Review Article

Status and outlook of pulmonary tuberculosis coinfection

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Coinfections with pulmonary tuberculosis (TB) occur in people with damaged lung structures, chronic malnutrition, and those with compromised immunity. Moreover, it is a common clinical challenge that leads to poor clinical outcomes and contributes to increased morbidity and mortality in patients with TB. Coinfection in the lungs can prolong hospital stay and increase the cost of treatment for TB patients, which imposes a heavy burden on families and society. Therefore, pulmonary TB (PTB) combined with pulmonary infections should be diagnosed and treated promptly. This review describes trends in epidemiology and other factors that influence the incidence of PTB coinfection. Current and emerging diagnoses well as infection treatments are discussed.

Key words: Coinfection(s), microorganism, pulmonary infection, tuberculosis

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INTRODUCTION

Pulmonary tuberculosis (TB) patients with coinfections often lack specific clinical manifestations, which makes clinicians ignore the possibility of coinfections, thus delaying treatment. It is, therefore, necessary to understand the epidemiology, pathogenesis, diagnosis, and treatment of pulmonary infections in patients with pulmonary TB (PTB), and develop rational and effective treatment options.

EPIDEMIOLOGY

Bacteria

Ishikawa *et al*. retrospectively studied 761 Japanese PTB patients with positive sputum smears between 2007 and 2012.[1] The relationship between microorganisms isolated from the sputum at admission and 180-day mortality was explored. Of 708 patients who were tested for sputum microorganisms, 128 (18.1%) had pathogenic bacteria, 23 had methicillin-resistant *Staphylococcus aureus*, 17 had *Klebsiella pneumoniae*, and 16 had *Pseudomonas aeruginosa*. The study showed that there were 51 deaths in patients with coinfections, and the mortality rate was significantly higher in TB patients with coinfection (39.8%) than in those without coinfection (10.2%) ($P < 0.01$).

Another retrospective study analyzed alveolar lavage fluid cultures from 216 patients with endobronchial TB in Korea between January 2013 and January 2019.[2] The analysis identified bacteria in 42 patients (19.4%), where 6 patients (2.8%) had mixed infections with multiple bacteria. The most common microorganisms were *S. aureus* ($n = 14$, 33.3%), followed by *Klebsiella* ($n = 12$, 28.6%), *Streptococcus* ($n = 5$, 11.9%), *Enterobacter* ($n = 4.9$, 5%), and *P. aeruginosa* ($n = 3$, 7.1%) [Table 1].

Attia *et al*. retrospectively analyzed 137 pulmonary infections in Cambodia and found that out of 40 TB patients with positive sputum tests, 13 had coinfection with pulmonary bacteria. The Gram-negative bacilli (*Klebsiella* and *Pseudomonas*) were the most common pathogens in the TB pulmonary coinfections.[3]

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In a prospective study conducted between 2011 and 2012 by Shimazaki *et al*. which analyzed 466 patients hospitalized with suspected TB, 228 were positive for TB-PCR. Out of the 228 patients, 135 (29.0%) had bacterial pathogens in their sputum samples. *Haemophilus influenzae* was the most common (*n* = 99, 21.2%), followed by *Streptococcus pneumoniae* (*n* = 37, 7.9%). They reported that bacterial coinfections are common and increase the risk of early death in TB patients.[4]

In a 2016–2017 cross-sectional study in Nigeria, Iliyasu *et al*. analyzed patients with PTB secondary to bacterial pneumonia.[5] In 141 TB patients, sputum cultures showed 141 strains of bacteria, 63 of which were Gram-negative bacilli (*Escherichia coli*, *Klebsiella* spp., and *P. aeruginosa*), the same as *S. pneumoniae*. This was in sync with previous findings which demonstrated an increase in the proportion of Gram-negative and conditionally pathogenic bacteria infecting TB patients with pulmonary infections,[6] and were the main pathogens in pulmonary infections in TB patients.

