Review

*Discovery Medicine* 2024; 36(182): 437–447
https://doi.org/10.24976/Discov.Med.202436182.41

# Mycobacterial Endocarditis, A Rare Form of Infective Endocarditis

John Dawi[1], Scarlet Affa[2], Abraham Chorbajian[1], Yura Misakyan[1], Aishvaryaa Shree Mohan[1], Brandon Norris[1], Jacob Ochsner[1], Sonyeol Yoon[1], Vishwanath Venketaraman[1,*]

[1]College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, Pomona, CA 91766, USA
[2]Department of Chemistry, Physics, and Engineering, Los Angeles Valley College, Valley Glen, CA 91401, USA
*Correspondence: vvenketaraman@westernu.edu (Vishwanath Venketaraman)
Published: 20 March 2024

**This research project delves into the multifaceted dynamics of Mycobacterium tuberculosis (M.tb) endocarditis, a significant yet uncommon manifestation of tuberculosis (TB). Beginning with an overview of M.tb and the global challenges posed by TB, we navigate through the bacterium's evolution, transmission modes, and the intricate host immune response. The pathology and pathophysiology of M.tb endocarditis are explored, emphasizing its complexities and the host's efforts to contain the pathogen. The study extends to atypical mycobacterial endocarditis, highlighting the emergence of species like M.chimaera, M.fortuitum, and M.chelonae, with a focus on their association with life-threatening mycobacterial endocarditis. Clinical presentations and complications of M.tb endocarditis are detailed, addressing challenges in diagnosis, drug-resistant, co-infections with Human Immunodeficiency Virus (HIV), and potential sepsis. The research underscores the need for a deeper understanding of M.tb endocarditis to enhance prevention, diagnosis, and treatment strategies. Examining the genetic and environmental factors influencing M.tb endocarditis, the study discusses the interplay of immune-related genes, environmental conditions, and predispositions contributing to infection susceptibility. Despite challenges in treatment due to its rarity, the research highlights current protocols, surgical interventions, and promising pharmaceutical developments. Lastly, unraveling these intricate factors is crucial for refining strategies and conducting large-scale trials to address this global health threat effectively.**

**Keywords:** endocarditis; Mycobacterium tuberculosis; atypical mycobacterium; diagnostic criteria; clinical manifestation; M.tb endocarditis treatment

## Introduction to Mycobacterium Tuberculosis

Mycobacterium tuberculosis (M.tb), an aerobic, gram-positive, acid-fast, non-motile, non-spore-forming bacilli, is the causative agent of tuberculosis (TB). TB is a global health concern associated with severe pulmonary and extrapulmonary complications despite being a curable and preventable disease [1]. Astonishingly, in 2021, approximately 1.6 million people succumbed to TB, highlighting the ongoing threat it poses, ranking it as the 13th leading cause of death worldwide. TB is a disease that knows no bounds, affecting individuals across all age groups and regions, with a staggering 10.6 million cases reported in 2021 [2]. The incidence of Mycobacterium tuberculosis (M.tb) endocarditis in the United States is quite low, and it's considered a rare clinical entity. Mycobacterial endocarditis, including M.tb endocarditis, is infrequently encountered compared to other forms of endocarditis, such as those caused by bacterial species like Staphylococcus or Streptococcus [1]. It's challenging to provide precise incidence figures because of its rarity and the fact that cases are sporadic [1].

Among its array of complications, M.tb can give rise to cardiac diseases such as pericarditis (2%–5% frequency), myocarditis (0.14%–2% frequency), or aortitis (0.3% frequency) [3]. In its evolutionary journey, M.tb has adeptly adapted to exploit the physiological and pathological intricacies of the human host. M.tb employs several routes of entry into host cells, ranging from the injured dermal layer and mucous membranes to the gastrointestinal system. However, it predominantly gains entry via the respiratory system [4]. M.tb is primarily airborne, and its transmission primarily occurs through respiratory droplets. This mode of transmission allows it to access the respiratory tract and become ensnared within the lung parenchyma. Once within the host, M.tb can interact with the host's immune system through various mechanisms, often invading immune cells, such as macrophages, mast cells, dendritic cells, and neutrophils [5]. Notably, the bactericidal activity of macrophages may be compromised due to the presence of surfactants within alveolar sacs. This results in the aerosol route becoming the primary path of infection [4]. Consequently, an immune response is triggered, marked by the

activation of host defense cytokines and chemokines such as interleukin-1 (IL-1), tumor necrosis factor-$\alpha$ (TNF-$\alpha$), IL-12, IL-6, and lipoxins. These elements work in concert to either destroy infected cells through necrosis or induce apoptosis via prostaglandins [6].

In contrast, key chemokines like Chemokin (C-C motif) ligand 19 (CCL-19) and CCL-21, along with IL-12, facilitate the activation and differentiation of CD4 T cells into T-helper (Th1) cells in M.tb-infected dendritic cells. These Th1 cells subsequently release TNF-$\alpha$ and interferon-$\gamma$ (IFN-$\gamma$), which are pivotal in the activation of macrophages when exposed to M.tb, setting the stage for inflammatory processes [7]. This immune response leads to the formation of granulomas, essentially aggregations of macrophages encapsulating the pathogen. Initially, the granuloma is surrounded by foamy macrophages and phagocytic mononuclear cells enclosed by lymphocytes. The granuloma's ability to shield itself is significantly bolstered by cytokines such as TNF-$\alpha$, IFN-$\gamma$, and IL-1$\beta$, while IL-10 acts as a chief negative regulator of the inflammatory response [8].

The pro-inflammatory cytokines, including TNF-$\alpha$ and IFN-$\gamma$, play vital roles. TNF-$\alpha$ promotes granuloma formation, while IFN-$\gamma$ enhances antigen presentation and recruits $CD4^+$ T lymphocytes and cytotoxic T lymphocytes, mediating mycobacterial elimination. On the other hand, IL-10, with its anti-inflammatory properties, is produced by macrophages and T-cells upon M.tb infection. IL-10 dampens macrophage function by downregulating TNF-$\alpha$ expression, reducing IFN-$\gamma$ production by T-cells, ultimately facilitating M.tb survival [8]. These cytokines are carefully regulated and secreted by macrophages and dendritic cells upon detecting specific pathogen-associated molecular patterns (PAMPs) via pattern-recognition receptors (PRRs) that recognize M.tb's signature molecules [8]. PRRs play a pivotal role in initiating both the innate and adaptive immune responses to M.tb [9]. Within macrophages, two distinct pathways are responsible for detecting M.tb infectious molecular patterns. The first pathway involves the inflammasome complex, NOD-like receptor pyrin domain-containing 3 (NLRP3). This complex recognizes DNA and leads to the maturation of pro-interleukin-1$\beta$ (pro-IL-1$\beta$) into mature IL-1$\beta$ [10]. The second pathway, which complements the first, is responsible for the expression of type I interferons after the activation of the PRR STING sensor protein, which senses cyclic dinucleotides [8].

As the infection progresses, granulomas evolve, developing a fibrous capsule, reduced blood vessel supply, and an increase in foamy macrophages within the capsule. The fate of granulomas hinges on the host's immune competence, as they can either contain the pathogen within the capsule or lead to the release of pathogenic contents through liquefaction and cavitation, resulting in lung tissue damage. This process can cause productive cough, enabling pathogen spread to different lung areas [11]. The bacterium may also remain dormant in a non-replicating granuloma state, leading to a latent form of M.tb [12] (Fig. 1). Under conditions of immunosuppression and reactivation, the pathogen can disseminate to various organ systems, giving rise to a diverse range of symptoms and diseases affecting lymph nodes, meninges, the heart, and bones [7,8,13] (Fig. 1). M.tb predominantly presents as pulmonary tuberculosis in approximately 85% of cases. However, it can manifest as extra-pulmonary TB in individuals with a history of immunosuppression, such as those with Human Immunodeficiency Virus (HIV), organ transplant recipients, and individuals with diabetes mellitus [7]. Clinical presentations of M.tb infection are often nonspecific, characterized by slow development and nonspecific symptoms, including productive cough, purulent or bloody mucus discharge, chest pain, fatigue, dyspnea, fever, and night sweats [14]. Through the lymphatic and circulatory systems, M.tb may disseminate to other areas, including the brain, leading to meningitis. Less commonly, it can travel to the heart, causing pericarditis or endocarditis [15].

