Change of Gut Microbiota and its Role in Tuberculosis

Cleine Michaela, Syifa Mustika***

[*]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine Universitas Brawijaya, Malang Indonesia
[2**]Gastroentero-Hepatology Division, Department of Internal Medicine, Faculty of Medicine, Universitas Brawijaya, Malang Indonesia

Corresponding author:
Cleine Michaela. Department of Pulmonology and Respiratory Medicine,Universitas Brawijaya Malang, Indonesia, Email: cleinemichaela@gmail.com

ABSTRACT

Introduction: Tuberculosis (TB) is a prevalent infectious illness and a leading cause of death globally. An alteration in the microbial communities heightens vulnerability to TB. The changes mentioned below are responsible for pulmonary disease, as well as a decrease in the body's ability to resist the invasion of harmful external microorganisms or the depletion of beneficial bacteria.

Literature review: Adults diagnosed with pulmonary TB exhibited a stool microbiome that contained a greater abundance of anaerobic microorganisms. This was found to be linked to proinflammatory immunological pathways in the host and was also associated with the severity of TB. Relapsed TB was correlated with elevated Actinobacteria and Proteobacteria levels and decreased Bacteroidetes levels. The pathogenesis of Mycobacterium tuberculosis infection and the onset of TB symptoms may be influenced by changes in the gut-lung microbiome axis. Medication availability, efficacy, and adverse effects can be impacted by the gut flora in several ways. Currently, researchers recommend exploring the potential of combining TB medicine with gut-focused probiotics to improve treatment response and outcomes.

Conclusion: The microbiome has the potential to be a modifiable risk factor for TB. The human microbiota may have a role in the development of M. tuberculosis and treatment for tuberculosis can disrupt the balance of microorganisms, leading to dysbiosis, which can in turn impact the host's immune system. Probiotics and postbiotics demonstrate anti-TB properties, suggesting their ability to address problems arising from the use of various antibiotics.

Keywords: Tuberculosis, microbiome, dysbiosis, gut-lung axis

INTRODUCTION

Tuberculosis (TB) is a prevalent infectious illness and a leading cause of death globally. The year 2019 saw an estimated 10 million newly reported cases of TB, along with 1.4 million deaths directly attributed to TB and an additional 250,000 deaths caused by antibiotic resistance. Indonesia is the second highest TB cases in the world after India, with approximately 10% (~1 million) of global cases with ~150.000 deaths. Approximately 10-20% of cases affect children, particularly those aged 0-4, who face an increased risk of death and widespread disease.[1]

Soon after birth, the mucosal surfaces of the body begin to be colonized by certain microorganisms. *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Proteobacteria* are the four phyla that make up the microbiome that is found in the lungs of persons of good health. The most common microbiota genera were *Prevotella, Streptococcus, Veillonella, Fusobacterium,* and *Haemophilus*. [2]

It is known that alterations in these microbial communities heighten vulnerability to TB. The abnormalities mentioned are responsible for the development of pulmonary disease. Additionally, these alterations also result in decreased resistance to the colonization of foreign pathogens or the depletion of commensal bacteria. [3] The microbiome has been strongly implicated in the development of lung illnesses. Increasing evidence indicates that an imbalance in the human microbiota, known as dysbiosis, may influence the likelihood of being infected with *M. tuberculosis,* the development from latent TB infection (LTBI) to active TB, and the effectiveness of anti-TB treatment.4 There is a correlation between the composition of the gut microbiome and changes in respiratory and systemic immune responses.[5] Thus, this review will provide an in-depth discussion regarding the role of these gut microbiotas changes in TB disease.

