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Review Article

Latent tuberculosis and COVID-19 disease

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ABSTRACT

Since the start of the COVID-19 pandemic in 2020, there has been chaos in the world. With the COVID-19 cases rising, many other medical diseases have been ignored and not prioritized. One of these crucial diseases is Tuberculosis (TB). TB is a highly infectious bacterial respiratory disease. Every year there are millions of cases that are registered all around the world. TB is seen in two forms, an active and a latent form. In both of the states, the individual with TB is immunocompromised. This is of great importance, as COVID-19 is known to readily infect individuals in an immunocompromised state more than those with a healthy immune system. Although a little investigation about coexisting infections with COVID-19 and TB is conducted, it is important to consider many factors that can be beneficial to help treat these patients with both conditions effectively and promptly. A few of these factors are pathophysiological relation, diagnostic measurements, effects of each condition on the other, and approaches to treatment. Through a literature review of available information, we summarized the knowledge regarding the correlation between Latent TB infection and COVID-19 infection. The main objective of this publication is to provide a brief overview of how the two conditions overlap with one another. The article also provides a clinical review of how to approach these two conditions in a scenario where an individual is found to be infected with both Latent TB and COVID-19.

SUMMARY

Keywords

Latent Tuberculosis, COVID-19, Tuberculosis, BCG vaccine, mRNA COVID-19 vaccine.

Abbreviations

Latent Tuberculosis Infection (LTBI); Tuberculosis (TB); Bacillus Calmette-Guerin (BCG); Centers for Disease Control and Prevention (CDC); World Health Organization (WHO); Mycobacterium tuberculosis (MTB); Isoniazid (INH); Rifapentine (RPT); Rifampin (RIF); Tumor Necrosis Factor (TNF); Human Immunodeficiency Virus (HIV); Disseminated Intravascular Coagulation (DIC); Acute Kidney Injury (AKI); Tuberculin Skin Test (TST); Interferon-Gamma Release Assays (IGRAs); C-reactive Protein (CRP); Interleukins (IL); Interferons (INF); Neutrophil- to-Lymphocyte Ratio (NLR); C-C Motif Chemokine Ligand (CCL); C-X-C motif chemokine ligand (CXCL).

1. Introduction

The COVID-19 pandemic has thrown the world in a disarray. The symptoms of the disease are variable. It primarily affects the lungs[1]. About one-third of the world is suffering from latent TB. Progression to tuberculosis disease (TB) occurs from interaction with the environment, host, and the pathogen itself. The T-cell response is a determiner of the resolution, dormancy, or clinically evident disease development[2]. The COVID-19 pandemic has had a huge impact on the global healthcare system and thus had impacted the TB burden as well. Even though lockdown and social distancing would have reduced the spread of TB, Patients with TB had reduced consultations and follow-up visits during the pandemic. Given that such a significant world population has latent TB, COVID 19 pandemic will surely spike the incidence of active TB. Identification of latent TB is necessary for patients with atypical presentation of COVID-19 as well, especially in TB endemic areas. If the COVID-19 virus activates dormant TB cases, it could affect the global health and economic situation. The current study aims at identifying any association between the two and possible recommendations to help avert the COVID pandemic and TB epidemic.

SARS-CoV-2 can lead to a temporary immunosuppressive effect, which can make a person prone to active TB if the individual has latent TB infection. During the Spanish flu pandemic there was an increase in the number of lung TB cases. Mortality among cases with influenza as well as TB was very high. The 2009 HIN1 flu pandemic had similar trends as well.

2. Epidemiology: Geographic distribution and cases

Epidemiology is essential to the fight against any disease; the first case of COVID-19 was reported in Wuhan in late 2019. Globally, over 175 million confirmed cases of COVID-19 have been reported. However, epidemiology is constantly changing, and many epidemiologists are collaborating across the globe. Data has been shared through online platforms. Latent TB is present in populations around the world. According to U.S. Centers for Disease Control and Prevention (CDC), nearly 7174 TB cases were reported in the U.S in 2020 and up to 13 million people are estimated to have the latent form of the disease in the U.S. alone, Globally More than 1.7 billion people are estimated to have M. tuberculosis[3,4]. In 2003 the incidence of TB reached its peak but has been declining since then[4]. In 2020 World Health Organization (WHO)stated that ten million people became ill with TB and 1.5 million had died due to the disease[4].