Lastly, Mycobacterium tuberculosis is a remarkable pathogen known for its ability to circumvent the human immune system. Its impact extends beyond the respiratory system, affecting multiple organ systems when left unchecked. The intricate interplay between the bacterium and the host's immune response results in a complex disease process with varied clinical presentations. Understanding this dynamic is crucial for improving TB prevention, diagnosis, and treatment.

## Pathology and Pathophysiology of M.tb Endocarditis

Endocarditis is a medical condition characterized by the inflammation of the heart valves, predominantly affecting the mitral and aortic valves. The presence of pre-existing valvular damage and underlying cardiac diseases significantly predisposes individuals to this ailment. It's important to distinguish between infective and non-infective endocarditis, with tuberculous endocarditis being a distinct form of infective endocarditis. Infective endocarditis is a complex interplay of various factors leading to inflammation. It typically begins with bacteria attaching themselves to and colonizing the valve tissue [16] (Fig. 2). This adhesion involves specific interactions with molecules like fibrinogen and other surface proteins, such as clumping factors and coagulase, providing the foundation for prolonged bacterial adherence [17] (Fig. 2). A study in animal models has even revealed increased dextran synthesis within platelet-fibrin matrices as a result of bacterial adherence, particularly in the context of aortic valve endocarditis [18]. Once the environment becomes conducive to the proliferation of bacterial pathogens, new masses comprised of fibrin and platelets, known as vegetations, begin to form. These vegetations produce toxins that degrade valvu-

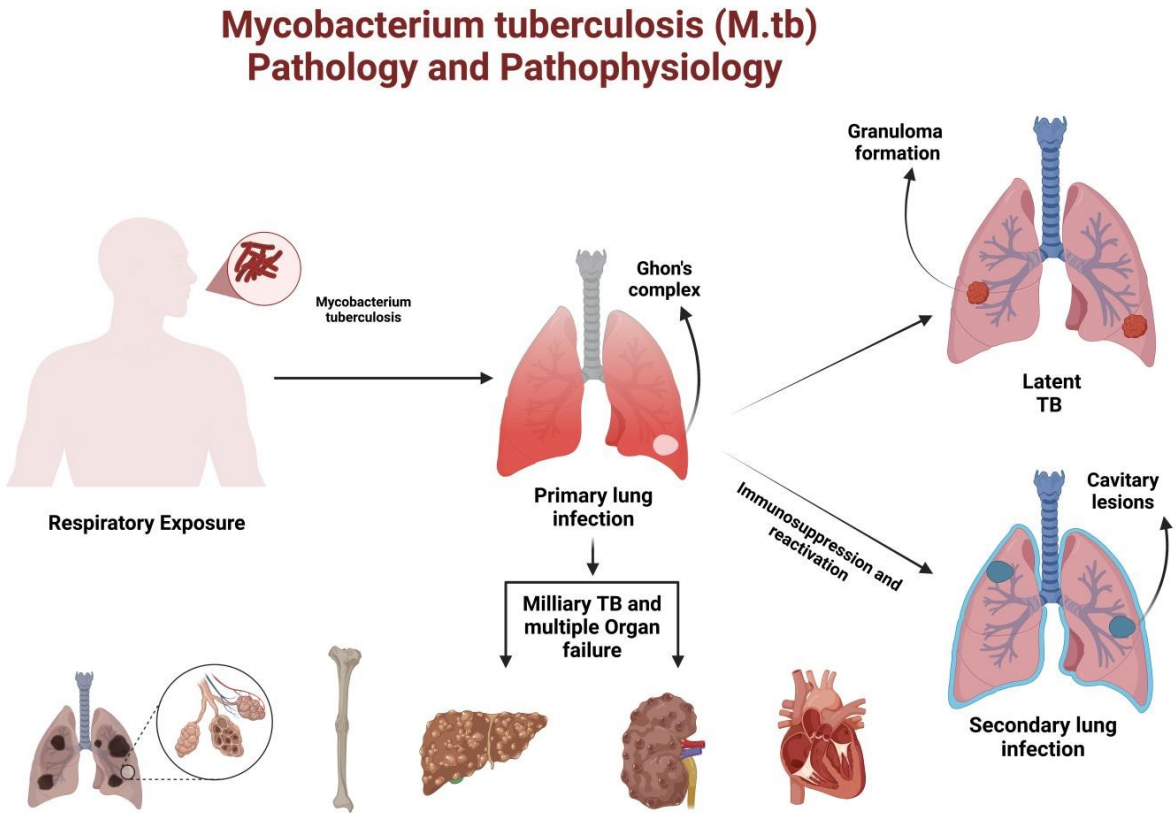


**Fig. 1. Mycobacterium tuberculosis (M.tb) Pathological manifestations.** M.tb infects the human airway through inhalation. Its primary presentation leads to Ghon's complex and granuloma formation, consisting of macrophages and giant cells, including the pathogenic species, prompted by tumor necrosis factor-$\alpha$ (TNF-$\alpha$). Primary infections commonly enter a latent stage, where a patient's lung usually develops fibrosis and scarring. Upon reactivation of M.tb or immunosuppression, patients can present with secondary tuberculosis (TB) and develop lung lesions. M.tb can also gain access to the bloodstream if the infection is not contained and could lead to a systemic manifestation known as Miliary TB. In Milliary TB, patients can suffer multiple organ failure, and the infection could be lethal. (The figure was created by Biorender. https://www.biorender.com/).

lar tissues, ultimately leading to further fibrin-platelet aggregation and the activation of extrinsic clotting pathways (Fig. 2). This process results in a cytokine storm and initiates a positive feedback loop. As the vegetations continue to grow, they promote a pro-inflammatory chemokine response, further exacerbating the progression of infective endocarditis [19,20]. This cycle is exemplified by the formation of circulating immune complexes, especially in patients with infective endocarditis, and is often associated with ocular, renal, and skin manifestations [21].

Infective endocarditis, by affecting the heart valves, interferes with the ability of arterial blood to flow efficiently from the heart to the rest of the body, resulting in systematic pathological manifestations. These effects cascade into end-organ complications, often giving rise to abscess formation in local tissues and triggering immune responses due to bacteremia. Beginning within the heart, the growth of vegetations on the lining of the aortic and mitral valves can lead to the destruction of the valve leaflets, papillary muscle, and interventricular septum. This progressive damage may ultimately lead to conditions such as myocardial infarction and acute coronary syndrome, primarily affecting the mitral and aortic valves [22]. Tricuspid valve infections, although less common, can lead to emboli depositions in the lungs when infective endocarditis affects the right side of the heart. This is due to the natural blood flow from the heart to the lungs, resulting in septic emboli. In some cases, this condition may cause pleural effusions and pneumonia, as the clots formed from infected thrombus can appear as round pulmonary infiltrates, occasionally mistaken for tumors on chest radiographs [23,24]. Additionally, infective endocarditis frequently exhibits skin findings like Osler's nodes and Janeway lesions, which are characteristic of its progressive focal necrotizing vasculitis [25]. Osler's nodes, characterized by painful red lesions, are a consequence of immune complex depositions and emboli lodging in the glomus apparatus of the dermis [26].