Change Of Gut Microbiota in Tuberculosis

The heightened immune response that the body has in response to bacterial infections was the impetus for the discovery of the gut-lung axis. IL-1, IL-6, and tumor necrosis factor are cytokines that are produced in response to infections. There is a risk that these cytokines may induce fatal side effects, organ failure, respiratory distress syndrome, and other conditions. The absence of commensal bacteria in mice leads to the manifestation of severe lung illness, highlighting the importance of gut bacteria in preventing respiratory infections. The study also discovered that when Toll-like receptor 4 (TLR4) is activated, there is an upregulation of alveolar macrophage populations along with the synthesis of IL-1 and IL-6, and macrophage inflammatory protein-2 (MIP-2). Consequently, this increase in immune response enhances the elimination of commensal organisms in the lungs. Changes in the populations of microorganisms in the respiratory tract and intestines can affect the way the immune system responds to a wide range of respiratory infections caused by bacteria and viruses.[6] A recent study found that persons with pulmonary TB exhibited a higher presence of anaerobic microorganisms (namely *Anaerostipes, Blautia*, and *Erysipelotrichaceae*) in their stool microbiome prior to starting antibiotic treatment. The presence of these enhanced anaerobic bacteria in the gut is linked to the activation of inflammatory immunological pathways in the host, which are known to be connected to the severity of TB disease. The implications of this finding lends additional credence to the idea that the gut microbiota play a role in the progression of TB.[7]

Children diagnosed with TB had elevated levels of proinflammatory bacteria such as *Prevotella* and opportunistic pathogen *Enterococcus,* while seeing a reduction in helpful bacteria like *Bifidobacteriaceae, Ruminococcaceae, Faecalibacterium prausnitzii*, and the *Bacteroidaceae* family. Significantly, during a one-month course of antituberculosis therapy, the diversity of the bacteria that live in the gut was found to have significantly decreased. A possible function for the stability of the gut microbiota in TB development is suggested by this. This is because the imbalance in the interaction between the lungs and the gut, which results in a disruption in the immunological responses of the hosts, may be a condition in which the immunological responses of the hosts are disrupted.[8]

Commensal metabolites can also impact the progression of tuberculous infection by enhancing the quantity and effectiveness of innate T cell subsets that respond to germs, as immortalized Mucosal-associated invariant T cells (MAIT) and natural killer T cells. The microbiome may exert an influence on the formation and function of MAIT cells.[9] Recent findings have demonstrated that people who are exposed to *M. tuberculosis* and are resistant to early infection experience a strong activation of MAIT cells. The number of particular gut microorganisms is directly linked to the amounts and function of these cells.[10]

Co-infections of TB can also influence the intensity

of the illness and the equilibrium of the gut microbiota. Individuals with HIV/TB, regardless of age, generally have a more severe TB infection and a greater mortality rate compared to those who are HIV-negative. There has been a decline in the variety of the gut microbiomes of individuals who are HIV-positive, but there has been an increase in the number of pathobionts. There is a possibility that HIV infection will result in a decreased CD4+ T cell activity. These cells are responsible for creating regulatory responses, which are essential for fostering tolerance to beneficial bacteria.[11]

Additionally, dietary factors may influence the make-up of the gut microbiota, which may in turn have an effect on the immune system's ability to regulate *M. tuberculosis* infection. A diet rich in fat may induce a *proinflammatory* reaction in rats, thereby accelerating the progression of active TB. This could be linked to an imbalance in the gut bacteria and a decrease in the ratio of *Firmicutes* to *Bacteroidetes.* It is specifically correlated with a decrease in the presence of the *Barnesiella* genus, which belongs to the Porfiromonadaceae family. It is important to mention that consuming a diet high in fat leads to a rise in the abundance of *Alistipes, Parasuterella, Mucispirillum*, and *Akkermansia* bacteria, which have been associated with intestinal dysbiosis.[12]

THE ROLE OF GUT MICROBIOTA IN DIFFERENT STATES OF TB

According to the findings of a recent human investigation that included persons with active pulmonary TB, latent TB infection (LTBI), and healthy controls, both active and latent forms of TB were observed to result in an alpha diversity of the gut microbiota that is somewhat lower than that of healthy persons. Alterations in the relative prevalence of the genus *Bacteroides* were the primary factor that led to this state of affairs.[13]