Literature describing COVID-19 in patients with Latent TB is fairly limited and only five studies that were case reports and case series reported data on COVID-19 in people with latent TB infection[5-9]. Most of these reports of patients with latent TB infected with COVID-19 had favorable outcomes. However, one study stated that COVID-19 complicated diagnosis of LTBI due to an altered immune system[9].

3. A comparison between COVID 19 and Latent TB infection

Communalities have been found between COVID-19 infection and latent tuberculosis; both are infectious diseases that mainly affect the lungs. Mycobacterium tuberculosis is transmitted via droplets; however, SARS-CoV-2 has multiple transmission pathways; droplet, aerosol, and possibly fomite transmission[10,11]. Both diseases have a significant epidemiological burden and have strained health care systems; individuals with comorbidities are at increased risk of severe disease. In patients with latent TB, this increased vulnerability can cause the development of active TB. Rapid diagnostic tests have been developed to identify latent TB and COVID-19 infection. And like asymptomatic carriers of SARS-COV-2, LTBI

presents with no signs and symptoms. Preventive measures are important in both diseases (Table 1).

Regarding differences, MTB infection in humans can be traced back to 9,000 years ago in Atlit Yam (a city now under the Mediterranean Sea, off the coast of Israel). COVID-19 infection was recently identified in Wuhan, China, in December 2019[10].

Individuals with latent TB are not infectious and cannot transmit the MTB infection, instead asymptomatic carriers of SARS-COV-2 can transmit the virus.

There is a treatment regimen for LTBI that eradicates the pathogen, it includes Isoniazid (INH), Rifapentine (RPT), and Rifampin (RIF). In the case of COVID-19 infection, there are ongoing clinical trials, support measures, and limited treatment data.

Established policies have been developed to eradicate tuberculosis. Even though almost all countries have implemented TB programs (prevention, diagnosis, treatment, and guidelines), these have not been correctly implemented, developing countries have a high incidence of MTB. COVID-19 policies have been executed rapidly, such as travel restrictions and quarantine, and are being continuously improved. (Table 1)[10].

4. Pathological Pathways connecting Mycobacterium Tuberculosis and SARS-CoV-2

SARS-CoV-2 and Tuberculosis pathological pathways haven't been fully elucidated. What is known so far is that the hyperinflammatory response present in SARS-CoV-2 is the mechanism responsible for the disease severity and mortality[10,18,19]. This aggressive inflammatory response is characterized by increased levels of inflammatory serum markers (CRP, ferritin, and D-dimer), increased secretion of cytokines (IL-1β, IL-6, TNF-α, IL-2, IL-4, IL-10, and type I and III interferons), and inflammatory chemokines (CCL2, CCL3, CCL5, CCL8, and CXCL10). High levels of IL-6 have been associated with poor prognosis in COVID 19 disease. High and persistent IFN-γ production could be responsible for macrophage hyperactivation. Also, CXCL10 and CCL2 may contribute to lymphopenia. In addition, increased neutrophil- to- lymphocyte ratio (NLR), total T cell depletion, and poor antibody response are significantly present. Low levels of $CD4^+$ and $CD8^+$ T cells are observed in COVID 19 patients, together with T cell exhaustion[10,19-22].

Likewise, a systemic cytokine response exists in mycobacterium tuberculosis infection. T cells and the cytokine storm play an important role in the host immune response. High levels of IFN-γ, IL-12, and TNF-α have been identified. IL-1β directly kills MTB in macrophages. TNF-α and IFN-γ are fundamental cytokines for the control of MTB infection, by acting synergistically in the formation and maintenance of granulomas. On the other hand, IL-4 and IL-10 are associated with LTBI, reactivation, and advanced Tuberculosis. IL-2 and IL-10 are possible markers to distinguish ATB (active tuberculosis) from LTBI[19,23-26].

In addition, a large-scale meta-analysis identified shared dysregulated pathways between COVID -19 and TB. These common pathways include antigen presentation, membrane trafficking, ROS/RNS production, activation of complement, cytokine production, and platelet activation. Hence, both SARS-CoV-2 and Mycobacterium tuberculosis involve cell-mediated immunity and high levels of cytokines related to disease severity[27].