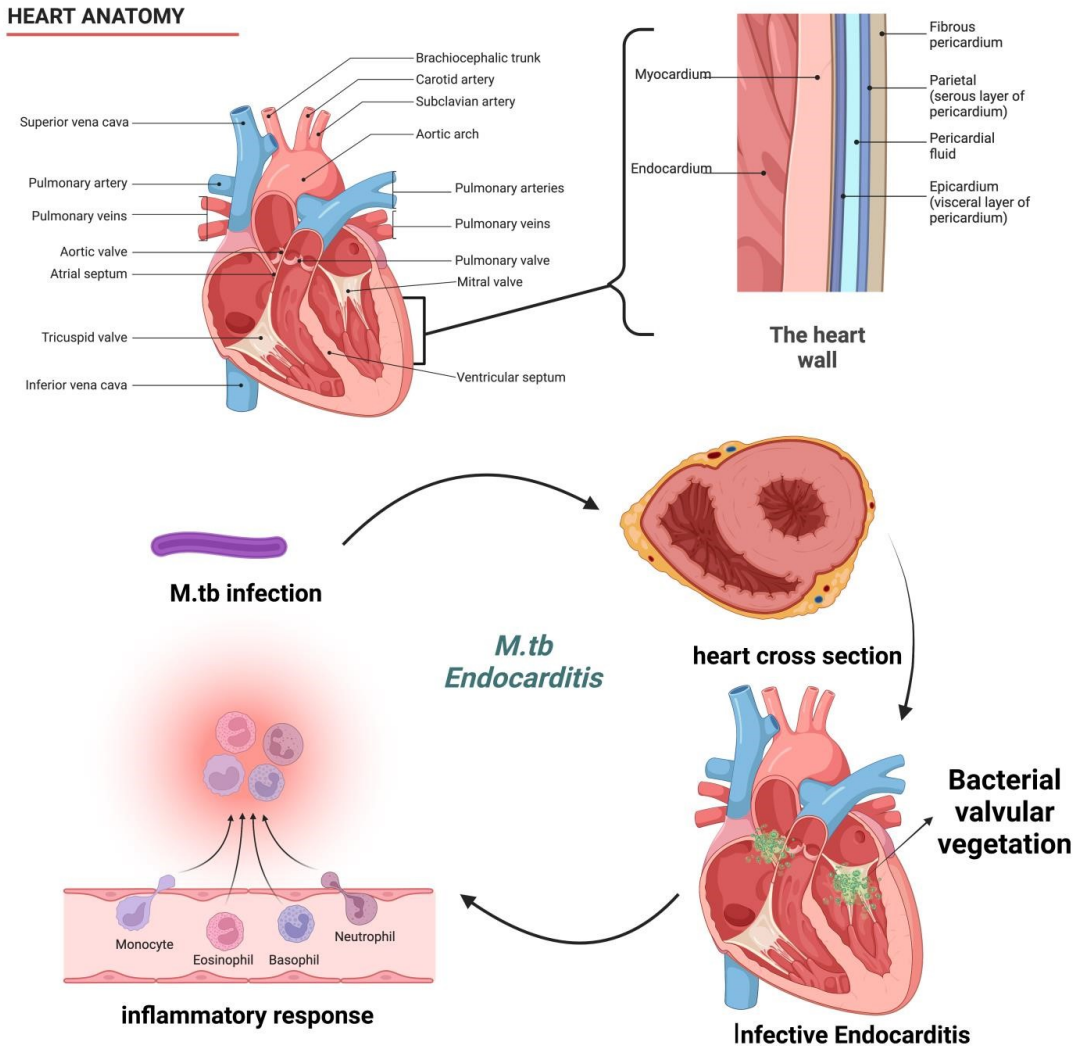


**Fig. 2. Heart Wall Anatomy and M.tb Endocarditis.** The top section Illustrates the Heart wall anatomy, which consists of 3 layers: the Pericardium, Myocardium, and Endocardium. The bottom section shows the mechanism by which Miliary M.tb infection can access the cardiac wall tissue and infect the endocardium. The heart valves are of particular interest, where M.tb can attach to valvular tissue and form bacterial vegetations that can activate the immune system and lead to an inflammatory response. (The figure was created by Biorender. https://www.biorender.com/).

The accumulation of emboli can lead to the formation of aneurysms in cerebral vessels, particularly due to damage inflicted on the vasa vasorum and smaller arteries that are essential for cerebral blood flow. The middle cerebral artery and its branches are among the most commonly affected. Although this can result in symptomatic presentations of cerebral aneurysms, many patients with infective endocarditis may have cerebral lesions from cerebrovascular complications identified only through magnetic resonance imaging (MRI), often without any neurological symptoms [27,28]. Furthermore, in smaller vessels, some of these emboli may accumulate in the nerve layer of the retina, presenting as retinal hemorrhages known as Roth spots [29]. In advanced stages of infective endocarditis, especially when directly infected by *Staphylococcus aureus* (*S. aureus*), ocular infections may occur, leading to conditions like endophthalmitis. This inflammatory condition affects the vitreous and aqueous humor of the eye, causing discomfort and visual disturbances [30].

While *S. aureus* is the most common bacterial agent associated with infective endocarditis [31], tuberculous endocarditis represents a rare and intriguing variation of this condition, which warrants further exploration. Tuberculous endocarditis, much like other bacterial agents, leverages a similar pathophysiological mechanism to infect valvular structures of the heart [32]. Despite tuberculosis posing a significant global health threat, there are documented case reports that shed light on the signs and symptoms characteristic of TB endocarditis. For example, one patient with TB endocarditis displayed significant calcification and granulomas on the anterior mitral leaflet [33]. Another case involved a 17-year-old girl who was diagnosed with infec-

tive endocarditis via transthoracic echocardiography [34]. Her examination revealed that she was tachycardic, tachypneic, hypotensive, and febrile [34]. The echocardiogram indicated the presence of large vegetations on both mitral valve leaflets, with dimensions of 32 × 15 mm on the posterior mitral leaflet [34]. Additionally, vegetations were observed on the septal leaflet of the tricuspid valve and the aortic valve, along with moderate acute and chronic inflammation, fibrin, and granulation tissue formation, alongside granulomas. The mitral valve displayed focal necrosis with calcification, characterized by typical epithelioid cells and multinucleated giant cells. This case serves as an illustrative example of infective endocarditis and the accompanying severe aortic regurgitation. The confirmation of tuberculosis was made through histopathological analysis of the vegetation [34]. It's essential to note that valvular endocarditis attributed to Mycobacterium tuberculosis is exceedingly rare and is typically reported within the context of miliary tuberculosis. For instance, Cope *et al*. [35] reported a case of disseminated tuberculosis that was accompanied by echocardiographically documented aortic valvulitis. This condition was resolved through anti-tuberculous therapy. Moreover, three cases of right-sided tuberculous endocarditis have been observed in individuals who were intravenous drug abusers with HIV and had disseminated tuberculosis. The histopathological evaluation of these cases indicated the presence of endocardial miliary tubercles, polypoidal tubercles resembling myxomas, nodules on valves, and thrombi containing entrapped tubercle bacilli. Interestingly, there are no reports in the literature of valvular endocarditis attributed to Mycobacterium tuberculosis occurring independently of miliary tuberculosis in immunocompetent patients [34]. Recent cases have even involved infants presenting with intracardiac tuberculomas in the context of miliary tuberculosis [36]. In some instances, the right atrium has also been found to be involved in cases of TB endocarditis [37]. Nevertheless, due to the slow growth rate of mycobacteria, the diagnosis and assessment of Mycobacterial endocarditis can be challenging to achieve prior to death, contributing to the limited understanding of its pathophysiology [38].

In conclusion, endocarditis is a complex condition with infective endocarditis presenting as a multifaceted ailment that significantly impacts heart valves and can lead to widespread, systemic complications. While *Staphylococcus aureus* is the primary causative agent for infective endocarditis, tuberculous endocarditis represents a rare variant of this condition, necessitating further research to enhance our comprehension of this intricate medical phenomenon.