Fungi

Bongomin showed that pulmonary aspergillosis occurred mainly in people with impaired lung structure and immune deficiency, and was prevalent in patients with TB.[7] 20%–40% of TB patients experienced cavity formation in their lungs after treatment.[8] A retrospective analysis suggests the main risk factors for PTB complicated with pulmonary aspergillosis were the application time of antibiotics ≥1 month and the application time of hormones ≥1 week.[9] chronic pulmonary aspergillosis (CPA) prevalence among post-TB patients was found to be around 5% in a previous study from Northern Uganda.[10] At the conclusion of their TB treatment in Indonesia, 22% of GeneXpert/smear-negative individuals had CPA; this is in addition.[11] In a meta-analysis of PTB coinfection with *Aspergillus pulmonarius* from 2001 to 2019, Hosseini *et al*. noted that the prevalence of PTB coinfection with *A. pulmonarius* ranged between 3.7% and 33.3%.[12] Besides, the study showed a prevalence of 14.7% of mixed *Aspergillus* infections in Asian patients with TB and an overall prevalence of 17.7% of mixed *Aspergillus* infections in African patients, with *Aspergillus fumigatus* being the most common fungus. Interestingly, Bhatt *et al*. developed an *in vivo* model of coinfection where BALB/c mice were aerosolized with *Mycobacterium tuberculosis* (MTB) at 200 colony-forming units (CFUs) to better understand the interaction between these two pathogens (CFU). Systemic candidiasis is brought on by an intravenous *Candida albicans* infection. Although no mortality was seen in mice only infected with MTB for the stated duration, the mice that were coinfected evidently had a higher mortality rate than animals that were simply infected with *C. albicans*.[13] A cross-sectional study in sub-African in 2020 showed that *Candida* infections accounted for 25.7% of patients with TB combined with pulmonary fungal infections, with *C. albicans* being the most common, followed by *Pseudomonas tropicalis* and *Candida smoothus*.[14] Another study demonstrated that *C. albicans* was the most common coinfecting fungal species in TB patients[15] (80%–90%). Other studies have shown that the prevalence of mixed *Candida* infections in TB patients ranges from 2.8% to 55%.[16] However, some scholars argue that *C. albicans* is an oral respiratory tract colonizing bacteria and not a pathogenic bacterium.[17]

A retrospective study in Taiwan, China, which analyzed TB coinfection with cryptococcal infection between 1993 and 2006 showed that 0.6% of patients with TB had coinfection with cryptococcal infection and 5.4% of patients with cryptococcal coinfection had TB. Most of the patients (83%) recovered well after dual antifungal and anti-TB treatment.[18]

Nontuberculous mycobacteria

Another study retrospectively analyzed HIV-negative PTB patients in northern Tunisia from 2002 to 2016 and isolated non-TB mycobacteria from 60 (0.6%) of 10466 sputum specimens.[19] The most common were *Mycobacterium kansasii* type 1 (23.3%), while others included *Mycobacterium gordonii* (6.6%), *Mycobacterium cadetum* (6.6%) and exotic *Mycobacterium bovis* (3.3%). However, *Mycobacterium avium*, which is the most common non-TB *Mycobacterium* globally was not found.

In a multicenter clinical study, Gao *et al*. showed that 286 patients with multidrug-resistant-TB (MDR-TB) treated with bedaquiline developed nine mixed nontuberculous mycobacteria (NTM) infections during treatment. The infectious agents included *Mycobacterium abscessus* (five strains), followed by *M. avium* (two strains) and *Mycobacterium intracellulare* (one strain).[20]

Another retrospective cohort study showed that NTM was isolated from 113 specimens in 68 patients between anti-TB treatments. The NTM included *M. abscessus* (*n* = 35, 31%), *Mycobacterium incidentalis* (*n* = 17, 15%), *M. avium* complex (*n* = 9, 8%), and *M. gordonii* (*n* = 9, 8%).[21] The study found that cultures from 48 (71%) patients had only one type of NTM, 20 (29%) patients had two or more NTMs, while two (3%) of the patients were positive for *M. abscessus* after anti-TB treatment.