5. Effects of COVID-19 on Tuberculosis

The COVID-19 pandemic has intimidated the world leader's commitment to end tuberculosis by 2030. The World Health Organization (WHO) estimates that 1.4 million fewer people received care for tuberculosis (TB) in 2020 than in 2019. In 2019, 6.3 million cases were reported, contrasting with the provisional data of 4.9 million cases reported in 2020. Monthly case notifications for tuberculosis in 2020 dropped significantly. Furthermore, the WHO predicts half a million more TB deaths could have occurred in 2020[28].

This pandemic has increased the global vulnerability for tuberculosis by affecting medical care services (diagnosis, treatment, and prevention) and increasing poverty. Strict lockdowns, medication shortages, overwhelmed health care systems, medical efforts prioritizing the COVID-19 infection have potentially worsened TB outcomes and increased the risk for multi-drug resistant TB. Patients infected with TB are facing double stigma and fear of SARS-CoV-2 infection, restricting their access to medications, thus decreasing treatment compliance[29].

Although the preventive measures used for SARS-CoV-2 could reduce TB transmission; the

Table 1. Similarities and differences between COVID-19 infection and Latent TB

Features	COVID-19 infection	Latent TB	Additional information
Infectious agent	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	Mycobacterium tuberculosis (MTB)	
Epidemiology	193 million cases worldwide 4.14 million deaths globally	The global burden of LTBI is around 1.7 billion (a quarter of the population)[12]	High epidemiologic burden in both infections.
History of human exposure	Recent (2019)	Ancient	The first human TB infection was recorded 9,000 years ago in Atlit Yam. First case of COVID-19 was reported in December 2019 in Wuhan, China
Transmission	Droplets, aerosol, fomites	LTB is not infectious and cannot be transmitted[13].	Asymptomatic COVID-19 infected individuals are contagious, while LTB individuals are not. Active TB is transmitted via droplets.
Infected organs	Mainly affects the lungs. Multisystemic involvement	Remains inactive, encapsulated in the lungs.	Severe COVID 19 can cause multi organ failure)[14]. If reactivation of LTBI, MTB spreads to lung (pulmonary TB) and the bloodstream, affecting several organs (Miliary TB)
Comorbidities that increase the risk of severe disease	Cancer, chronic kidney disease, chronic lung diseases, smoking, obesity, alcohol use disorders, heart conditions, sickle cell disease, HIV, immunocompromised state, type 2 diabetes, mellitus	Organ transplantation, silicosis, close contacts, TNF-alpha inhibitors hemodialysis, HIV	Latent TB can become reactivated with immunosuppressive states.[15].
Symptoms	None (if asymptomatic carrier) Fever, chills, cough, shortness of breath, fatigue, muscle aches, anosmia, pleuritic pain, sore throat, congestion, runny nose, nausea, vomiting, diarrhea.	None	The symptoms addressed in this table (listed by the CDC), are the most commonly observed in COVID-19 infection[16]. If severe COVID-19, patients present with features of multiorgan failure. ARDS, acute myocarditis, DIC, AKI, liver failure, etc)[14].
Diagnostic tests	Nasopharyngeal or oropharyngeal swab	Tuberculin skin test (TST), interferon-gamma release assay (IGRAs)	LTB is a clinical diagnosis. Asymptomatic presentation and negative chest X-ray. Vaccinated individuals against TB could have a false positive PPD skin test; hence in these patients, IGRAs are a better test.
Treatment	Supportive treatment	Isoniazid (INH), Rifapentine (RPT), and Rifampin (RIF).	In the treatment of COVID 19, support measures such as oxygen and mechanical support can be needed. Corticosteroids are used in severe cases.