## Atypical Mycobacteria Endocarditis.

Endocarditis is traditionally associated with bacterial species like Staphylococcus and Streptococcus. However, atypical mycobacteria have emerged as rare yet critical contributors to life-threatening mycobacterial endocarditis. Noteworthy species among these atypical mycobacteria include Mycobacterium chimaera (M.chimaera), Mycobacterium fortuitum (M.fortuitum), and Mycobacterium chelonae (M.chelonae), which have been linked to endocarditis [39] (Table 1). These species are generally categorized as opportunistic pathogens and are commonly associated with immunocompromised individuals and those with pre-existing cardiac conditions. Atypical mycobacteria can be found in various natural reservoirs, including soil, domestic and wild animals, water, food products, and even sewage [39]. Previous research indicates that atypical mycobacteria can produce biofilms, which enhance their resistance to antimicrobial agents. However, further studies are necessary to fully comprehend the implications of these species in the disease process [39].

**Table 1. Types of Atypical Mycobacterial species.**

| Non-tuberculous (Atypical) Mycobacteria | |
|---|---|
| Rapid Growing | Slow Growing |
| M.chelonae | M.avium complex |
| M.fortuitum | M.intracellulare |
| M.marinum | M.chimaera |
| M.uclerans | M.haemophilum |
| M.chelonae-abscessus complex | M.xenopi |
| M.abscessus subsp.massiliense | M.kanasasii |
| M.absessus subsp. bolletii | M.simiae |
| M.smeqmatis | M.terrae complex |
| M.vaccae | M.gordonae |
| | M.tuberculosis complex |
| | M.leprae |
| | M.marinum |
| | M.uclerans |
| Key Opportunistic Pathogens | Saprophytes True Pathogens |

Endocarditis caused by M.chimaera has shown a strong association with a history of heart valve surgery. Typically, M.chimaera is known to primarily cause pulmonary disease; however, recent cases have revealed it as a cause of prosthetic valve endocarditis following heart valve surgery [37]. Public Health England (PHE) has identified that M.chimaera can lead to severe infections in a small portion of patients following cardiac surgery. The UK, in collaboration with various international organizations, has linked these infections to contaminated heater-cooler units (HCUs) used during cardiopulmonary bypass surgery [38]. The European Center for Disease Prevention and Control (ECDC) reported 52 cases of invasive cardiovascular infections caused by M.chimaera. These cases involved patients who had previously undergone open-heart surgery in seven European countries since 2011 [38]. M.chimaera can exhibit long latency periods following cardiothoracic surgery, with the time between surgery and symptom development varying from 2 to 58 months [38]. A Swiss investigative

team identified the source of M.chimaera during the years 2014–2015. They determined that the bacterium originated from the 3T HCU of cardiopulmonary bypass equipment, which transmitted the bacteria to the surgical site via contaminated water [38]. Invasive Mycobacterium chimaera infections after open-heart surgery have been reported internationally and are associated with aerosols generated by contaminated HCUs used during surgery [39]. M.chimaera is now recognized as an emerging pathogen causing severe infections of heart valve prostheses, vascular grafts, and disseminated infections after open-heart surgery [40]. A study has identified aerosol release through breaches in heater-cooler tanks, leading to the recovery of Mycobacterium chimaera and other pathogens from water and air samples [41].

Additional reports of endocarditis have established a clear link between M.chelonae and patients with a history of heart disease. In one case report, an immunocompromised patient was diagnosed with disseminated M.chelonae infection following pacemaker-lead endocarditis [42]. The patient had experienced persistent pacemaker malfunction, necessitating multiple replacements, which increased the risk of infection. Notably, this was the first reported case of pacemaker-lead endocarditis due to M.chelonae, and the patient achieved full recovery following a brief period of combination therapy [42]. In another case report, an immunocompromised patient with a history of rheumatic heart disease was diagnosed with endocarditis despite having no prior history of heart disease, recent surgery, or skin infection. The patient fell ill after developing cerebral infarction due to embolization from the aortic valve [43].

Similar associations have been observed in endocarditis cases related to M.fortuitum. For instance, a patient with a history of mitral valve replacement eight years prior was diagnosed with M.fortuitum pulmonic valve endocarditis [44]. Another patient with a surgical history of cardioverter-defibrillator implantation was diagnosed with native valve endocarditis and M.fortuitum pacemaker infection [45]. A Serbian study found that three children received combination treatment for M. fortuitum-related endocarditis shortly after cardiac surgery [46]. These studies, along with others, suggest that individuals with a history of cardiac surgery and pre-existing cardiac conditions face a heightened risk of developing atypical mycobacterial endocarditis.

Table 1 shows the different types of mycobacterial species, which belong to three categories, opportunistic, true pathogenic, and Saprophytes. Opportunistic species, like M.chelonae, are usually not infective in healthy adults and can cause pathology in immunocompromised individuals. True pathogens, such as M.leprae, come equipped with infective properties and can cause disease in healthy and immunocompromised individuals. Saprophytes, like M.gordonae, obtain their nutrition from dissolved organic materials and can usually cause disease in immunocompromised individuals only. Besides, atypical mycobacterium species can be classified as rapid-growing or slow-growing, which can be Saprophytic, true pathogenic, or opportunistic.

## Clinical Presentation and Complications of M.tb Endocarditis

### *Clinical Presentation*

Tuberculosis (TB) stands as a persistent global health threat and has been a leading cause of mortality worldwide. It held the grim distinction of being the single most significant cause of death attributed to a single infectious agent until the recent emergence of the SARS-CoV-2 virus, which has overshadowed it in terms of global impact [47]. An estimated one-quarter of the world's population is believed to have been exposed to Mycobacterium tuberculosis (M.tb), the causative agent of TB. However, only a small fraction of individuals exposed to M.tb will progress to develop symptomatic disease and become capable of transmitting the infection to others [47]. In the absence of treatment, TB carries a high mortality rate, estimated at approximately 50 percent [47]. However, the prolonged duration of TB treatment introduces concerns related to patient compliance, healthcare coverage, and the emergence of drug-resistant forms of the disease [48–50].

From an epidemiological perspective, M.tb can infect virtually any organ within the human body, including the intestines, meninges, lymph nodes, heart, kidneys, bones, joints, skin, and lungs [51,52]. In all forms of M.tb disease, the infection can enter a prolonged latency phase before becoming active, symptomatic, and potentially transmissible [52]. Pulmonary TB, which is responsible for the majority of M.tb cases (85 percent), presents with a spectrum of symptoms. The most common symptoms include chronic productive cough, hemoptysis, fever, night sweats, loss of appetite, fatigue, weight loss, and malaise [53]. Pulmonary TB can co-occur with various conditions such as lymphadenitis, kidney involvement, bone and joint infections, meningitis, or miliary disease [52].

M.tb endocarditis, on the other hand, is a rare form of extra-pulmonary TB in which M.tb infects the inner lining of the heart, primarily around the heart valves [50]. Cases of M.tb endocarditis are often superimposed on other extra-pulmonary TB forms, notably miliary TB disease. The diagnostic challenge lies in the fact that the symptoms of miliary TB may overshadow the presence of concurrent endocarditis. Remarkably, in older case reports dating back to the early 1900s, the diagnosis of endocarditis was frequently established during autopsies after patients had succumbed to miliary TB [50,54,55]. The clinical presentation of M.tb endocarditis typically mirrors the symptoms of miliary TB disease, featuring common manifestations such as fever, chest pain, dyspnea, and cardiac murmurs [50,56] (Fig. 3). TB endocarditis rarely co-occurs with symptoms

of other cardiovascular diseases, like pericarditis, which may involve severe chest pain upon coughing and breathing [50]. Recent case reports have unveiled instances of TB endocarditis during surgical procedures on both native and prosthetic heart valves. These cases were characterized by the presence of valvular vegetations, later histologically confirmed to contain M.tb within cardiac tissue [50,51]. Unlike pulmonary TB, sputum testing is not a reliable diagnostic tool for M.tb endocarditis. The M.tb infection is confined to the patient's blood and cardiac tissue, rendering the presence of bacteria in sputum unlikely unless pulmonary symptoms co-occur with endocarditis, which is a rare scenario [50]. Additionally, it is important to note that Myocardial endocarditis is only contagious when accompanied by pulmonary symptoms [50,57].

