The maximum daily dosage for adults is 2 grammes, or 15 to 30 mg/kg. In individuals with decreased creatinine clearance, the dose needs to be modified in accordance with the degree of renal function.

***Other first line drugs**

(1) Rifabutin: Mycobacterial RNA polymerase is inhibited by rifabutin, a semi-synthetic derivative of rifamycin S. Refampin should not be used for the treatment of people who also have HIV; instead, rifabutin should be used. Who are using non-nucleoside reverse transcriptase inhibitors or protease inhibitors, notably nevirapine.

(2) Rifapentine: Rifapentine is a semi-synthetic form of cyclopentyl rifamycin that works similarly to rifampin. As rifapentine is lipophilic and has a long half-life, it can be used once weekly or twice weekly together with isoniazid. The recommended dose is 10 mg/kg up to 600 mg. This regimen is not advised for individuals who also have HIV infection because to greater risks of recurrence.

(3) Streptomycin: The first antimycobacterial drug used to treat TB was streptomycin. is a descendent of streptomyces griseus. Streptomycin has low-level early bactericidal action but is bactericidal against dividing M. tuberculosis organisms. Only IM approaches are used to administer this medication. Because of its toxicity, streptomycin is rarely used in affluent countries**.**

Mechanism of action: Streptomycin binds to a specific location on the 30s mycobacterial ribosome to prevent protein production.

Dosing: After a 1g dosage, the serum level of streptomycin peaks at 25–45 mg/ml. Streptomycin is often administered intramuscularly (IM) five days a week or daily at a dosage of 15 mg/kg for adults and 20–40 mg/kg for children, with a daily maximum of 1 g for both. For pt > 60 years of age 10mg/kg is suggested daily dosage.

**** Treatment Schedules of TB**

*** Regimens for the treatment of latent tuberculosis infection in adults:**

Regimen	**Schedule**	**Duration**
Isoniazid	300mg/d(5mg/kg) alternative:900 mg twice weekly (15mg/kg)	9 months (6 months acceptable)
Rifampin	600 mg/ld (10mg/kg)	4 months
Isoniazid + Rifapentine	900 mg (15mg/kg) weekly + 900 mg weekly	3 months

*** Treatment of active tuberculosis (TB) in adults:**

Culture results	**Intensive phase**	**Continuation Phase**	**Extension of total treatment**
Culture positive	HRZE for 2 months, daily or intermittent (with dose adjustment)	HR for 4 months, daily or 5 day/week or HR for 4 month, intermittent.	To 9 months, if 2 months of Z is not completed or culture conversionis prolonged and cavitation is evident on plain radiograph
Culture negative	HRZE for 2 month	2 months	To 6 month if
Extrapulmonary	HRZE for 2 months	HR for 4-7 months, daily or 5 day/weekb	To 9-12 months in TB meningitis. Some recommended 9 months for bone/joint TB.
Resistant to R	HZEQ(IAa) For 2 months	HEQ(S) for 10-16 months	Prolonged culture conversion, delay

			response.
Resistant to HRe	ZEQ(1Ab)+alternative agents for 18-24 months		Prolonged culture conversion.

Second line antituberculosis drugs

Second line antituberculosis agents are indicated for treatment of drug-resistant TB, for patients who are intolerant or allergic to first line agents, and when first-line supplemental agents are unavailable.

(1) Fluoroquinolones: Mycobacterial DNA gyrase and topoisomerase IV are both inhibited by it. Preventing cell replication and protein synthesis and are bactericidal the later generation fluoroquinolones, levofloxacin & moxifloxacin are the most active against M. tuberculosis and due recommended for the treatment of MDR-TB. Levofloxacin's optional dose for this use is still being researched, however doses of at least 750 mg are often utilised.

