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Review Article

Endocarditis caused by *Mycobacterium tuberculosis*

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Abstract. *Mycobacterium tuberculosis* (TB) is a worldwide danger to human health, with the potential to spread to all parts of the body, including the heart. Tuberculous endocarditis (TBE) is a rare form of tuberculosis that is often associated with miliary TB and the replacement of an infected prosthetic or native valve. Despite advances in the diagnosis of tuberculosis, extra-pulmonary tuberculosis remains a challenge due to its difficulty in diagnosis. In most cases, TBE is only detected post-mortem. In order to better manage TBE in the future, there is a need to accelerate and develop more accurate diagnostic methods. This review paper looks at the literature on TBE from 1970 to 2021. The diagnosis of TBE is complicated by the fact that the symptoms can vary greatly depending on the individual, and the disease can remain asymptomatic for long periods of time. The most common symptoms of TBE include fever, fatigue, joint pain, and an irregular heartbeat. Other symptoms can include chest pain, shortness of breath, and swelling of the extremities. Diagnosis is often made through a combination of physical examination, laboratory tests, and imaging. Treatment usually involves a combination of antibiotics and surgery. In some cases, valve replacement may be necessary. It is important to note that the prognosis of TBE is variable and depends on the individual's overall health, the stage of the disease, and the type of treatment received. Better management of TBE in the future requires acceleration and evolution of diagnostic methods. In this study, we review the literature on TBE from 1970 to 2021.

Keywords: *Mycobacterium tuberculosis*, Endocarditis, heart valves, diagnosis of mycobacterial infections.

Introduction

Mycobacterium tuberculosis (TB) is a pathogenic species in the genus *Mycobacterium* that causes tuberculosis. This aerobic bacterium is resistant to gram staining due to the presence of wax on the wall, and for this reason, the Zill Nelson method is used for its staining. The most important clinical diagnostic methods for TB include: tuberculin skin testing, acid-fast staining Zill-Nelson, and chest X-ray [1]. Infection begins mainly through respiration and aerosols in the lungs.

According to the World Health Organization (WHO) , 1.4 million people died of tuberculosis in 2012 [2].When bacteria are engulfed by alveolar macrophages, they cannot digest the bacteria because the bacteria prevent the fusion of phagosomes with lysosomes [3]. The bacterium infects macrophages in the lungs and is then transmitted to the blood through the lymphatics. Blood transfusions stimulate CD4 and CD8 Which activate the immune system and then remove bacteria from the blood. With the stimulation and accumulation of immune cells and the formation of tuberculous granulomas, the center gradually undergo caseation and only some bacilli remains inactive, leading to miliary disease [2, 4]. When the infection spreads beyond the lungs and respiratory system, it can cause infections in other organs such as the nervous system, bones, and urogenital tract, which is called extrapulmonary tuberculosis. The human heart is no exception to this rule [5]. As we know, the heart wall has four layers and TB can affect different parts such as the pericardium, epicardium, myocardium, and endocardium. Tuberculous endocarditis (TBE) is usually with miliary tuberculosis that Which occurs when a prosthetic valve is inserted [6]. The term miliary TB was described in 1700 [7]. Miliary TB is a diagnostic challenge due to its varied clinical symptoms. It is a letal type of disseminated TB that results from lympho hematogeneous diffusion from a TB focus and has been described as discrete pulmonary opacities, That about 2 mm in diameter [8-10]. In People with immunocompetence,

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miliary TB rates about 20% of all extra-pulmonary TB (EPTB) cases [2]. We used "TB endocarditis", "tuberculosis endocarditis", "tuberculous endocarditis" keywords, reviewed the literature on TBE in PubMed and Google Scholar databases. This study was conducted to collect and summarize the results of previous research. We hope that new treatment strategies will be developed to prevent this infection in the future.