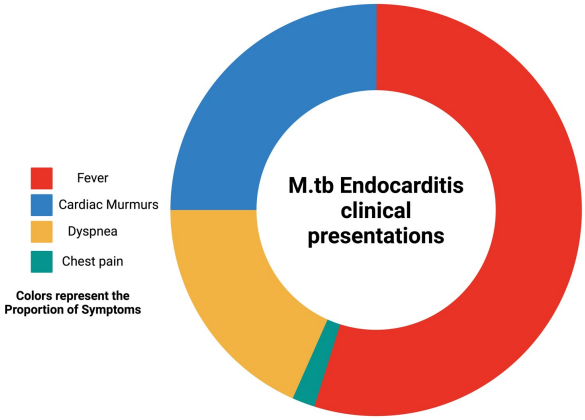


**Fig. 3. Clinical Symptoms of Infective TB Endocarditis.** Fig. 3 shows the most common clinical manifestations of M.tb endocarditis, ordered from most common to least common, including fever, cardiac murmurs, Dyspnea, and chest pain. (The figure was created by Biorender. https://www.biorender.com/).

### *Complications of M.tb Endocarditis*

A major concern in the management of M.tb endocarditis is the emergence and increasing prevalence of drug-resistant TB variants. The World Health Organization (WHO) has classified these variants as isoniazid-resistant TB, multi-drug-resistant TB, and extensively drug-resistant TB [47]. The growing prevalence of drug-resistant forms poses a significant challenge in treating various TB presentations. TB endocarditis is often complicated by co-infection with other diseases, particularly HIV. HIV infection impairs the immune system, making it more susceptible to TB, and extra-pulmonary TB variants, including TB endocarditis, are notably more common in patients with both TB and HIV. A study suggests that TB endocarditis should be considered a possibility in all patients with HIV and valvular heart disease [57]. Sepsis, a potentially fatal complication, is more common in individuals with compromised immune systems, further complicating the diagnosis and treatment of TB endocarditis [58,59]. Some cases of M.tb endocarditis may present with massive hemoptysis, a complication arising from M.tb reaching the blood supply in the lungs, specifically in the bronchial or pulmonary systems [59]. Chronic complications, such as valvular tissue scarring, lung airway and parenchymal damage, bronchiectasis, chronic obstructive pulmonary disease (COPD), and aspergillomas, may persist even after the effective clearance of the TB infection from the patient's system [58,59].

## Environmental and Genetic Predispositions to M.tb Endocarditis

The interplay between various factors, including genetics and environmental predispositions, can result in increased susceptibility to the development of M.tb infections. Many genes have a vital role in the immune system's overall efficacy of the body's response when encountering a pathogen, such as M.tb. Previous research has demonstrated polymorphisms in human leukocyte class II genes (*HLA*), specifically *HLA-DRB1*14*, have been associated with higher susceptibility to M.tb, as these genetic variations were more prevalent in patients with active M.tb infections [60]. Additionally, polymorphisms of the toll-like receptor (*TLR2*) gene in Moroccan populations were associated with increased susceptibility to TB, as the TLR signaling pathway is responsible for the body's ability to recognize and combat M.tb infection [61,62]. Patients with the homozygous genotype of the Arg753Gln polymorphism in the *TLR2* gene have nearly a 6-fold higher risk of developing M.tb [63]. Genetic variability in the immune response contributes to the predisposition to acquiring diseases such as M.tb.

Vitamin D receptor genes are also heavily involved in the innate immune system, and the FokI-FF polymorphism, in conjunction with Vitamin D deficiency (measured through plasma vitamin D levels), showed a higher risk for M.tb infections [64]. Single nucleotide polymorphisms (SNPs) in specific cytokine genes are highly associated with M.tb infection risk. The G-308A variant in the promoter region of the *TNF-*$\alpha$ gene has been shown to affect the downstream signaling of the pro-inflammatory response related to M.tb [65]. Similarly, other SNPs in IL-10 (–1082 G/A) and IFN-g (+874 T/A) have been associated with the development of M.tb infections, as they alter the levels of these cytokines, which play a vital role in the regulation of a healthy immune response [65,66].

One study demonstrated patterns of inheritance, as those residing in densely populated regions rampant with M.tb developed a resistance to the disease. In contrast, those more susceptible to developing M.tb had ancestors from M.tb-free regions [67]. In addition, twin studies have also played a vital role in proving host gene prevalence, with higher incidence seen in monozygotic twins [68].

Several environmental factors have contributed to the development of M.tb infections over time. A prior epidemiological study has shown a correlation between overcrowding, homelessness, and urbanization with higher rates of M.tb infection [69]. Sociodemographic studies performed in Malaysia showed a higher rate of M.tb cases in prisons, as they involved dense inmates in poorly ventilated environments with drug addicts, HIV carriers, and other high-risk groups [70]. Understanding predisposing environmental factors that harbor higher M.tb infection rates will help provide information regarding which populations require a higher priority for TB screening and control.

Infectious endocarditis is an inflammation resulting from a bacterial infection within the inner lining of the heart chambers and valves [71] (Fig. 2). Individuals with weakened immune systems, possibly due to SNPs, are at a higher risk of developing extra-pulmonary TB, including TB endocarditis. In a case study, a patient presented with findings of M.tb infection but received a negative M.tb test result. This led clinicians to consider extra-pulmonary screening to identify better and treat blood culture-negative infective endocarditis [72]. SNPs within *TLR2*, specifically R753Q, which were previously associated with M.tb infections, also increased susceptibility to infective endocarditis [62]. Another case study of a patient in Nepal demonstrates how environmental risk factors, including intravenous drug use, smoking, and heavy alcohol use, can increase the risk of infective endocarditis due to M.tb [66]. A 19-month-old from a developing country, newly diagnosed with HIV, had a unique presentation of focal neurological deficits as a symptom of extra-pulmonary TB [73]. The immunocompromised environment of HIV and the predisposition of limited access to care increase the risk of conditions such as infective endocarditis [73]. Currently, there is limited research regarding the genetic and environmental predispositions contributing directly to TB endocarditis, so the generalizability of case study results cannot be applied.

## Treatment Options (Including Current and Future Perspective) of M.tb Endocarditis

### *Current Treatment Protocol*

Designing and testing an effective treatment protocol for M.tb endocarditis presents inherent challenges. Studies are typically conducted retrospectively, and they often encompass mixed clinical presentations [74]. Because M.tb endocarditis is relatively rare, treatment protocols are typically extrapolated from the historical success of managing pulmonary or miliary TB [75]. The current treatment regimen relies on a combination therapy involving four drugs: isoniazid, rifampicin, ethambutol, and pyrazinamide, with distinct dosages for initial and continuation phases [74]. Dosages may vary, but successful outcomes have been reported with ethambutol (20 mg/kg/day), isoniazid (10 mg/kg/day), pyrazinamide (25 mg/kg/day), and rifampicin (10 mg/kg/day). The treatment duration extends to six months if the pathogen is confirmed as M.tb culture-positive. In cases where pyrazinamide was initially omitted, the treatment duration should be extended to nine months [76]. In select instances, only isoniazid and rifampicin are retained for the continuation phase, which is typically of an extended duration; moreover, anti-TB treatment is extended to 12 months in most scenarios [76]. Due to the slow growth rate of M.tb and the unreliability of blood culture sensitivity, the initial phase frequently commences before pathogen confirmation is available [71]. An Xpert MTB/RIF assay may be conducted to assess rifampin resistance, thereby aiding in preventing overtreatment and averting the development of drug-resistant infections.