Injectable agents

(1) Capreomycin: When additional resistance to aminoglycosides is documented, capreomycin, a cyclic peptide antibiotic derived from streptomycin capreolus, is an important first-choice second-line agent used to treat MDR-TB. A dosage of 15 mg/kg per day is given five to seven times per week (maximum daily dose, 1 g), and this produces peak blood levels of 20 to 40 mg/ml. Capreomycin is administered intramuscularly (IM), while an inhaled formulation is now being studied. The dosage may be reduced to 1g two or three times per week 2-4 months after Mycobacterial cultures becomes negative. For individuals > 60 years of age, the dose should be reduced to 10mg/kg per day (maximal daily dose 750mg) (maximal daily dose 750mg). A minimal duration of 3 months is recommended for MDR-TB treatment. Penetration of capreomycin into theCSF is believed to be poor.

(2) Amikacin & Kanamycin: Aminoglycosides like kanamycin and amikacin work to kill mycobacteria by attaching to the 16s ribosomal subunit. Amikacin and kanamycin's range of antibiotic activity include M. aerobic gram-negative and gram-positive bacteria, TB, and a number of Nontuberculous Mycobacteria (NTM) species. The normal daily adult dosage of both Amikacin & Kanamycin is 15-30 mg/kg administered IM (Maximal daily dose, 1g) with a decrease to l0 mg/kg for patients > 60 years old.

Other second-line agents

(3) Ethionamide: Ethionamide is derivative of isonicotinic acid. Its mechanism of action is through inhibition of the inhA gene product enoyl-acyl carrier protein (acp) reductase, which is involved in mycolic acid synthesis. Ethionamide is bacteriostatic against metabolically active M. tuberculosis and same NTM. It is used for the treatment of drug resistant TB.

(4) Cycloserine: Cycloserine is an analog of the amino-acid D-alanine and prevents cell wall synthesis. It inhibits the action of enzymes, including alanine racemase, that are involved in the production of peptidoglycans. Cycloserine is active against a rangeof bacteria, including M. tuberculosis. The usual adult dosage is 250mg two or three times per day.

(5) Para aminosalicylic acid: Para-aminosalicylic acid (PAS, 4- amino salicylic acid) is an oral agent used in the treatment of MDR and XDR-TB its bacteriostatic activity is due to inhibition of folate synthesis and of iron uptake. PAS has relatively little activity as an anti TB agent enteric coated PAS granules (4g orally every 8h)

(6) Clofazimine: Clofazimine is a fat soluble Riminophenazine dye used primarily in the treatment of leprosy world wide. It is currently gaining popularity in the management of MDR and XDR-TB because of its low cost and intracellular and extra cellular activity.[11]

*** Treatment for drug resistant TB**

(1) MDR-TB (Multidrug resistance TB)

- Early MDR-TB detection and the promptinitiation of an effective treatment are important factor in obtaining successful outcomes.
- The intensive phase of MDR-TB treatment should consist of at least four second- line-anti-TB drugs that are likely to be effective. (Including an injectable anti-TB drug) as well as pyrazinamide (conditional recommendation, very low quality evidence).
- MDR regimens should include at least pyrazinamide a fluoroquinolone, an injectable anti-TB drug, ethionamide (or prothionamide) and either cycloserine or PAS (para-aminosalycylic acid) if cycloserine can not be used (conditional-recommendation, very low quality evidence
- A fluoroquinolone should be used (strong-recommendation, very low quality

evidence).

- A later-generation fluoroquinolone rather than an earlier-generation, fluoroquinolone should be used (Conditional recommendation, very low quality evidence).
- In the treatment of patient with MDR-TB ethionamide (or prothionamide) should be used (Strong recommendation, very low quality evidence).