In comparison to healthy individuals, contrary to what one might expect, the gut microbiota of adults with recurrent TB shows an increase in Actinobacteria and Proteobacteria species and a decrease in Bacteroidetes species. Additionally, it was discovered that individuals who had recently been diagnosed with active TB as well as those who had recurrent TB had a lower abundance of the Lachnospira species (which belongs to the Firmicutes phylum) and the Prevotella genus (which belongs to the Bacteroidetes phylum) in comparison to those who were healthy controls. Lachnospira and Prevotella had a positive link with the quantity of peripheral CD4+ lymphocytes in patients who had just been diagnosed with TB. On the other hand, they demonstrated a negative correlation with CD4+ cell counts in persons who had suffered recurrent TB.[14]

During an infection caused by Mycobacterium tuberculosis, it is plausible to postulate that various commensal bacteria and metabolites in the gut send out signals that influence innate immune cells as well as adaptive immune cells, while simultaneously producing pro-inflammatory and anti-inflammatory cell types in a state of microbial equilibrium. This suggests that the immunological signals produced by the gut microbiota will add to the group of lymphocytes that are brought to the airways when the body is infected with *M. tuberculosis*. Thus, the diversity in the immune response guarantees a balanced and stable cytokine milieu in the lungs. This equilibrium in the immune system can result in two potential outcomes: (1) complete elimination of the infection through natural responses, either (2) TB skin testing or the interferon gamma release assay (IGRA) comes back negative, or (3) macrophages, T cells, and B cells all get to work, either killing the infection or trapping it in granulomas, resulting in latent TB infection (LTBI). The preservation of granuloma integrity effectively prevents the transition to active TB. [15]

Furthermore, the coexistence of HIV infection with TB disrupts the equilibrium of the microbiota community. Changes in the gut microbiota and composition of metabolites can result in impaired activation of T cells. (2) An overabundance of a certain type of white blood cell called T lymphocytes in the lungs leads to an imbalance between pro- and anti-inflammatory proteins, or (3) an increased and unregulated immune response including Th1 and Th17 cells. As a result, the body's natural immune responses are weakened, and there is also a lack of effective collaboration between T and B cells, as well as a hindered ability to produce granulomas. Inadequate management of infection facilitates the release of *M. tuberculosis* from granulomas, leading to the infection of nearby lung tissues and the advancement to active TB illness [15]

THE ROLE OF GUT MICROBIOTA IN TB SUSCEPTIBILITY

Annually, a substantial number of individuals acquire latent TB infection (LTBI), with 5-10% of these instances advancing to active TB disease. In specific instances, there is no evident immune deficiency,

indicating the presence of other, yet-to-be-identified risk factors. As a result, there is a suggestion that alterations in the connection between the gut and lung microbiota could contribute to the development of *M. tuberculosis* infection and/or the emergence of TB symptoms. There are three ways in which the microbiota of the gut might affect the risk of *M. tuberculosis* infection and the progression of latent infection to active disease: (1) causing changes in the composition and function of immune cell subsets in the gastrointestinal tract and the airways; (2) affecting the absorption and efficacy of antibiotics utilized for TB treatment; and (3) controlling the spread of Mycobacterium TB through the production of antimicrobials or immunomodulatory compounds.[9]

Evidence suggests that the human microbiome is affected by HIV, diabetes, alcoholism, smoking, malnutrition, and pollution, all of which are major risk factors for TB. These risk factors affect the population of some beneficial bacteria in the mouth; HIV affects both lung (increasing *Prevotella, Veilonella,* and *Strepotococcus*) and gut (reducing *Bacteroidaceae, Lachnospiraceae, and Ruminococcaceae*) microbiota. Pollution affects mainly the gut microbiota by increasing the lung population of Neisseria and Streptococcus, and reducing Tropheryma. Diabetes, smoking, and malnutrition mainly affects the gut microbiota; Smoking reduces the gut population of Porphyromonas, Neisseria, and Gemella; Consuming excessive amounts of alcohol results in intestinal dysbiosis, characterized by a decrease in Bacteroides and an increase in *Proteobacteria*; and Malnutrition increases *Enterococcus* and *Streptococcus*, among others. These changes, in turn, lead to a disruption in the permeability of the intestinal lumen and the translocation of molecules that regulate inflammation.[16]