A retrospective study by Carneiro *et al*. demonstrated that out of 100 Brazilian patients with NTM, 85 had received prior anti-TB treatment, and the most common NTM was *M. avium* complex (MAC = 35%), *M. kansasii* (17%), and *M. abscessus* (12%).[22]

In 2018, Xu *et al*. retrospectively analyzed 1208 patients with suspected PTB, and showed that out of 390 sputum culture-positive cases, 358 (91.8%) were infected with MTB, 24 (6.2%) with NTM, and 8 (2.0%) with both MTB and NTM.[23] The study further showed that 7 of the 8 patients with both MTB and NTM were extensively anti-TB drug resistant. A retrospective study in China suggests a total of 837 MDR-TB isolates were analyzed, of which 22 isolates (2.6%) were found to contain a mixture of NTM and MTB organisms. The most prevalent species detected was *M. intracellulare* (15/22, 68.2%), while prevalence rates of the other identified coinfecting mycobacterial species were as follows: *M. avium* (4/22, 18.2%), *M. kansasii* (1/22, 4.5%), *M. abscessus* (1/22, 4.5%), and *Mycobacterium malmoense* (1/22, 4.5%).[24] The study in Beijing included 89 patients with recurrent TB after screening for nearly 12 years (January 2008–December 2019). Nine patients were discovered to have NTM infections during the time of the investigation. Six patients were infected with various mycobacterial strains, half of which underwent NTM to MTB and MTB to NTM transformations.[25]

Virus

In a South African study that analyzed a total of 2959 patients with suspected TB or influenza between June 2010 and December 2011, 423 (14%) were positive for TB, 275 (9%) were positive for influenza, while 34 (1%) had influenza and TB coinfection. Patients with the coinfections had a significantly increased risk of death in individuals who experienced respiratory symptoms for ≥7 days.[26] In another report from South Africa, 10% of the cases that died during the 2009 H1N1 pandemic were comorbid with TB.[27] In addition, although the incidence of TB in severe pandemic influenza cases has been shown to be high, the available data remain low.[28] However, studies have previously demonstrated that influenza coinfection in TB cases is associated with a pro-inflammatory response, increased mycobacterial load,[29] and mortality in animal models and patients.[30]

In a cohort study in Taiwan, China, Su *et sal*. collected blood samples from 101 untreated TB patients and 101 healthy controls and showed that the seropositivity rate for human herpesvirus (HHV) type 8 antibodies was higher in TB patients (30/101) compared with the control group (15/101) (P = 0.01).[31] The study showed that TB patients, like HIV-positive patients, were susceptible to HHV type 8 infection.

In another cohort study which included 49 patients with confirmed TB, 10 out of 19 patients (52.6%) who were on anti-TB treatment were successfully diagnosed with SARS-CoV-2 virus after 1–2 months of treatment.[32] According to a meta-analysis, COVID-19 coinfection will increase the risk of death of TB patients (1.4 times).[33] This finding suggested that patients with active TB are more susceptible to SARS-CoV-2 virus infection and that SARS-CoV-2 virus may develop more rapidly and severely in TB patients.

PATHOGENESIS

Imbalanced intestinal flora

Immunomodulation of the gut microbiota has also been shown to be critical in the host anti-TB response, including prevention of TB infection, reduction of latency progression, reduction in disease severity, and reduction in the incidence of drug resistance and coinfection.[34]