2. TBE: Occurrence and prevalence

Infectious endocarditis (IE) is an infection of the inner part of the heart endocardium as well as the heart valves, including the mitral valve, tricuspid valve, aortic valve, and pulmonary valve, which is caused by bacteria. TBE is not a common infection and is associated with miliary TB or occurs after the implantation of an infected prosthetic valve. Because of the slow growth of bacteria, diagnosis is difficult, rarely occurs when the patient is alive and often is after autopsy [11-14]. Beare and et al. reported 16 cases of cardiac tuberculosis out of 3,500 autopsies. Most patients had miliary tuberculosis, and involvement was observed in the pericardium, myocardium, and endocardium. Only one case was identified by Zill Nelson staining, valve involvement [15]. Sultan et al. reported a patient with mitral valve endocarditis that has immunocompetent and is alive. The mitral valve was replaced with a prosthetic valve. A number of yellow masses were observed in the right atrium and vegetation was observed in the mitral valve, but the culture results were negative. Twenty days after surgery, a positive TB culture was reported [16].

3. TBE coinfection

According to the WHO in 2010, the incidence of tuberculosis was 8.8 million, of which 1.1 million (%13) were HIV positive [17]. The WHO estimates that TB is the cause of death in% 24 of people living with HIV. Tuberculosis infection occurs when a susceptible person inhales particles containing TB (produced by coughing, sneezing, screaming, or singing in people with pulmonary or laryngeal tuberculosis). The immune response usually limits the proliferation of tuberculosis bacilli within 2-12 weeks after infection. However, the bacilli survive for years, a condition called latent TB infection [17, 18]. In 2002, Fumagalli et al. reported a case of TBE with AIDS, Had tachycardia and hepatosplenomegaly [19]. In 2016, a person with AIDS who was diagnosed with tricuspid valve endocarditis and tuberculosis at the same time was identified. The patient was a 37-year-old man with a previous Epstein abnormality as well as hepatitis C. Cardiographic results attributed the diagnosis to tuberculosis or staphylococcal infection. Later, Vegetation in the ventricle was seen. Finally, tuberculosis was confirmed by preparing a smear from sputum and seeing acid-fast bacilli. With the use of the antibiotics rifampin, isoniazid, and Ethambutol, the symptoms of TB improved and there were no acid-fast bacilli in the sputum [20]. A case of TBE coinfection with acute respiratory distress syndrome (ARDS) has been described by Nakamura et al. The patient was a 61-year-old woman who had been hospitalized for arthritis mutilans. She had no history of TB infection. By echocardiography and observation vegetation on mitral valve, to be suspected of IE. The patient died due to a deteriorate condition, Granuloma with giant cells in caseous necrosis was shown after autopsy. Also, Acid-fast bacilli were seen by Ziehl-Neelsen staining [21]. A case of endocarditis, with spondylodiscitis by Saboe and et al. has been reported. The patient had shortness of breath, fever, and weight loss, and also suffered from back pain and lower limb weakness. The sputum smear and GeneXpert MTB/RIF were negative for Acid Fast Bacilli. Results of transthoracic echocardiography (TTE), a mass at the posterior mitral leaflet (PML) was shown. Echocardiography confirmed the presence of vegetation and Magnetic resonance imaging (MRI) small abscesses. Due to multiple negative blood cultures, diagnosed blood culture-negative infective endocarditis (BCNIE). However, with RT-PCR, the method which revealed MTB DNA in vegetation tissue, TB infection was confirmed. The authors Considered MTB as a cause of BCNIE, in endemic areas [22].

4. TBE and Immunocompetence

As we know, TBE is an infection that is usually associated with miliary tuberculosis and immunodeficiency [6]. Abbara and colleagues report a 50-year-old man with TBE who had immunocompetence and no miliary tuberculosis. He went to the doctor because of weight loss and fever and had no contact with the person with tuberculosis. Echocardiography showed that all the valves of the heart were normal, except for the aortic valve, which regurgitation had. Sputum smear was positive for Acid-fast bacilli. By anti TB treatment, the symptoms improved, but the aortic regurgitation became more severe and a new valve was replaced. Aortic valve histology showed the presence of immune cells and epithelioid granulomas [23]. Ward et al. described a case that had high blood pressure, general weakness, and bloody sputum. A radiogram showed that the heart was enlarged and that in the left atrium and ventricle, miliary tuberculosis was seen. He died ten months later [24].