### *Future Perspective*

DNA gyrase, a type II topoisomerase enzyme crucial for DNA processes in M.tb, is inhibited to induce bacterial death. This inhibition, crucial for transcription, replication, and recombination, leads to permanent double-strand breaks and the accumulation of cleaved DNA fragments [77]. Chemical entities targeting GyrB, especially aminobenzimidazoles, exhibit potent activity against drug-resistant TB [78]. The optimization of these entities led to the development of SPR720, representing a novel class of GyrB inhibitors [78]. This discovery underscores the potential for GyrB as a target for tackling drug-resistant TB and introduces SPR720 as a promising candidate in this regard [78].

The diarylquinoline bedaquiline (BDQ), a recently approved anti-TB drug, inhibits the c subunit of mycobacterial Adenosine Triphosphate (ATP) synthase, disrupting energy metabolism and reducing intracellular ATP levels in M.tb [79,80]. However, BDQ poses challenges due to potent inhibition of the human ether-a-go-go-related gene (hERG) cardiac potassium channel, associated with QT prolongation and arrhythmia, leading to a black box warning [81]. To address these issues, next-generation lead optimization aimed at reducing lipophilicity and cardiotoxicity was initiated, resulting in the identification of two compounds, TBAJ-587 and TBAJ-876 [81]. In animal models, TBAJ-587 demonstrates better efficacy than BDQ, while TBAJ-876 shows comparable activity. Importantly, the hERG inhibitory activities of TBAJ-587 and TBAJ-876 are lower than BDQ [82]. Both compounds are currently in Phase I clinical trials [78]. These developments highlight promising alternatives to BDQ with improved safety profiles and enhanced anti-TB efficacy [83].

The cytochrome b subunit (QcrB) of the cytochrome bc1 complex in M.tb has emerged as a target, and imidazopyridine amides (IPAs) were identified through phenotypic screening as potent inhibitors of QcrB [84]. Q203, an optimized IPA derivative, exhibited strong growth inhibition against DS M.tb H37Rv strain (MIC50 = 2.7 nM) and MDR/XDR M.tb clinical isolates (MIC90 <0.43 nM

for most DR strains) [84]. It demonstrated minimal cytotoxicity, good tolerance in mice, and low risk of cardiotoxicity, advancing into Phase II clinical trials (Telacebec) [84]. Another QcrB inhibitor, TB47, a pyrazolo [1,5-a] pyridine-3-carboxamide derivative, showed potent anti-TB activities against various M.tb clinical isolates [85]. TB47 displayed promising pharmacokinetics (PK) and toxicity profiles, synergizing with pyrazinamide (PZA) and RIF in mouse infection models, suggesting potential efficacy in combination therapies [85]. These compounds present valuable candidates targeting QcrB, showcasing both potent anti-TB activities and favorable safety profiles [84,85].

## Conclusion

The diagnosis and assessment of tuberculous endocarditis present significant challenges, mainly due to the slow growth rate of mycobacterial agents, leading to a limited understanding of its pathophysiology. Despite the infrequency of mycobacterial endocarditis, its prognosis can be severe. The intrinsic resistance of mycobacterial species to various antimicrobial agents complicates treatment, emphasizing the need for prompt and precise therapeutic interventions. Further investigations are crucial to refine treatment strategies and achieve accurate differential diagnoses, especially considering the potential involvement of atypical mycobacterial species. Given the challenges in treating mycobacterial endocarditis, there is a pressing need for extensive research efforts to explore preventive measures. This includes the development of an enhanced tuberculosis vaccine. Additionally, gaining comprehensive insights into the synergistic interplay between genetic predispositions and environmental factors influencing Mycobacterium tuberculosis (M.tb) infections and infectious endocarditis holds promise. This knowledge can pave the way for more personalized approaches to clinical diagnosis, management, and prevention. Overall, addressing these challenges requires a multidisciplinary effort to enhance our understanding and develop effective strategies for tackling mycobacterial endocarditis.

## Author Contributions

Conceptualization, VV, JD, SA, AC, YM, AM, BN, JO, SY; software, JD; investigation, JD; writing—original draft preparation, JD, SA, AC, YM, AM, BN, JO, SY, VV; writing—review and editing, JD, SA, VV; visualization, JD; supervision, VV; project administration, VV and JD; All authors have read and agreed to the published version of the manuscript. All authors agree to be accountable for all aspects of the manuscript.

## Ethics Approval and Consent to Participate

Not applicable.

## Acknowledgment

Not applicable.

## Funding

This research received no external funding.

## Conflict of Interest

The authors declare no conflict of interest.

## References

[1] Heemskerk D, Caws M, Marais B, Farrar J. Tuberculosis in Adults and Children. 2015. Available at: https://www.ncbi.nlm.nih.gov/books/NBK344402/ (Accessed: 28 July 2023).

[2] World Health Organization. WHO & World Health Organization: WHO. 2023. Available at: https://www.who.int/news-room/fact-sheets/detail/tuberculosis (Accessed: 5 July 2023).

[3] López-López JP, Posada-Martínez EL, Saldarriaga C, Wyss F, Ponte-Negretti CI, Alexander B, *et al*. Tuberculosis and the Heart. Journal of the American Heart Association. 2021; 10: e019435.

[4] Maison DP. Tuberculosis pathophysiology and anti-VEGF intervention. Journal of Clinical Tuberculosis and other Mycobacterial Diseases. 2022; 27: 100300.

[5] Chai Q, Zhang Y, Liu CH. *Mycobacterium tuberculosis*: An Adaptable Pathogen Associated With Multiple Human Diseases. Frontiers in Cellular and Infection Microbiology. 2018; 8: 158.

[6] O'Garra A, Redford PS, McNab FW, Bloom CI, Wilkinson RJ, Berry MPR. The immune response in tuberculosis. Annual Review of Immunology. 2013; 31: 475–527.

[7] Davis AG, Rohlwink UK, Proust A, Figaji AA, Wilkinson RJ. The pathogenesis of tuberculous meningitis. Journal of Leukocyte Biology. 2019; 105: 267–280.

[8] Ferraris DM, Miggiano R, Rossi F, Rizzi M. Mycobacterium tuberculosis Molecular Determinants of Infection, Survival Strategies, and Vulnerable Targets. Pathogens (Basel, Switzerland). 2018; 7: 17.

[9] Hossain MM, Norazmi MN. Pattern recognition receptors and cytokines in Mycobacterium tuberculosis infection–the double-edged sword? BioMed Research International. 2013; 2013: 179174.

[10] Lopez-Castejon G, Brough D. Understanding the mechanism of IL-1β secretion. Cytokine & Growth Factor Reviews. 2011; 22: 189–195.

[11] Ndlovu H, Marakalala MJ. Granulomas and Inflammation: Host-Directed Therapies for Tuberculosis. Frontiers in Immunology. 2016; 7: 434.

[12] Salina EG, Makarov V. *Mycobacterium tuberculosis* Dormancy: How to Fight a Hidden Danger. Microorganisms. 2022; 10: 2334.

[13] Ramakrishnan L. Revisiting the role of the granuloma in tuberculosis. Nature Reviews. Immunology. 2012; 12: 352–366.

[14] Luies L, du Preez I. The Echo of Pulmonary Tuberculosis: Mechanisms of Clinical Symptoms and Other Disease-Induced Systemic Complications. Clinical Microbiology Reviews. 2020; 33: e00036-20.

[15] Sharma SK, Mohan A, Sharma A. Miliary tuberculosis: A new look at an old foe. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases. 2016; 3: 13–27.