(2) XDR-TB (Extensive drug resistance TB):

- Use pyrazinamide and any other group'1 agent that may be effective.
- Use an injectable agent to which the strain is susceptible and consider andextended duration of use (12 months or possible the whole treatment). If resistant to all injectable agents it is recommended to use on the patient has never used before or consider designing the regimen without an injectable agent.
- Use a higher-generation fluoroquinolone such as moxifloxacin or gatifloxacin
- Use all group 4 agents that have not been used extensively in a previous ragimen or any that are likely to be effective.[12]

MATERIALS AND METHODS

(a) Study Design and Site

The study is planned as a retrospective and analytical study from the case records and Nikshay portal data of patients of Tuberculosis reporting at the Nodal TB centre of Ananta Institute of Medical Sciences and Research Centre, Rajsamand, Rajasthan**.**

(b) Study materials

Data will be collected from old case records maintained registers for TB patients and Nikshay Portal of the Nodal centre for TB at Ananta Institute of Medical Sciences and Research Centre. Additional data will also be collected from Medicine and Pulmonary Medicine OPD records to find out cases presented with suspected TB who xxx further investigation.

(c) Study duration

12 months (March 2021 to February 2022)

(d) Inclusion criteria

Data will be collected of only suspected cases of TB which are later confirmed by investigations.

(e) Exlcusion criteria

1. COPD
2. Other respiratory disease

Study procedure

Study will be retrospective (past 12 months) and analytical. All patients who reported to pulmonary medicine and General Medicine OPDs during the period from March 2021 to February 2022, and had been suspected to suffer from TB will be taken into account.

Then out of total suspected cases, those who were confirmed to suffer from TB by sputum testing and X-ray will be selected for analysis.

Additional investigations done to find out co-morbidities or confirm a doubtful case would also be noted.

Once confirmed of diagnosis of TB patients details are recorded in Nikshay Portal, provided by Government of India to keep track and monitor all aspects for NTEP (National TB Eradication Programme).

Hence Nikshay Portal data would be collected for all patients (both pulmonary and extra-pulmonary TB). Which would include their ID number on the portal, their registration all investigation done, treatment plan, place of collection of monthly medicine, payments made to patients and TB centres, follow-up and finally outcome of treatment.

All the above data would then be compiled and analyzed to arrive at results of the finding.

Statistical analysis

Data collected and compiled will be entered in MS-Excel. Where it will be further cleaned and imported to SPSS version 25.0 for analysis.

RESULT

Table: Pulmonary Tuberculosis, Co-morbidities and Management.

Month	Total Suspected TB patients	Pulmonary TB	Extra-Pulmonary TB	TB with Diabetes	TB with HIV	TB with other Co-morbidities	Treatment had to be alter due to weight	Referred to other centre	Drug resistance cases
March	126	15	3	-	1	-	N	All	-
April	40	4	1	-	-	-	1**	All	-
May	8	3	-	-	-	-	N	All	-
June	22	6	3	1	1	-	1**	All	-
July	117	23	4	-	-	-	2*	All	-
August	71	13	6	2	2	-	N	16	-
September	65	7	6	-	-	-	N	All	-
October	44	4	3	-	-	-	N	All	-
November	54	3	4	-	-	-	N	5	-
December	65	7	4	2	1	-	N	7	-
January	69	7	4	-	-	-	N	9	-
February	64	14	2	-	-	-	2*	All	-
Total	745	106	40	5	5	0	6	37	0

*Overweight Patients
**Underweight Patients

Above table shows the number of patients of confirmed Pulmonary Tuberculosis reported at Ananta Institute of Medical Sciences and Research Centre during the period between March 2021 to February 2022 out of the total suspected cases.

The small number of Extra-Pulmonary Tuberculosis cases are also depicted.

Common co-morbidities of TB like diabetes mellitus & HIV have been tested for and the number of patients testing positive for either are reported.
There were no other co-morbidities reported.

In a small number of patients the dosage of the drug had to be decreased / increased due to their body weight.

Majority of the patients were referred to different centres for continuation of their treatment where as a few took treatment from Ananta Institute of Medical Sciences and Research Centre. No cases of drug resistance TB were reported.