Table 1. Similarities and differences between COVID-19 infection and Latent TB (continued)

Features	COVID-19 infection	Latent TB	Additional information
Vaccines available	Examples of COVID-19 Vaccines Authorized for Emergency are produced by Pfizer-BioNTech, Moderna, Johnson and Johnson, AstraZeneca	BCG	
Preventive measures	-Infection control with handwashing -Social distancing -Wearing masks -Contact tracing of individuals -Lockdowns, quarantines, curfews	-Rapid diagnosis of persons with active TB -Early treatment of LTBI to stop MTB spreading	Contact tracing is important in both diseases.
Stress in health care systems	High and rapid	High and slow	
Economic impact	High	High (active infection)	Tuberculosis costs the world economy $616 billion from 2000–15, and between 2015-2030 almost US$1 trillion17. Asian Development Bank announced that the COVID-19 pandemic could cost the global economy $5.8 - $8.8 trillion (May 2020).
Policies developed	Rapid	Slow	Policy development for TB has been slow but not correctly implemented.

stay-at-home orders increase transmission of TB among household members[29,30].

Even though there is limited information on COVID-19 infection in patients with TB, it is expected that these patients will have a worse prognosis especially if they lack TB treatment adherence.

6. Diagnostic Errors with COVID-19 and TB Coexistence

Diagnosing TB and COVID-19 appropriately is of utmost importance as both conditions have debilitating effects on the human body. However, both conditions present with similar symptoms and it becomes difficult to differentiate between the two conditions[31].

Currently, there are not any tests that directly identify Mycobacterium Tuberculosis[32]. The diagnosis of latent TB lies on the immune response achieved against the TB antigen[32]. The two current tests that are used to detect the immune responses are the Tuberculin skin test (TST) and interferon-gamma release assay (IGRA)[32]. Although these tests are the most accurate, they have certain risk factors for false-negative results. A recent meta-analysis by Yamasue et al. concluded that advanced age and low peripheral lymphocyte count are significantly associated with false-negative results in IGRA[33]. Coincidently, a low peripheral lymphocyte count is noted with COVID-19[34]. Hence, a conclusion can be drawn that co-infection with COVID-19 in TB patients may result in some sort of a diagnostic error with IGRA.

There is a sense of urgency in diagnosing COVID-19 with accuracy and speed. The diagnostic model for COVID-19 includes radiological findings such as ground-glass opacities, focal consolidations, and honeycomb appearance[35]. Some of these features are noticed in TB imaging as well[36]. With some of these overlapping features in radiology, with urgency to diagnose COVID-19; it is a possibility that diagnosis of TB may be missed.

7. BCG vaccine and its relation with COVID-19

Bacillus Calmette-Guerin (BCG) vaccine has historically been used to confer immunity against some forms of TB[37]. Through a few clinical trials, the BCG vaccine has been also known to offer some protection against some other infections such as Respiratory Syncytial Virus and Malaria[38]. Since the pandemic started in 2020, it has been speculated that the BCG vaccine may offer a certain level of protection against the COVID-19 virus as well.

The BCG vaccine induces a complex series of immunomodulation with effects on innate and adaptive immune systems. The immunomodulation results in increased bone marrow stem cell production, altered maturation of dendritic cells, reduction in non-specific infectious load and viremia, increased pro-inflammatory cytokines and chemokines, and protection against infectious viruses[39]. With these vast numbers of modulations in one's immunity, it is hypothesized that the vaccine should have a boosted immune-defense system against COVID-19[39]. Theoretically, the vaccine would inhibit viral replication, lower systemic inflammation, and reduce the viral load[39]. In 2020, there were approximately 20 clinical trials ongoing to evaluate the therapeutic effects of the BCG vaccine on COVID-19. Fortunately, in 2021, there have been multiple effective vaccines against COVID-19 that have been created such as Pfizer-BioNTech, and Moderna vaccines[40].

8. Use of Corticosteroids for COVID-19 Therapy: Potential Implications on Tuberculosis

There are two main forms of TB: Latent and Active. It is a well-known fact that suppression in the immune system may turn latent TB into its deadly active form. The latter can then cause a highly infectious pulmonary infection; if in co-existence with COVID-19, can cause a catastrophic condition on any individual.