The following is a list of the primary pieces of evidence that support the hypothesis that human microbiota homeostasis is associated with susceptibility to TB: (1) Individuals with a respiratory infection caused by *M. tuberculosis* have lower microbial diversity in their gut and lung microbiota compared to healthy controls; (2) Coinfection with Helicobacter species in the intestine impacts the vulnerability to MTB infection and the advancement to active TB; (3) Anaerobic bacteria, when inhaled from the mouth into the lungs, generate metabolites that can compromise lung immunity and forecast the occurrence of an active TB infection; (4) The diminished existence of T cell antigenic epitopes in the intestinal commensal microbial flora, specifically nontuberculous mycobacteria, is also a contributing factor, may explain why patients who have previously received TB treatment are more susceptible to reinfection; and (5) Prolonged use of antibiotics during TB treatment leads to changes in the composition of the gut microbiota over time.[17]

Multiple studies have shown that mice become more susceptible to *Mycobacterium* TB when the commensal bacterium Helicobacter hepaticus is introduced to their gut microbiome. Damage to the lungs, impaired immunological response to *M. tuberculosis* infection in the lungs, and an imbalance in the gut microbiota are all consequences of H. *hepaticus* being present in the intestines. Helicobacter pylori, in contrast to other bacteria found in the intestines and liver, seems to possess immunomodulatory characteristics. H. *pylori* has developed a comparable method of causing disease that enables it to persist in the lungs through the gut-lung connection, so preventing *M. tuberculosis* infection.[18]

The Role of Gut Microbiota in TB Treatment Response and Outcome

When it comes to cases of multi-drug resistance TB (MDR-TB), the duration of the treatment regimen for TB can range anywhere from six months for persons who have recently infected with the disease to nine months. Patients who have recently been diagnosed with TB (TB) are treated with a specific combination of medications for a period of two months. This combination includes rifampicin (R), isoniazid (H), pyrazinamide (Z), and ethambutol (E). After the initial two months, the treatment continues for an additional four months with rifampicin (R) and isoniazid (H) alone.[19]

The gut microbiota influences the way medications are processed and distributed in the body, which is known as pharmacokinetics. The liver's main role is to synthesize primary bile acids and metabolize drugs, while the primary responsibility of the gut microbiota is to produce secondary bile acids. Moreover, there is compelling data indicating that the gut microbiota has an impact on the expression levels of transporters and drug-metabolizing enzymes. The gut microbiota can influence the availability, effectiveness, and potential harm of drugs through various mechanisms. One such mechanism is the production of enzymes that either activate or deactivate drugs. For example, enzymes produced by the gut microbiota can convert sulfalazine into its active form, 5-amino 5-salicyclic acid. Another mechanism is the direct binding of drugs by the gut

microbiota, which can affect their availability. An example of this is the altered bioavailability of L-DOPA due to its binding with H. *pylori.*[20]

Frequent treatment failure in TB therapy occurs when exposure to doses below the approved therapeutic range leads to the establishment of resistant strains of *M. tuberculosis*. Notable differences in the way pyrazinamide, isoniazid, and ethambutol are processed in the bloodstream have also been recorded. These discrepancies were attributed to factors such as age, HIV infection, antiretroviral therapy, and malnourishment. Interestingly, a number of these characteristics also have an impact on the composition of the gut microbiome. Hence, the influence they have on the metabolism of anti-TB medications potentially associated with the changes they bring about in the microbiome. One potentially severe outcome is that changes in the levels of anti-TB medications in the blood may occur due to the disruption of the gut microbiota generated by the drugs. In light of recent evidence, it cannot be dismissed that an anti-TB medicine may lead to a significant disruption of the gut microbiome, known as dysbiosis.[15]