[16] Holland TL, Baddour LM, Bayer AS, Hoen B, Miro JM, Fowler

VG, Jr. Infective endocarditis. Nature Reviews. Disease Primers. 2016; 2: 16059.
[17] McDevitt D, Francois P, Vaudaux P, Foster TJ. Molecular characterization of the clumping factor (fibrinogen receptor) of Staphylococcus aureus. Molecular Microbiology. 1994; 11: 237–248.
[18] Sullam PM, Drake TA, Sande MA. Pathogenesis of endocarditis. The American Journal of Medicine. 1985; 78: 110–115.
[19] Chu V. Pathogenesis of vegetation formation in infective endocarditis. 2023. Available at: https://www.uptodate.com/contents/pathogenesis-of-vegetation-formation-in-infective-endocarditis (Accessed: 31 July 2023).
[20] Yao L, Berman JW, Factor SM, Lowy FD. Correlation of histopathologic and bacteriologic changes with cytokine expression in an experimental murine model of bacteremic Staphylococcus aureus infection. Infection and Immunity. 1997; 65: 3889–3895.
[21] Bayer AS, Theofilopoulos AN, Eisenberg R, Dixon FJ, Guze LB. Circulating immune complexes in infective endocarditis. The New England Journal of Medicine. 1976; 295: 1500–1505.
[22] Manzano MC, Vilacosta I, San Román JA, Aragoncillo P, Sarriá C, López D, *et al*. Acute coronary syndrome in infective endocarditis. Revista Espanola De Cardiologia. 2007; 60: 24–31.
[23] Stawicki SP, Firstenberg MS, Lyaker MR, Russell SB, Evans DC, Bergese SD, *et al*. Septic embolism in the intensive care unit. International Journal of Critical Illness and Injury Science. 2013; 3: 58–63.
[24] Miró JM, del Río A, Mestres CA. Infective endocarditis and cardiac surgery in intravenous drug abusers and HIV-1 infected patients. Cardiology Clinics. 2003; 21: 167–184, v–vi.
[25] Parashar K, Daveluy S. Osler Node and Janeway lesions. 2023. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32491553 (Accessed: 1 January 2023)
[26] Von Gemmingen GR, Winkelmann RK. Osler's node of subacute bacterial endocarditis. Focal necrotizing vaculitis of the glomus body. Archives of Dermatology. 1967; 95: 91–94.
[27] Brown SL, Busuttil RW, Baker JD, Machleder HI, Moore WS, Barker WF. Bacteriologic and surgical determinants of survival in patients with mycotic aneurysms. Journal of Vascular Surgery. 1984; 1: 541–547.
[28] Duval X, Iung B, Klein I, Brochet E, Thabut G, Arnoult F, *et al*. Effect of early cerebral magnetic resonance imaging on clinical decisions in infective endocarditis: a prospective study. Annals of Internal Medicine. 2010; 152: 497–504, W175.
[29] Loughrey PB, Armstrong D, Lockhart CJ. Classical eye signs in bacterial endocarditis. QJM: Monthly Journal of the Association of Physicians. 2015; 108: 909–910.
[30] Okada AA, Johnson RP, Liles WC, D'Amico DJ, Baker AS. Endogenous bacterial endophthalmitis. Report of a ten-year retrospective study. Ophthalmology. 1994; 101: 832–838.
[31] Ji Y, Kujtan L, Kershner D. Acute endocarditis in intravenous drug users: a case report and literature review. Journal of Community Hospital Internal Medicine Perspectives. 2012; 2: 10.3402/jchimp.v2i1.11513.
[32] Liu A, Nicol E, Hu Y, Coates A. Tuberculous endocarditis. International Journal of Cardiology. 2013; 167: 640–645.
[33] Klingler K, Brändli O, Doerfler M, Schluger N, Rom WN. Valvular endocarditis due to Mycobacterium tuberculosis. The International Journal of Tuberculosis and Lung Disease: the Official Journal of the International Union against Tuberculosis and Lung Disease. 1998; 2: 435–437.
[34] Shaikh Q, Mahmood F. Triple valve endocarditis by mycobacterium tuberculosis: a case report. BMC Infectious Diseases. 2012; 12: 231.
[35] Cope AP, Heber M, Wilkins EG. Valvular tuberculous endocarditis: a case report and review of the literature. The Journal of Infection. 1990; 21: 293–296.
[36] Cantinotti M, De Gaudio M, de Martino M, Assanta N, Moschetti R, Veneruso G, *et al*. Intracardiac left atrial tuberculoma in an eleven-month-old infant: case report. BMC Infectious Diseases. 2011; 11: 359.
[37] Adefuye MA, Manjunatha N, Ganduri V, Rajasekaran K, Duraiyarasan S, Adefuye BO. Tuberculosis and Cardiovascular Complications: An Overview. Cureus. 2022; 14: e28268.
[38] Sogabe O, Ohya T. A case of tuberculous endocarditis with acute aortic valve insufficiency and annular subvalvular left ventricular aneurysm. General Thoracic and Cardiovascular Surgery. 2007; 55: 61–64.
[39] Faria S, Joao I, Jordao L. General Overview on Nontuberculous Mycobacteria, Biofilms, and Human Infection. Journal of Pathogens. 2015; 2015: 809014.
[40] Tortoli E, Rindi L, Garcia MJ, Chiaradonna P, Dei R, Garzelli C, *et al*. Proposal to elevate the genetic variant MAC-A, included in the Mycobacterium avium complex, to species rank as Mycobacterium chimaera sp. nov. International Journal of Systematic and Evolutionary Microbiology. 2004; 54: 1277–1285.
[41] Dalvi S, Das P. Prosthetic heart valve surgery and potential risk of -developing Mycobacterium chimaera endocarditis. Clinical Medicine (London, England). 2018; 18: 301–303.
[42] Hooda A, Pati PK, John B, George PV, Michael JS. Disseminated Mycobacterium chelonae infection causing pacemaker lead endocarditis in an immunocompetent host. BMJ Case Reports. 2014; 2014: bcr2014206042.
[43] Jagadeesan N, Patra S, Singh AP, Nagesh CM, Reddy B, Badnur SC, *et al*. Spontaneous endocarditis caused by rapidly growing non-tuberculous Mycobacterium chelonae in an immunocompetent patient with rheumatic heart disease. Journal of Cardiovascular Disease Research. 2013; 4: 254–256.
[44] Mulhall AM, Hebbeler-Clark RS. Native Pulmonic Valve Endocarditis due to Mycobacterium fortuitum: A Case Report and Literature Review. Case Reports in Infectious Diseases. 2015; 2015: 274819.
[45] Al Zoubi M, Cheng J, Dontaraju VS, Evans CE, Spier AB. Native valve endocarditis and pacemaker infection with Mycobacterium fortuitum. IDCases. 2021; 25: e01200.
[46] Vuković D, Parezanović V, Savić B, Dakić I, Laban-Nestorović S, Ilić S, *et al*. Mycobacterium fortuitum endocarditis associated with cardiac surgery, Serbia. Emerging Infectious Diseases. 2013; 19: 517–519.
[47] Bagcchi S. WHO's Global Tuberculosis Report 2022. The Lancet. Microbe. 2023; 4: e20.
[48] Kruk ME, Schwalbe NR, Aguiar CA. Timing of default from tuberculosis treatment: a systematic review. Tropical Medicine & International Health: TM & IH. 2008; 13: 703–712.
[49] Chiang CY, Van Weezenbeek C, Mori T, Enarson DA. Challenges to the global control of tuberculosis. Respirology (Carlton, Vic.). 2013; 18: 596–604.
[50] Dheda K, Barry CE III, Maartens G. Tuberculosis. Lancet (London, England). 2016; 387: 1211–1226.
[51] Acharya B, Acharya A, Gautam S, Ghimire SP, Mishra G, Parajuli N, *et al*. Advances in diagnosis of Tuberculosis: an update into molecular diagnosis of Mycobacterium tuberculosis. Molecular Biology Reports. 2020; 47: 4065–4075.
[52] Barry CE, 3rd, Boshoff HI, Dartois V, Dick T, Ehrt S, Flynn J, *et al*. The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. Nature Reviews. Microbiology. 2009; 7: 845–855.
[53] Adigun R, Singh R. Tuberculosis. 2023. Available at: https://www.ncbi.nlm.nih.gov/books/NBK441916/ (Accessed: 11 July 2023).
[54] World Health Organization. Global Tuberculosis Report 2017.