Approximately 40% of the body's lymphocyte pool is located in the gut, suggesting that gut microbiota play a key role in the development of the immune system and functions.[35] A positive correlation has been reported between the gut microbiota and the peripheral CD4 + T cell count in TB patients.[36] Antibiotic therapy can alter the composition of the microbiota and, in some cases, adversely affect health of the patients.[37] Previous studies have shown that in the pulmonary-intestinal axis, pneumonia may lead to the destruction of the intestinal microbiota.[38] The pulmonary microbiota and its metabolites enter the intestine through the blood and vice versa.[39] Various anti-TB treatment regimens often contain broad-spectrum antibiotics such as rifampicin and moxifloxacin, whose intensity and duration of application are high. Therefore, there is potential selection pressure of the intestinal flora.[40] For instance, rifampicin is mainly excreted through the intestine and feces, which has a greater impact on the intestinal flora. Through animal studies, Khan *et al*. showed that the H-Z and the R regimen alone induce different structural changes in the flora.[41] The H-Z regimen led to an increase in the relative abundance of clostridial flora and the changes in the flora were associated with reduced expression of MHC II receptors, decreased mitochondrial function as well as decreased expression of pro-inflammatory cytokines (tumor necrosis factor-alpha [TNF-α], interleukin-1β [IL-1β]) in alveolar macrophages, which led to decreased clearance of MTB by macrophages. It has been shown that anti-TB drugs act on the intestinal flora and impair the body's immunity to MTB, a finding that was also demonstrated by Luo *et al*.[36] Although it has also been shown that first-line anti-TB treatment has little effect on the composition of the microbiota in the gut in TB patients, there is an alteration of relative abundance of certain groups of organism.[42] More interestingly, a study on MDR-TB cases sampled during treatment showed that long-term treatment with second-line drugs depletes intestinal flora.[43] Gastrointestinal disorders were frequent during

bedaquiline administration. Data on adverse events of bedaquiline-containing regimen are currently scant.

Decreased body immunity

Most of the TB patients have underlying diseases such as diabetes, chronic kidney disease, immunosuppression, or compromised immunity. In particular, diabetic patients are susceptible to TB and diabetes mellitus type 2 (T2DM) triples the risk of TB. Gut microbes may be key mediators of TB and T2DM.[36] Disruption of glucose metabolism in diabetes causes impairment of the body's immune function, disorders the protein and fat metabolic cycles, which results in changes in the levels of serum proteins and lipids. These changes lead to a significant decrease in the patients' immune functions, providing an ample environment for the growth and reproduction of MTB.[44] It is worth noting that 2-h postprandial blood glucose (2h PG) is one of the important indicators of the status of glycemic control in diabetic patients. A 2h PG of >11.1 mmol/L shows high blood glucose level for a long time, which often leads to an increase in plasma osmolality, followed by inhibition of lymphocyte division, suppressed neutrophil functions, and a decrease in natural killer cell activity,[45] which eventually leads to impaired immunity. Dalton *et al*. demonstrated that diabetes affects the development of PTB, which exacerbates the symptoms of abnormal glucose tolerance in patients.[46] Besides, the study showed that this interaction can affect the clinical effects of diabetes treatments through interference with glucose metabolism, and the patients experience further reduced immune function and thus prone to secondary pulmonary infections. MTB infection and colonization may predispose the lungs to SARS-CoV-2 infection by down-regulating the host immune response, allowing virus survival, growth, and pathogenesis. Suppressed host immune response in COVID-19-tb coinfection may lead to exacerbation of TB. Furthermore, reactivation of latent to active TB suggests that sars-cov-2 infection can aggravate MTB pathogenesis.[47]

The past and present research demonstrates that IL-10, TNF-α, IFN class I-III, TGF-β, IL-35, and regulatory T cells (T-regs) are all important contributors to the characteristics of host response to MTB. It has also been noted with current research that IL-10, TNF-α, IFN Class I, II, and III, TGF-β, ACE-2, and T-regs are also important contributors to the host response to the SARS-CoV-2 virus in different ways than they are to the TB pathogen. It has suggested a synergistic or additive effect when MTB and SARS-CoV-2 share the same host, leading to increased severity of disease.[48]

Previous studies have shown that, due to reduced immune function, pulmonary NTM disease is more common in older patients.[49,50] Aging TB patients have a gradual reduction of clearance of their respiratory tract and suppressed immune defense functions in their lungs, which lead to the occurrence of respiratory infections.[51]