Initially, in 2020, World Health Organization (WHO) and the Center for Disease Control and Prevention (CDC) did not recommend routine corticosteroid use for the treatment of COVID-19[41]. They reported that there were no reported survival benefits and created possible harms with usage, this was based on a systemic review of observational studies[41]. Corticosteroids have certain immunosuppressive properties that eventually lead to decreased viral clearance. At the same time, corticosteroids also have potent anti-inflammatory properties[42]. In severe cases of COVID-19, it was suggested that the patient experiences cytokine storm syndrome along with hyper-inflammation[42]. The mechanism of potent anti-inflammatory properties was then suggested to be therapeutic for the severe cases of COVID-19, and corticosteroids were considered as treatment options[43]. Multiple small trials have been performed to understand the effects of corticosteroids. Most of the trials conducted were on severe to critical patients and the results yielded that there was a faster resolution in fever, faster improvement in radiological findings, improvements in oxygen saturation, and better survival rate in Acute Respiratory Distress Syndrome[41]. A larger RECOVERY study was conducted in 2020 and the concluding results were that the use of dexamethasone resulted in lower 28-day mortality in patients who received mechanical ventilation or oxygen alone; no advantage was seen in patients who did not need any respiratory support[44].

M. Tuberculosis is initially engulfed by innate immune cells and eventually produces an excess amount of cytokines, resulting in a cytokine storm, one that is similar to in COVID-19. In TB, the cytokines induce more immune cells to surround the infection site in layers to create a bigger granuloma. The bacteria have certain ways to protect themselves that result in the prevention of phagocytic cells from destroying the bacteria, resulting in an asymptomatic latent TB[45]. When a patient starts using corticosteroids, there is a higher chance of contracting active TB. A study showed that any 1-gram increase in prednisone dosage resulted in an approximate 23% increase in the chance of developing TB[46]. However, there is little clinical data available that links a short course of corticosteroid use with the reactivation of latent TB[46]. With the use of corticosteroids, there is also a 2.8-to-7.7-fold increased chance of reactivating the TB[46]. Thus, while there are therapeutic effects of corticosteroids in severely ill COVID-19 patients, there is a higher possibility of reactivating latent TB. Conversion of latent TB to active TB along with COVID-19 can result in a possible coinfection and result in a catastrophic pulmonary and possibly disseminated infection.

9. When and how to treat Latent Tuberculosis?

It is estimated that if left untreated, 5-10% of the total cases of LTBI will progress to active tuberculosis. This accounts for about 80% of the active TB cases in the USA. Hence it is very essential to detect and treat latent tuberculosis infection.

The treatment for latent TB should be started only after excluding the active TB disease.[47, 48]

High-risk LTBI patients for whom the treatment is of priority, include:[49,52]

- Patients with a positive Interferon Gamma release assay
- Patients with tuberculin skin test reaction > 5 mm, along with:
    1. Positive HIV test.
    2. Contact with a patient with active tuberculosis.
    3. Fibrotic changes on chest x-ray consistent with old TB.
    4. Organ transplant recipients.
    5. Immunocompromised.
- Patients with tuberculin skin test reaction > 10 mm who are
    1. Residents from the countries where TB is common.
    2. Intravenous drug users.
    3. Residents and employees of high-risk congregate settings like nursing homes, the homeless, hospitals, prisons, and other health care workers.
    4. Microbiology lab personnel, people with malnourishment, diabetes, smokers, alcoholics, people with malignancy, head and neck tumors, and silicosis.
    5. Children less than 4 years of age.
- Everyone with no risk for tuberculosis with either a positive IGRA result if their tuberculin skin test reaction is > 15 mm.

The 3 main medications used for the treatment of latent tuberculosis are:[53-56]

- Isoniazid (INH)
- Rifapentine (RPT)
- Rifampin (RIF)

These drugs can be used either on their own as monotherapy or in combination with other drugs.

There are 2 different types of treatment regimens available:[53-61]

- **Short Course Therapy**- This is recommended by the CDC and NTCA. It is a rifamycin-based treatment that is given for a short duration of 3-4months. It is found to have an increased compliance rate and is safer for the patient.

    - 3 months of once-weekly Isoniazid and Rifapentine (3HP) - recommended for patients above 2 years of age with HIV and AIDS, taking antiretroviral drugs. It is found to be much safer and equally effective for LTBI patients with HIV and more effective for those patients without HIV when compared to INH monotherapy. However, the drug is more expensive, and patients have to take numerous pills at once.