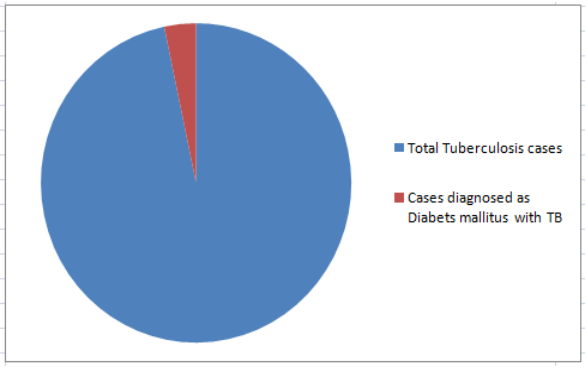

Figure 1: Diabetes as a co-morbidity of TB.

Figure 1 depicts total number of 146 patients were confirmed as Tuberculosis and out of 146 patients, 5 patients were diagnosed as Diabetes mallitus (i.e. 3.42% patient had Diabetes mallitus as co-morbidity.

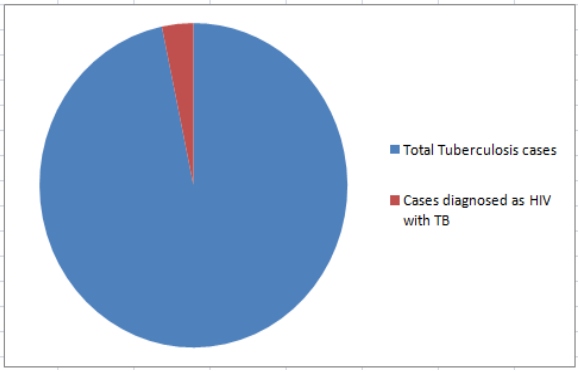

Figure 2: HIV as a co-morbidity with TB.

Figure 2 depicts total number of 146 patients were confirmed as tuberculosis and out of 146 patients, 5 patients were diagnosed as HIV. (i.e. 3.42% patients are HIV suspected patients).

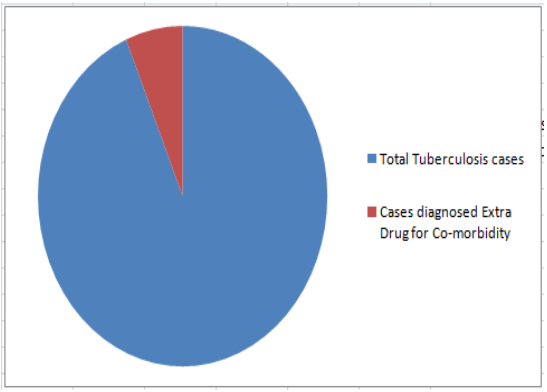

Figure 3: Additional anti-tubercular drugs needed.

Figure 3 depicts total number of 146 patients were confirmed as tuberculosis and out of 146 patients, 10 patients had to be put on additional anti-tubercular drug (Alongwith HRZE) due to co-morbidities. (i.e. 6.84% patients had to put on additional anti-tubercular drug).

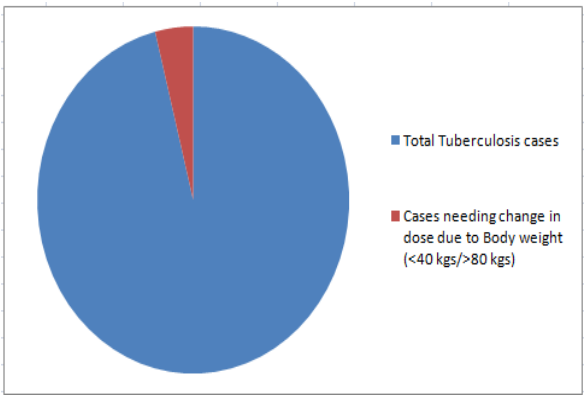

Figure 4: Alteration required in dosage.

Figure 4 depicts total number of 146 patients were confirmed as tuberculosis and out of 146 patients, 6 patients had to be changed in dose due to Body weight. (i.e. 4.10% patients had to be changes dose of medicine due to Body weight).

DISCUSSION

Drop-outs or defaulters, death) etc. The present work was undertaken at a tertiary medical centre, namely Ananta Institute of Medical Sciences and Research Centre, Rajsamand. This hospital was chosen as it is a Nodal Tuberculosis centre (NTC).