Table 1. Factors that increase the likelihood of developing TB and have an impact on the composition of the gut or lung microbiota, as well as the metabolism of antituberculosis drugs in the liver. 16

	Gut Microbiota	Antituberculosis Drug-Induced Hepatotoxicity
HIV	↓Rikenellaceae	Increases risk
	↓Bacteroidaceae	
	↓Lachnospiraceae	
Alcohol	↑Proteobacteria	Increase Risk
	↓Bacteroidetes	
Malnutrition	↑Entreococcus faecalis	Increase Risk
	↑Streptococcus gallolyticus	
	↓Faecalibacterium prauznitzii	
	↓Bacteroides spp.	
	↓Bifidobacterium spp	
Smoking	↑Proteobacteria	No Data
	↑Bacteroidetes	
	↓Actinobacteria	
	↓Firmicutes	
Air Pollution	↑Firmicutes	Unknown
	↓Bacteroidetes	

According to a recent study utilizing a mouse model, Isoniazid therapy caused a shift in the population of gut microbiome and resulted it comes to the removal of the innate immune response to an MTB infection. One of the consequences of the reduction in MHC-II and CD86 expression was a reduction in the lung's ability to deliver antigens and activate myeloid dendritic cells. As a further point of interest, mice that were infected with MTB and given INH therapy showed a decrease in the expression of innate receptors (TLR2, Mincle, and Nod2) as a consequence of disruptions in the microbiota. Based on these data, it appears that the microbiota may have a role in the development of resistance to the disease as well as the effectiveness of treatment in the future.[21]

THE ROLE OF PROBIOTICS IN TB TREATMENT

A definition of probiotics has been supplied by the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO). According to this definition, probiotics are defined as "live microorganisms that, when given in sufficient quantities, provide a health advantage to the host." Practitioners frequently recommend probiotics as a remedy for the potential adverse effects of antibiotics. The majority of probiotics assert their ability to

enhance and restore the makeup of the microbiota within the human body. They specifically target certain regions of the body and a wide range of disorders.[19] Probiotics consist of microorganisms that naturally inhabit our mucosal surfaces, such as *Lactobacillus spp*., *Bifidobacterium spp.*, *Streptococcus salivarius,* and *Escherichia coli.*[22]

Some of the most extensively researched and widely accessible probiotic species include *Bifidobacterium* (*adolescentis, animalis, bifidum, breve,* and *longum*) and *Lactobacillus* (a*cidophilus, casei, fermentum, gasseri,* j*ohnsonii, reuteri, paracasei, plantarum, rhamnosus,* and *salivarius*). The International Scientific Association for Probiotics and Prebiotics has established that these species can offer overall health advantages, including restoring the imbalanced gut microbiota, regulating intestinal movement, outcompeting harmful microorganisms, and producing Short Chain Fatty Acids (SCFA).[23]

Probiotics are essential for restoring the balance of gut bacteria and promoting beneficial functions of microbial communities. This can help reduce or avoid gut inflammation and other symptoms related to intestinal or systemic disorders. The probiotic *Lactobacillus rhamnosus* was the initial focus of investigation in this area and has demonstrated advantageous impacts on gut immunity. *Lactobacillus rhamnosus* improves the strength of the intestinal barrier, supporting the immune response and reducing the movement of bacteria through the intestinal lining. Presently, experts recommend exploring the potential of co-administering a TB medicine with probiotics targeted at the gut to augment treatment response and outcomes.[15,19]

Probiotics have the ability to modify the immunological response of the host's entire body and the immune response of the mucous membranes by interacting with the cells of the immune system and the cells that line the mucous membranes. Intestinal mucosal lining IgA immune response stimulation, cytokine and chemokine activation or suppression, cell recruitment and activation, and enhancement of functions pertaining to protection and repair of the intestinal barrier and epithelial cells are all intricate steps in the functioning of these mechanisms. These acts will most closely mimic the way bacteria and hosts interact in nature. [22]