    - **4 months of daily Rifampin (4R)** - Recommended for LTBI patients who are HIV negative. The therapy is as effective as INH monotherapy but less hepatotoxic. This drug however has to be used with caution with warfarin, OCP, Azole antifungal, methadone, and HIV medications. Rifabutin is an alternative to Rifampin when the latter is contraindicated. In HIV-positive patients with reduced CD4+ leucocyte count, the risk of asymptomatic TB and subclinical TB is increased. Hence the monotherapy with Rifampin for LTBI in these patients increases the risk for resistance to the drug if active TB develops.

    - 3 months of daily Isoniazid and Rifampin (3HR) - recommended for all age groups and HIV-positive patients. It is less hepatotoxic compared to INH monotherapy.

- **Long Course Therapy** – This involves the use of **monotherapy with Isoniazid** for a period ranging from 6-12 months depending on the patient's HIV status and response to treatment. It can be used when Rifampin is contraindicated. This treatment has a higher discontinuation rate and greater risk for hepatotoxicity (Table 2 and Table 3).[56,60,61]

Table 2. Latent TB infection treatment regimen (reproduced from the CDC website)[47]

Drug(s)	Duration	Dose	Frequency	Total Doses
Isoniazid (INH)* and Rifapentine (RPT)†	3 months	Adults and Children aged 12 years and older: INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum RPT: 10–14.0 kg 300 mg 14.1–25.0 kg 450 mg 25.1–32.0 kg 600 mg 32.1–49.9 kg 750 mg ≥50.0 kg 900 mg maximum Children aged 2–11 years: INH*: 25 mg/kg; 900 mg maximum RPT†: as above	Once weekly	12
Rifampin (RIF)§	4 months	Adults: 10 mg/kg Children: 15-20 mg/kg ‖ Maximum dose: 600 mg	Daily	120
Isoniazid (INH)* and Rifampin)§	3 months	Adults: INH*: 5 mg/kg; 300 mg maximum RIF§: 10 mg/kg; 600 mg maximum Children: INH*: 10-20 mg/kg; 300 mg maximum RIF§: 15-20 mg/kg; 600 mg maximum	Daily	90
Isoniazid (INH)	6 months	Adults: 5 mg/kg Children: 10–20 mg/kg ¶ Maximum dose: 300 mg	Daily	180
		Adults:15 mg/kg Children: 20–40 mg/kg ¶ Maximum dose: 900 mg	Twice weekly‡	52
Isoniazid (INH)	9 months	Adults: 5 mg/kg Children: 10–20 mg/kg ¶ Maximum dose: 300 mg	Daily	270
		Adults:15 mg/kg Children: 20–40 mg/kg ¶ Maximum dose: 900 mg	Twice weekly‡	76

*Isoniazid (INH) is formulated as 100 mg and 300 mg tablets; †Rifapentine (RPT) is formulated as 150 mg tablets in blister packs that should be kept sealed until use; ‡Intermittent regimens must be provided via directly observed therapy (DOT), that is, a health care worker observes the ingestion of medication; §Rifampin (rifampicin; RIF) is formulated as 150 mg and 300 mg capsules; ‖The American Academy of Pediatrics acknowledges that some experts use RIF at 20–30 mg/kg for the daily regimen when prescribing for infants and toddlers (American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2018 Report of the Committee on Infectious Diseases. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:829–853); ¶The American Academy of Pediatrics recommends an INH dosage of 10–15 mg/kg for the daily regimen and 20–30 mg/kg for the twice weekly regimen.

All the treatment must be modified according to the patient's exposure to drug-resistant MTB bacteria, and depending on other coexisting medical conditions and drug interactions. Treatment can be

Table 3. Recommendations for regimens to treat latent TB infection (reproduced from the CDC website)[47]

Priority Rank*	Regimen	Recommendation (strong or conditional)	Evidence (high, moderate, low, or very low)
Preferred	3 months Isoniazid plus Rifapentine given once weekly	Strong	Moderate
Preferred	4 months rifampin given daily	Strong	Moderate HIV regimen **
Preferred	3 months isoniazid plus rifampin given daily	Conditional	Very low (HIV negative)
Alternative	6 months isoniazid given daily	Conditional	Low (HIV positive)
Alternative	9 months isoniazid given daily	Strong^	Moderate (HIV negative)

HIV - Human immunodeficiency virus; Preferred - excellent tolerability and efficacy, shorter treatment duration, higher completion rates than longer regimens, therefore higher effectiveness; Alternative - excellent efficacy, but concerns regarding longer treatment duration, lower completion rates, therefore lower effectiveness; Strong – strong recommendation for those patients unable to take a preferred regimen (eg: due to drug intolerance or drug-drug interaction; ; ** - no evidence recorded in HIV positive patients;

administered as Self-Administered Treatment (SAT) or Direct Observed Treatment (DOT) - which is under the supervision of a health care worker. DOTs therapy has been found to have better compliance and outcome when compared to SAT [62-64].