All Patients who had reported to the general medicine and pulmonary Medicine OPDs during the period of March 2021 and February 2022 were taken into consideration for collection of data Month-wise medical case records were scrutinized and the collective data was compiled for the entire 12 months period.

For each month, collection of data included total number of case of suspected tubercular infection, their registration in Nikshay Portal, sputum testing for AFB, X-ray chest, testing for diabetes and HIV, initially.

After above cases confirmed as Tuberculosis were noted. Which was again classified as pulmonary and Extra-pulmonary cases of TB. All patients of tuberculosis were provided with banking facilities, where a monthly amount of Rupees 500/- would be deposited for their better nutrition & well being.

Those patients who were doubtful were tested by CBNAAT & FNAC (in lymphadenopathay) for confirmation of tuberculosis.

All cases of confirmed TB were given their quota of monthly anti-tubercular medicine

either from the Nodal centre itself or from only other referral centre as per their convenience.

If patients had any complaints, co-morbidities etc. They could report back at their centre each patient (Unless specified) received 6 months of routine anti-tubercular treatment. After completion, they were again clinically evaluated for eradication of disease.

The outcome of all patients (Successful completion, was recorded.

I took up this study at a Nodal TB centre (NTC) – nearby Ananta Institute of Medical Science & Research Centre, Rajsamand and collected, compliled and analysed the data from retrospective period of one year (March 2021 to Febuary 2022)

From the available records and the Nikshay Portal, I identified, monthwise, the new cases of chronic respiratory illness reporting at the general medicine and pulmonary medicine OPDs who were suspected to have tuberculosis.

There were 745 such suspected cases in the whole year and they were registered in the Nikshay Portal. Thereafter screening investigations were carried out free of cost at the Nodal centre itself. Sputum for AFB, X-ray chest wise. Done to detect & diagnose tuberculosis.

Out of 745, tuberculosis was confirmed in 146 patients. In certain doubtful case, further confirmation was done by sophisticated CBNAAT, again free of cost.

Out of 146 total cases, investigation & clinical examination revealed. 106(72%) cases of pulmonary TB & 40 (27%) of Extra-pulmonary tuberculosis.

At the initial stage, all 745 patients were also tested for Diabetes mellitus and HIV. This free of cost testing is made mandatory by our government to take into account the commonest two co-morbidities with TB & vice versa.

Since low immunity is a common factor for HIV & TB, one could give sizeto the other. In my study I found 5(%) patients to both TB & HIV, hence high blood sugar levels could be detected early. In my study, I found 5(%) of TB patients who were also diabetic.

There were three patients who had both HIV and diabetes as a Co-morbidity of TB.

No where in the records is there mention of any other serious Co-morbidities.

The other aspect of my study was to collect data regarding the management of the cases of pulmonary TB. From the Nikshay Portal, I could realise that after being diagnosed, patients had an option of taking treatment, either from this modal centre or any other referral centre as per their convenience.

Only 7 patients out of the total cases had decided to take treatment from this centre, rest of them chose different TB referral centres closes to there homes.

Science the tracking & monitoring was done through Nikshay Portal, I could understand that all patients collected their monthly quota of anti-tubercular medicines from there respective centres. At that time they were free to report any side- effects/complaints.

All patients received the standard therapy for 6 months. First two months of intensive therapy with Isoniazid, Rifampicin, Pyrazinamide & Ethambutol & next 4 months with isoniazid, rfampicin & Ethambutol.

6 patrents needed alteration in the dose due to their body weight 4 were below 40 kgs & 2 were more than 80 kgs).

Moreover patients having HIV received additional anti-tuberculas drugs from their respective centres.

Surprisingly, no mention was found of any of these cases as Multi-Drug resistant TB (MDR TB). Which would have needed additional monitoring and treatment.