Pathological structural changes in the lungs

More than two-thirds of patients with TB experience extensive structural changes in their lungs.[52] Although the disease is treatable, structural changes persist and are difficult to reverse. Besides, patients with PTB often have a combination of pathological changes, such as damage to the bronchial mucosa and submucosa, pulmonary tissue edema, diffuse proliferative lesions, and caseous necrosis, which create favorable conditions for pathogenic colonization. In particular, lung damage caused by fibrosis and cavitation may trigger active TB coinfection, leading to aggravation of the already impaired lung function.[53] In addition, with the development of invasive techniques and damage to lung tissue structures, the incidence of fungal infections and conditional pathogenic infections is on the rise, resulting in a significant increase in the incidence of fungal infections in lungs.[54,55] Bronchodilation is thought to be an important cause of impaired clearance of mucus cilia from bronchial tree pathogens.[23] In addition, NTM infections are more common in patients with bronchiectasis, which suggests an association between this structural lung disease and pulmonary NTM infections.[56] Factors affecting the PTB and their indirect effects on PTB coinfection are shown in Figure 1.

DIAGNOSIS OF LUNG INFECTION

Apart from the common PTB manifestation, sputum generation, fatigue, and excessive sweating in TB coinfection patients which are not obviously specific and often easily ignored. A combination of persistent or recurrent clinical symptoms, changes in chest computed tomography, white blood cell count, sedimentation, and C-reactive protein, as well as consideration of the

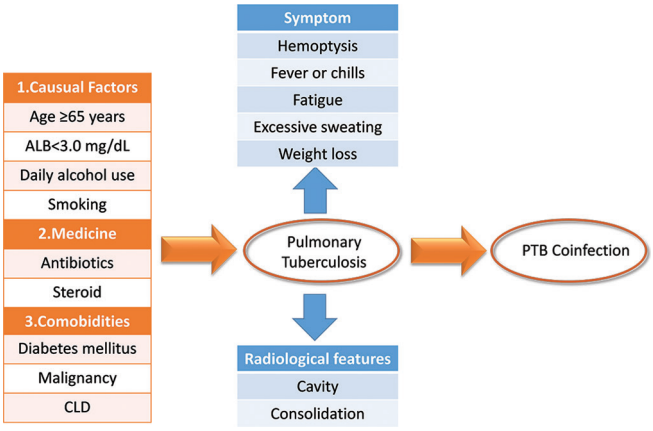

Figure 1: Factors affecting the pulmonary tuberculosis and their indirect effects on pulmonary tuberculosis coinfection. PTB = Pulmonary tuberculosis; CLD = Chronic lung disease; ALB = Albumin

patient's age and underlying disease, require that patients with PTB be excluded from potential coinfections. Currently, it is challenging to perform a timely diagnosis of TB coinfection. There are three diagnosis modalities: induced sputum, bronchoalveolar lavage (BAL), and tissue sampling. Induced sputum is readily available, noninvasive, and easy to collect. However, it is often prone to contamination with the upper respiratory and oral/nasopharyngeal colonizing microorganisms. BAL is unlikely to be contaminated by upper respiratory flora but requires invasive bronchoscopy. It is currently very widely used in clinical practice. To detect pathogens more accurately, bronchoscopy and alveolar lavage fluid are recommended, but not sputum specimens. Tissue specimen analysis includes bronchoscopic brushing and puncture pathology. However, the difficulty associated with specimen acquisition in TB coinfections cases persists.

There are new methods such as IS6110-based restriction fragment length polymorphism (IS6110 RFLP) analysis, and spacer oligonucleotide genotyping (spoligotyping). In recent years, macrogenomics has also been widely used. Many recent studies have tested the efficacy of stool in molecular of paucibacillary TB, whicle scare reports are available on coinfection patients.[57] The detection of mixed pathogens DNA in the stool of TB coinfection patients is potentially useful.