Probiotics have the ability to influence the immune response in the mucosal lining of the body, promoting a pattern of immunological tolerance and elevating the levels of IL-10. In addition, probiotics stimulate the development of CD4+ Foxp3+ T-reg cells by suppressing the production of *proinflammatory* cytokines and promoting the differentiation of T cells into the Th1 phenotype. *Lactobacilli* can protect the host from airway infections by interacting with the GALT (gut-associated lymphoid tissue) and indirectly boosting the respiratory immune cells. Some research has linked the protective effects of probiotics to the activation of alveolar macrophages and/or natural killer cells. Research on mice showed that adding *Lactobacillus pentosus* improves NK cell activity in the spleen and increases IFN-γ production. The contact between dendritic cells and *lactobacilli*, aided by TLR2 and TLR4, leads to the generation of IL-12 by CD11c+ dendritic cells, which in turn achieves this function. The capacity of various strains of *lactobacilli* to generate large amounts of IL-12 and, as a result, IFN-γ differs. Probiotics have an impact on T-reg and Th17 lymphocytes, as well as other types of inflammatory cells. Th17 cells are crucial in eliminating infections in both humans and animals, whereas T-regulatory cells govern the regulatory mechanisms of the immune response.[11]

Every lactobacilli shown a notable bactericidal impact at acidic pH against M. bovis, however, only *Lactobacillus plantarum* and *Lactobacillus casei* demonstrated antimycobacterial activity at a neutral pH. A collagen adhesion protein with antimycobacterial and immunomodulatory characteristics, as well as bacteriocins, were discovered by genome analysis of *Lactobacillus casei.* Furthermore, by means of an antagonistic competition mechanism, *Lactobacillus plantarum* successfully reduced macrophage uptake. There are theories suggesting that giving lactobacilli orally, which have antimycobacterial properties, could decrease the amount of M. bovis in the intestines and lower the chances of it spreading between domestic and wild animals.[24]

Only a small number of probiotic bacteria, such as *Lactobacillus* and *Enterococcus spp*., demonstrate antibiotic resistance. Certain probiotic strains are believed to have developed antibiotic resistance, which could be harmful as the resistance has the potential to disseminate to other bacteria via the transfer of genetic material either horizontally or vertically. Therefore, to avoid horizontal gene transfer, it is advisable to ensure that each probiotic is devoid of the plasmid responsible for immunity and undergoes testing for antibiotic resistance markers prior to commercialization. An effective strategy to decrease the probability of inheriting resistance is to include antibiotic-resistant

probiotics as a supplement in antibiotic-probiotic combination therapy.[25]

A recent study demonstrated that Bifidobacterium adolescentis displayed a higher level of resistance to extremely high dosages of rifampicin compared to multidrug-resistant *M. tuberculosis*. Resistance can occur due to mutations in the rpoβ gene. The rpoβ gene is found in almost all prokaryotes. It is a gene that is always active and essential for protein synthesis. It may not be affected by the transfer of resistance genes across different organisms. Moreover, Bifidobacterium adolescentis has the ability to adjust to varying levels of Rifampicin, perhaps aiding in the preservation of the human microbiome following medication therapy.[26]

SUMMARY

The microbiome has the potential to be a modifiable risk factor for TB. The human microbiota potentially influences the formation of *M. tuberculosis*, and TB treatment can cause temporary and lasting disturbance to the microbiota, which subsequently affects the host's immune response to the infection. The gut-lung axis is crucial in the prevention of TB and determining the effectiveness of treatment. Additionally, it has an effect on the immune response of the host against *M. tuberculosis*. Additionally, probiotics and postbiotics have been shown to be effective against TB in both laboratory settings and in living organisms, indicating that they have the potential to be utilized in the treatment of TB in order to overcome the challenges that are caused by the current reliance on multiple antibiotics.

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