10. Can COVID-19 flare Latent TB?

The coexistence of COVID-19 and LTBI has accelerated the reactivation of LTBI to active TB as compared with healthy patients with LTBI. The coexistence of COVID-19 and TB has also increased the aerosol spread of TB between individuals.[65,66]

The body's immune system forms fibrous capsules around the primary complex of TB infection in the lungs, holding the MTB bacteria dormant. This is known as latent TB infection. With a good immune response, these lesions in the lung can calcify in 3-4months period or can remain dormant in various organs for many years. The CD4+ T lymphocytes play an important role in the defense against tuberculosis. The SAR CoV-2 virus is known to affect the immune system by depleting the CD4+, CD8+ T cell lymphocytes and also causes functional exhaustion of the surviving T cells. This T cell depletion and dysfunction have been thought to promote the activation of latent TB infection, similar as in patients with HIV infection.[67-71]

Apart from this, the use of corticosteroids for more than 2 weeks in the treatment of moderate and severe/ critically ill COVID-19 patients requiring hospitalization and oxygen support, has a potentially increased risk of reactivating the latent TB infection. COVID-19 and tuberculosis have similar clinical presentations, thereby making it difficult to diagnose LTBI reactivation to tuberculosis. Several studies have proven the reactivation of LTBI in COVID-19 patients regardless of the use of corticosteroids within 7-10 weeks of COVID-19 infection.[66]

In another case study of severe COVID-19 infection, it is suggested that the use of a single dose of Tocilizumab leads to progressively symptomatic tuberculosis. Since the patient did not report any comorbidity, the impaired immune function/ immunosuppression due to COVID-19 alone or along with the use of corticosteroid has led to the reactivation of LTBI. Hence it is very important to test all COVID-19 patients for LTBI before the judicial use of corticosteroids.[69]

11. Can Latent TB reduce COVID-19 mortality?

Latent tuberculosis is a condition in which the patient does not exhibit any symptoms of the disease, but the MTB antigen constantly triggers the innate immune system similar to the action of the BCG vaccine. Several trials are underway to establish the protective effect of the BCG vaccine against COVID-19 mortality. These studies pave the way to find out if LTBI can also protect against COVID-19 mortality. An instrumental variable study (IV study) has established that a 10% increase in the latent tuberculosis infection prevalence would be expected to decrease the case fatality rate of COVID-19 mortality by about 0.2 percentage points. Hence, the regions with the highest LTBI burden (i.e., South-East Asian countries), with 5 times higher LTBI than the lowest LTBI region (i.e., Europe) should have a lower-case fatality rate of COVID-19 mortality by 3 percentage points. This explains the lower CFR for COVID-19 in South-East Asian countries when compared to Europe. Several European studies also confirm the prevalence of a negative correlation between the percentage of latent tuberculosis infection and COVID-19 cases per million population. A report also suggests that the early detection and treatment of latent TB reactivation in COVID-19 patients with anti TB medications improved the outcome and facilitated the recovery of the patient. More studies have to be encouraged in this area to get a definitive conclusion.[72-75]

12. Is there a relation between mRNA COVID-19 vaccine and latent tuberculosis?

The development of the messenger RNA COVID-19 vaccine has been a ray of hope and a crucial strategy in the prevention, control, and management of the pandemic. It has tremendously reduced morbidity and mortality due to COVID-19. This mRNA COVID-19 vaccine has a different mode of action when compared to the other vaccines available. In this, a small piece of the genetic code of the SARS-CoV2 virus is injected into the human host which incorporates into the host cells and signals the cells to produce the viral spike protein. These spike antigens, in turn, penetrate and infect the other host cells thereby, stimulating an immune response producing antibodies and developing memory B cells. These B cells will recognize and act if the body is infected by the actual virus in the future. These mRNA vaccines have shown to have an efficacy above 94% on average in the prevention of COVID-19 disease.[76-78]