The study thus showed, that of all suspected cases, above 20% turned out to be TB of the 146, TB cases, majority 72(%) were of pulmonary tuberculosis which is in accordance with general understanding of the disease.

All patents of pulmonary tuberculosis were sputum positive for AFB and had findings on X-ray chist. The investigations done at the first check-up thus allowed early detection and confirmation of the disease.

Patients of TB were directed to their convenient centres for collection ofmedicines as per the data obtained from Nikshay Portal, almost all patents complied with the entire regune of treatment. Only 3 patients did not complete the treatement (2 were lost to follow-up & 1 died during treatment).

Patients of diabetes were also started on anti-diabetic medications, HIV positivepatients were further examined at their centres for additional drugs and management of great surprise was the fact that none of these patients were labelled as MDR TB.

or XDR-TB, whether this was the real case or whether there was any discrepancy in reporting could not be established from the available records.

REFERENCE

1. Tripathi KD Essentials of medical pharmacology, 2021; 8.
2. https://en.m.wikipedia.org/wikl/.mycobacterium_tuberculosis
3. https://en.m.wikipedia.org/wiki/tuberculosis
4. Compbell Tan A, Bah-Sow oumou. Pulmonary tuberculosis: diagnosis and treatment. BMJ May, 2006; 20, 392(7551): 1194-1197.
5. Centers for disease control and prevention 1600clifton Rd. Atlanta, GA 30329, USA.
6. https://www.cde.gov/tb/topic/basics/tbinfection disease htm
7. tierney dylan, Nardell Edward A miliary tuberculosis (TB), MSD Publishing group, 2018. Last full review/rivision May 2018/content last modified Aug 2018
8. Bruchfeld Judith, correia Margarida and kallenius gunilla. Tuberculosis and HIV confection. Cold spring harb perspect Med, 2015; 5(7): 9017871.
9. Bates Matthew, Marais J. Ben, Tumla Alimuddin. Tuberculosis comorbidity with communicable and Noncommunicable disease. Cold spring Harb perspect Med, 2015.
10. Loto M. Olabisi and Awowole ibraheem. Tuberculosis in pregnancy: A Review. Jpregmnly, 2012; 2012: 319271. Published online, 2011; 1.
11. O'donnell MR, Reddy D, Saukkonen J.J, Autimycobacterial Agents. Harrisons principles of internal medicine, 2015; 3 19: 205e-1 to 205e-8.
12. World Health organization 2014 Geneva. Treatment strategies for MDR-TB and XDR-TB.
13. Tripathi KD. Essentials of medical pharmacology, 2021; 8.
14. https://en.m.wikipedia.org/wikl/.mycobacterium_tuberculosis

15. https://en.m.wikipedia.org/wiki/tuberculosis
16. Compbell Tan A, Bah-Sow oumou. Pulmonary tuberculosis: diagnosis and treatment. BMJ May, 2006; 20, 392(7551): 1194-1197.
17. Centers for disease control and prevention 1600clifton Rd. Atlanta, GA 30329, USA.
18. https://www.cde.gov/tb/topic/basics/tbinfection disease htm
19. tierney dylan, Nardell Edward A (2018) miliary tuberculosis (TB), MSD Publishing group. Last full review/rivision May 2018/content last modified Aug 2018
20. Bruchfeld Judith, correia Margarida and kallenius gunilla. Tuberculosis and HIV confection. Cold spring harb perspect Med, 2015; 5(7): 9017871.
21. Bates Matthew, Marais J. Ben, Tumla Alimuddin. Tuberculosis comorbidity with communicable and Noncommunicable disease. Cold spring Harb perspect Med, 2015.
22. Loto M. Olabisi and Awowole ibraheem. Tuberculosis in pregnancy: A Review. Jpregmnly, 2012; 2012: 319271.
23. O'donnell MR, Reddy D, Saukkonen J.J, Autimycobacterial Agents. Harrisons principles of internal medicine, 2015; 3, 19: 205e-1 to 205e-8.
24. World Health organization Geneva. Treatment strategies for MDR-TB and XDR, 2014.