2017. Available at: https://www.who.int/publications/i/item/9789241565516 (Accessed: 31 July 2023).
[55] David HL. Bacteriology of the mycobacterioses. U.S. Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, Bureau of Laboratories, Bacteriology Division, Mycobacteriology Branch: Washington. 1976.
[56] Fumagalli J, Bonifacio C, Gulotta H, Shinzato R, Troncoso A. Bacterial endocarditis: a role for Mycobacterium tuberculosis? AIDS (London, England). 2002; 16: 1845–1846.
[57] Murray PR, Rosenthal KS, Pfaller MA. Medical Microbiology. 9th Edn. Elsevier Health Sciences: United States. 2020.
[58] Gholoobi A, Masoudi-Kazemabad A, Meshkat M, Meshkat Z. Comparison of Culture and PCR Methods for Diagnosis of Mycobacterium tuberculosis in Different Clinical Specimens. Jundishapur Journal of Microbiology. 2014; 7: e8939.
[59] Meek WO. Tuberculous Endocarditis. Proceedings of the Royal Society of Medicine. 1908; 1: 116–123.
[60] Dheda K, Booth H, Huggett JF, Johnson MA, Zumla A, Rook GAW. Lung remodeling in pulmonary tuberculosis. The Journal of Infectious Diseases. 2005; 192: 1201–1209.
[61] Shah M, Reed C. Complications of tuberculosis. Current Opinion in Infectious Diseases. 2014; 27: 403–410.
[62] Sultan FAT, Fatimi S, Jamil B, Moustafa SE, Mookadam F. Tuberculous endocarditis: valvular and right atrial involvement. European Journal of Echocardiography: the Journal of the Working Group on Echocardiography of the European Society of Cardiology. 2010; 11: E13.
[63] Duarte R, Carvalho C, Pereira C, Bettencourt A, Carvalho A, Villar M, *et al*. HLA class II alleles as markers of tuberculosis susceptibility and resistance. Revista Portuguesa De Pneumologia. 2011; 17: 15–19.
[64] Arji N, Busson M, Iraqi G, Bourkadi JE, Benjouad A, Bouayad A, *et al*. Genetic diversity of TLR2, TLR4, and VDR loci and pulmonary tuberculosis in Moroccan patients. Journal of Infection in Developing Countries. 2014; 8: 430–440.
[65] Bustamante J, Tamayo E, Flórez S, Telleria JJ, Bustamante E, López J, *et al*. Toll-like receptor 2 R753Q polymorphisms are associated with an increased risk of infective endocarditis. Revista Espanola De Cardiologia. 2011; 64: 1056–1059.
[66] Ogus AC, Yoldas B, Ozdemir T, Uguz A, Olcen S, Keser I, *et al*. The Arg753GLn polymorphism of the human toll-like receptor 2 gene in tuberculosis disease. The European Respiratory Journal. 2004; 23: 219–223.
[67] Rashedi J, Asgharzadeh M, Moaddab SR, Sahebi L, Khalili M, Mazani M, *et al*. Vitamin d receptor gene polymorphism and vitamin d plasma concentration: correlation with susceptibility to tuberculosis. Advanced Pharmaceutical Bulletin. 2014; 4: 607–611.
[68] Adane G, Lemma M, Geremew D, Sisay T, Tessema MK, Damtie D, *et al*. Genetic Polymorphism of Tumor Necrosis Factor-Alpha, Interferon-Gamma and Interleukin-10 and Association With Risk of Mycobacterium Tuberculosis Infection. Journal of Evidence-based Integrative Medicine. 2021; 26: 2515690X211006344.
[69] Rajkarnikar R, Sharma S, Yadav S, Ghimire N. Culture-negative tricuspid valve endocarditis in an intravenous drug abuser masquerading as pulmonary tuberculosis in Nepal: a case report. Annals of Medicine and Surgery (2012). 2023; 85: 523–527.
[70] Stead WW. Genetics and resistance to tuberculosis. Could resistance be enhanced by genetic engineering? Annals of Internal Medicine. 1992; 116: 937–941.
[71] Sia IG, Wieland ML. Current concepts in the management of tuberculosis. Mayo Clinic Proceedings. 2011; 86: 348–361.
[72] Lienhardt C. From exposure to disease: the role of environmental factors in susceptibility to and development of tuberculosis. Epidemiologic Reviews. 2001; 23: 288–301.
[73] Mohidem NA, Osman M, Hashim Z, Muharam FM, Mohd Elias S, Shaharudin R. Association of sociodemographic and environmental factors with spatial distribution of tuberculosis cases in Gombak, Selangor, Malaysia. PloS one. 2021; 16: e0252146.
[74] Kamde SP, Anjankar A. Pathogenesis, Diagnosis, Antimicrobial Therapy, and Management of Infective Endocarditis, and Its Complications. Cureus. 2022; 14: e29182.
[75] Bernando J. Clinical manifestations, diagnosis, and treatment of miliary tuberculosis. 2017. Available at: https://medilib.ir/uptodate/show/8024 (Accessed: 1 July 2023).
[76] Vohra, S. Miliary tuberculosis. 2023. Available at: https://www.ncbi.nlm.nih.gov/books/NBK562300/ (Accessed: 15 April 2023).
[77] Bruch EM, Pétrella S, Bellinzoni M. Structure-Based drug design for tuberculosis: Challenges still ahead. Applied Sciences. 2020; 10: 4248.
[78] Locher CP, Jones SM, Hanzelka BL, Perola E, Shoen CM, Cynamon MH, *et al*. A novel inhibitor of gyrase B is a potent drug candidate for treatment of tuberculosis and nontuberculosis mycobacterial infections. Antimicrobial Agents and Chemotherapy. 2015; 59: 1455–1465.
[79] Koul A, Dendouga N, Vergauwen K, Molenberghs B, Vranckx L, Willebrords R, *et al*. Diarylquinolines target subunit c of mycobacterial ATP synthase. Nature Chemical Biology. 2007; 3: 323–324.
[80] Lu P, Lill H, Bald D. ATP synthase in mycobacteria: special features and implications for a function as drug target. Biochimica et Biophysica Acta. 2014; 1837: 1208–1218.
[81] Sutherland HS, Tong AST, Choi PJ, Blaser A, Conole D, Franzblau SG, *et al*. 3,5-Dialkoxypyridine analogues of bedaquiline are potent antituberculosis agents with minimal inhibition of the hERG channel. Bioorganic & Medicinal Chemistry. 2019; 27: 1292–1307.
[82] Alsayed SSR, Gunosewoyo H. Tuberculosis: Pathogenesis, Current Treatment Regimens and New Drug Targets. International Journal of Molecular Sciences. 2023; 24: 5202.
[83] Chahine EB, Karaoui LR, Mansour H. Bedaquiline: a novel diarylquinoline for multidrug-resistant tuberculosis. The Annals of Pharmacotherapy. 2014; 48: 107–115.
[84] Pethe K, Bifani P, Jang J, Kang S, Park S, Ahn S, *et al*. Discovery of Q203, a potent clinical candidate for the treatment of tuberculosis. Nature Medicine. 2013; 19: 1157–1160.
[85] Lu X, Williams Z, Hards K, Tang J, Cheung CY, Aung HL, *et al*. Pyrazolo[1,5- a]pyridine Inhibitor of the Respiratory Cytochrome bcc Complex for the Treatment of Drug Resistant Tuberculosis. ACS Infectious Diseases. 2019; 5: 239–249.