The most common side effects of the vaccine noticed in the majority of the population include pain, redness, and swelling at the site of the injection. Systemic side effects include fatigue, headache, joint pain, myalgia, fever with chills, nausea, anorexia, brain fog, reduced sleep quality, nasal stuffiness, and palpitation. Pericarditis, myocarditis, coronary vascular disease, coagulation abnormalities, anaphylaxis, kidney injury, paralysis, and psychiatric symptoms have also been reported. The long-term reactions of the vaccines are under continuous investigation.[79-83]

Since the vaccines have shown promising effects in the prevention and reduced severity of the COVID-19 disease, it is recommended for all individuals irrespective of their active tuberculosis disease or latent tuberculosis infection status. It can also be expected that as the vaccine prevents the progression of the disease from mild to severe it can thereby also be effective in preventing the conversion of latent tuberculosis to active tuberculosis. Detailed studies are recommended in this aspect of COVID-19 vaccination.

13. Implications and recommendations

Since TB and COVID-19 are parallel in terms of symptoms, it is of utmost importance that TB infection is identified in patients with COVID-19. Co-infection with TB and COVID-19 will result in poor outcomes for any patient. As of now, there have not been any official diagnostic recommendations for identifying TB in patients infected with COVID-19. However, a meta-analysis study recommended dual testing with COVID-19 real-time RT-PCR and Xpert MTB/RIF assay[84]. We would recommend testing patients synergistically for Latent TB infection and COVID-19 in endemic regions. This would allow a more appropriate course of treatment for the patient. Along with those recommendations, it is important to maintain appropriate contact tracing[85]. This process would allow a timely manner of identifying those who have been exposed to the infectious conditions, especially to quarantine them and treat them. The World Health Organization currently recommends an outpatient-based treatment for TB, unless a serious case

emerges, to reduce opportunities for hospital-based transmission[85].

There are some preventative measures that can be implied to reduce the chances of contracting and reactivating TB in coexistence with COVID-19. Following are a few preventative measures that can be applied:

1) Strengthening immune system through administration of COVID-19 Vaccine[86]. Vaccination will reduce the chances of contracting COVID-19 and a weakened immune system. This will help to reduce the contraction and reactivation of TB.

2) Transmission reduction through administrative, environmental, and personal protective measures. A few of these would include infection control measures, cough etiquette, and patient triage[86].

3) In the case that an individual has latent TB infection, an appropriate TB preventive treatment regimen should be initiated and maintained[86].

Adopting the above preventative measures along with appropriate and timely consultation with the nearest healthcare worker when respiratory symptoms arise can help to not only treat the individual with the infection but also help prevent the spread as well.

14. Conclusion

COVID 19 pandemic has had a significant impact on the world and has affected tuberculosis management and surveillance, especially in high TB burden countries. The evaluation and management of a large number of TB patients are affected due to the devastating effects of the COVID-19 pandemic on the health care system. Patients with tuberculosis are at an increased risk of infection and lung damage when coinfected with coronavirus. Considering this TB case isolation is important. Preliminary results of studies indicate that latent TB may get activated to active TB, increasing morbidity and mortality in patients with COVID-19. A few studies state that LTBI induces lifelong innate immunity, and this can have a protective immunological response against COVID-19. Strategies to mitigate the risk of COVID-19 transmission such as using PPE; practicing social distancing, maintaining hand hygiene, and respiratory precautions can prevent putting patients with latent TB at risk. Larger studies are required to evaluate the relation between latent TB and COVID-19 and whether the SARS-CoV-2 virus increases the risk of acquiring active TB infection in individuals with LTBI is an important issue and requires further analysis. Patients with LTBI treated with corticosteroids should be thoroughly checked for active tuberculosis. Due to pandemics and lockdown, many TB cases have already gone undiagnosed and untested. Early identification of patients with activation of latent TB and subsequent contact tracing is very crucial to help control the spread of TB amidst the COVID pandemic. However, data is significantly lacking regarding the association between them, and further studies should be performed to determine the connection between COVID 19 and latent tuberculosis.

Conflict of Interest

The authors declare no conflict of interest.

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