In addition, culture can be used if a fungus is clinically considered and a relevant subtype is identified. In species identification of colonies in sputum by sabouraud dextrose agar medium: *C. albicans* appears as light green, *Candida tropicalis* is blue, *Candida smoothis* is creamy white, and *Candida klebsiella* is purple.[58,59]

For NTM, culture plus DNA sequencing is useful in the identification of faster-growing nonTB mycobacteria, including *M. intracellulare, M. kansasii, M. abscessus,* and *M. incidentalis*.[60]

Mixed infections encompass a wide variety of pathogens, and it is important to distinguish whether they are colonizing or pathogenic. This can be achieved by at least three factors: Bacterial load, species isolated, and presence of recurrent clinical symptoms or progression of pulmonary CT.[61] On the other hand, patients with active TB should be monitored for the possibility of coinfection when accompanied by new or worsening chest imaging changes. Imaging of patients with dual infection of TB and SARS-CoV shows an increase in the number and extent of ground grass opacities with pattern "crazy paving" of the lung.[62] The diagnosis procedure is shown in Figure 2.

THERAPY

Basic treatment

Blood sugar control

Many patients with mixed infections often have a combination of elevated blood glucose or diabetes mellitus at basal status. Studies have shown that patients with diabetes mellitus have a higher incidence of pulmonary *Aspergillus* infection.[12] Sugawara and Mizuno showed that high blood glucose favors the growth and multiplication of MTB and that the growth of the MTB is directly proportional to blood glucose concentration in a certain concentration range.[63]

Enhancement of the body immunity

A poor nutritional status decreases energy production and substrates for respiratory muscles, increases protein decomposition and consumption, reduce weight and

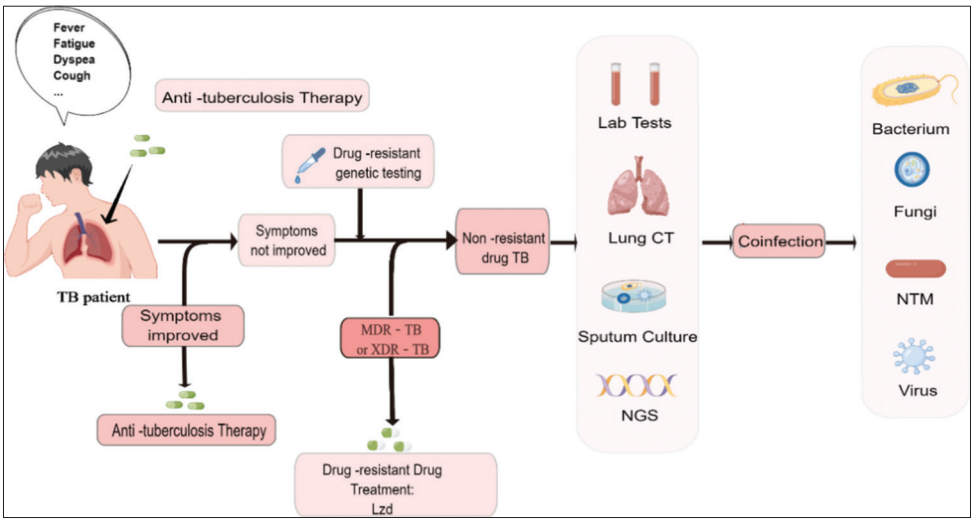

Figure 2: Diagnosis procedure of pulmonary tuberculosis coinfection. CT = Computed tomography; NTM = Nontuberculous mycobacteria; TB = Tuberculosis; MDR = Multidrug-resistant; XDR = Extensive drug-resistance; NGS = Next-Generation Sequencing technology

Table 1: Pathogens associated with pulmonary tuberculosis coinfection

Pathogens	Author	Year	Country	Type of study	Sample type	Sample size (TB+)	Coinfection (*n*)
Bacteria							
S. aureus	Kim *et al*.	2020	Korea	Retrospective	BAL	216	42
Methicillin-resistant *S. aureus*	Ishikawa *et al*.	2019	Japan	Retrospective	Sputum	761	128
Klebsiella and *Pseudomonas* spp.	Attia *et al*.	2019	Cambodia	Retrospective	Sputum	40	13
H. influenza	Shimazaki *et al*.	2018	Philippines	Prospective	Sputum	228	135
S. pneumonia	Iliyasu *et al*.	2018	Nigeria	Cross-sectional	Sputum	141	63
Fungi							
Aspergillus	Bongomin	2020	Uganda	Review			
				Retrospective	Sputum/tracheal aspirate protected sample brush/BAL	140	50
				Multicenter study	Sputum/blood	208	18
				Retrospective	Sputum/blood	124	17
Candida	Hadadi-Fishani *et al*.	2020	Iran	Systematic review and meta-analysis	Sputum/blood	2139	446
Aspergillus	Hosseini *et al*.	2020	Iran	Systematic review and meta-analysis	Sputum/blood	2868	352
Candida	Tong *et al*.	2017		Review	NA	NA	NA
Cryptococcus	Huang *et al*.	2010	China	Retrospective	Sputum/blood/tissue specimens	3833	23
NTM							
M. abscessus	Gao *et al*.	2020	China	Multicenter study	Sputum	286	9
M. kansasii	Gharbi *et al*.	2019	Tunisia	Retrospective	Sputum	10,466	60
M. intracellulare	Xu *et al*.	2019	China	Retrospective	Sputum	366	8
M. intracellulare	Huang *et al*.	2022	China	Retrospective	Sputum	837	22
NA	Li *et al*.	2022	China	Retrospective	Sputum	89	9
Virus							
COVID-19	Tadolini *et al*.	2020	European	Cohort study	Respiratory specimens	49	10
Influenza virus	Walaza *et al*.	2015	Africa	Retrospective	Nasal oropharynx swabs	423	34
Human herpesvirus type 8	Su *et al*.	2015	China	Cohort study	Blood	101	15

NA=Not available; BAL=Bronchoalveolar lavage; MAC=*Mycobacterium avium* complex; TB=Tuberculosis; NTM=Nontuberculous mycobacteria; *S. aureus=Staphylococcus aureus*; *S. pneumonia=Streptococcus pneumonia*; *H. influenza=Haemophilus influenza*; *M. abscessus=Mycobacterium abscessus*; *M. kansasii=Mycobacterium kansasii*; *M. intracellulare=Mycobacterium intracellulare*

thickness of respiratory muscles, decrease the strength and endurance of respiratory muscles, as well as ventilation dysfunction.[64]

Protection of intestinal flora

There has been substantial evidence linking gut microbial disturbances to immune and pulmonary airway inflammation as well as inflammatory conditions such as asthma, chronic obstructive pulmonary disease, and cystic fibrosis. The composition and diversity of the gut microbial community influence the generation of pulmonary inflammatory response.[65,66] For proper maintenance of intestinal flora, (1) probiotics can inhibit the growth of harmful pathogenic microorganisms by competing for nutrients, thus competitively inhibiting adhesion to epithelial cells, lowering intestinal pH, and secreting antimicrobial compounds, while improving intestinal mucosal barrier functions and regulating the liver's natural T-lymphocyte killing functions.[67] Previous studies have reported that probiotics can reduce bacterial translocation (BT) and effectively prevent the development of hepatic encephalopathy.[68] (2) fecal microbiota transplantation can restore much of the original diversity of the intestinal flora in animals exposed to antimicrobial drugs, but cannot be completely reversed.[69,70] However, whether they can be used to complicate mixed pulmonary infections needs to be further investigated. (3) Ginseng polysaccharides improve the metabolism and absorption of specific ginsenosides in the intestines, restore damaged flora and increase the abundance of lactic acid bacteria and *Bacillus* spp.[71] (4) Anti-TB treatment leads to direct damage of the intestinal mucosa in 20%–25% of TB patients,[72] while butyrate has been shown to maintain intestinal health to some extent by maintaining the integrity of the intestinal mucosa.[73] Other studies have also demonstrated that Vitamin D signaling pathway can promote benign growth of the intestinal microbiota through the alpha defensin of Paneth cells.[74] However, whether these two can provide new therapeutic options to maintain the balance of intestinal microecology needs to be further clarified experimentally.

Reasonable anti-infection treatment

Short-term empirical addition of β-lactam-enzyme inhibitor complexes and third-generation cephalosporins to anti-TB

therapy in patients with elevated inflammatory markers and poor general underlying conditions can reduce in-hospital mortality from TB coinfection with bacteria.[75] Notably, it should be recognized that antimicrobial drugs can cause secondary infections and that standardized anti-TB treatment as well as avoidance of long courses of antimicrobial drugs can reduce the coinfection of TB with other pathogens. Kan *et al*.[75] showed that additional antibiotics and anti-TB drugs may be beneficial for some patients with both TB and bacterial pneumonia.

Shimazaki *et al*. suggested that since coinfection with bacteria is more common in patients with PTB, there is a need to consider the use of antibiotics for nontuberculous respiratory pathogens as part of TB management.[4] Therefore, after clear laboratory tests and clinical diagnosis, there is a need to administer a rational anti-TB regimen. Besides, studies related to pharmacovigilance should be performed to generate strategies that promote the rational use of antimicrobial drugs.[76,77] There is a significant correlation between the history of rifampicin exposure and susceptibility to fluconazole by *C. albicans*. However, ketoconazole and itraconazole were shown to be ineffective.[78] Fluconazole is the first-line treatment option for *C. albicans* infections.[78] Ren *et al*. analyzed the effect of fluconazole on clinical outcomes and immune response in TB cases coinfected with *Fungi*, and showed that fungal infection significantly affects host immunity in TB patients and that fluconazole can effectively reverse this effect.[79] However, Bongomin *et al*. showed that the use of a combination of drugs should be avoided and that anti-TB drugs and triazoles have significant drug-related effects which reduce the efficacy of each other.[7] The treatment period of NTM is longer than that of TB. Resection of infected organs is a treatment option that can be explored when drugs are ineffective.[80] Studies have shown that most NTM infections are intrinsically resistant or partially susceptible to standard anti-TB drugs and that NTM requires identification of the species and treatment for at least 18 months.[81] In addition, treatment options vary from one NTM to another. In cases of NTM and TB coinfection, the overall 6-, 10-, and 14-yeat cumulative survival probabilities are 75.1%, 65.4%, and 57.0%, respectively.[82] A previous study showed that the long-term use of macrolides improved the survival of patients.[82] Macrolides inhibit bacterial protein synthesis[83] and confer anti-inflammatory effects.[84] Vaccination remains the most effective method of preventing influenza infection. However, since TB infection suppresses the immune response, there might be lower vaccine efficacy in this patient population. Further studies are needed to determine whether TB patients should be vaccinated against influenza earlier in the season. There are also recommendations for empirical antiviral therapy for influenza in PTB patients presenting with acute respiratory symptoms during an influenza pandemic.[85] Evidence from prior studies has demonstrated that anti-TB treatment offers limited or no protection against new coronary pneumonia infection and that new coronary pneumonia disease may occur even in the course of TB treatment.[32] Rivas *et al*. reported two rare cases of triple infection with SARS-CoV-2, MTB and HIV, which required anti-TB and antiretroviral therapy simultaneously.[86]

CONCLUSION

Patients with PTB are vulnerable to other pathogens such as bacteria, *Fungi*, viruses, and NTM. The pathogenesis includes imbalanced intestinal flora, decreased body immunity, and pathological structural changes in the lungs. Therefore, for TB patients with high-risk factors, clinicians need to clarify coinfecting pathogens early, analyze the drug susceptibility of microorganisms, and perform further exploration to determine the most effective antibiotic therapy.

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Conflicts of interest

There are no conflicts of interest.

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