The number of cases where a represents connection TB and endocarditis has been recorded is very few. In 1908, by Meek, two TBE cases were reported. The first was with symptoms of tuberculosis, as well as an enlarged spleen, general bronchitis, and heart murmurs. The autopsy results showed a cavity inside the lung and the presence of several caseous areas. There was in the mitral valve and aortic valve small vegetation. In the second case at the fringe of the mitral valve were, granules, seen after Post-mortem Examination. Few bacilli was seen throughout the vegetation [25].

5. Native valve endocarditis

A 70-year-old woman presented with symptoms of fever, lymphadenopathy, weight loss, and dyspnea. The PPD skin test and Quantiferon-TB test were positive. By Echocardiography, a mass in the mitral valve was seen. Lymphadenopathy biopsy revealed compatibility with the caseum. The diagnosis was ganglionar tuberculosis with endocardial and aortic involvement [26].

TABLE 1
CHARACTERISTICS OF PATIENTS WITH TUBERCULOUS ENDOCARDITIS

Author	Year	Diagnosis	Valve Involvement	Extra-intracardiac involvement	operation	AntiTB treatment	Reference
Meek	1908	Histology	Aortic / Mitral	Miliary TB	No	Supportive	(25).
Ward	1938	Histology	Mitral	Miliary TB	No	Supportive	(24).
Gilmore	1940	Staining	Pulmonary	Miliary TB	No	Supportive	(54).
Anyanwu	1976	Staining / Culture	Aortic / Mitral	Miliary TB	Yes	Unspecified	(14).
Wainwright	1979	Staining	Mitral	Miliary TB	Yes	Supportive	(59).
Soyer	1981	Staining	Aortic	Unspecified	Yes	(12 months)	(60).
Kannangara	1984	Staining	Mitral	Unspecified	No	Supportive	(12).
Cope	1990	Staining	Aortic	Miliary TB	No	(12 months)	(13).
Klingler	1998	Staining / Culture	Mitral	Unspecified	Yes	(12 months)	(61).
Fumagalli	2002	Culture	Tricuspid	Miliary TB /HIV	No	(6 months)	(19).
Sogabe	2007	Histology	Aortic	Unspecified	Yes	(9 months)	(62).
Sultan	2010	Culture	Mitral	Unspecified	Yes	(12 months)	(16).
Shaikh	2012	Histology	Mitral/ Aortic/ Tricuspid / Native	Foot Gangrene	Yes	Unspecifed	(63).
Nakamura	2014	Echocardiography	Mitral /Aortic	ARDS	No	Supportive	(21).
Abbara	2015	TTE	Mitral /Aortic	-	Yes	Unspecifed	(23).
Sass	2016	Staining/PCR/ LC-MS/MS	Mitral/ Native valve	Unspecified	Yes	(12 months)	(58).
Hangouche	2017	TTE	Mitral / Aortic / Native	Icterus/Lymphadenopathies/ Hepatomegaly	Yes	(9 months)	(26).
Spurnić	2017	Echocardiography	Tricuspid	HIV/ HCV	No	(9 months)	(20).
Liu	2019	IGRA/ NGS	Prosthetic	Unspecified	Yes	(2 weeks)	(30).
Saboe	2021	TTE	Mitral	Spondylodiscitis	Yes	Unspecifed	(22).

6. Prosthetic valve endocarditis (PVE)

Prosthetic valve endocarditis is a rare complication that occurs after surgery or valve replacement and its incidence rate is 0.3_1.2% and approximately accounts for about 30% of all cases of IE [27, 28]. Late prosthetic valve endocarditis is a condition that has been more than a year since the surgery and replacement of the prosthetic valve [29]. Liu et al described a patient that was hospitalized nine years after bental surgery with recurrent fever and weight loss. CT scan showed an abscess in the aortic valve. The results of the interferon-gamma release assay (IGRA) and next-generation sequencing (NGS) were positive . PVE was confirmed by the positive result of the culture aortic valve [30]. Table 1 summarized Cases of TBE between the '70s and 2021.

7. The appearance of MDR/XDR-TB and facing challenges

According to the WHO statement in2018, all MDR-TB cases are not diagnosed and just 51% of people with confirmed TB were tested for resistance to rifampicin. Overall estimated about 19 million people have latently MDR-TB. Diagnosis of MDR-/XDR-TB is based on universal drug-susceptibility testing (DST) [31, 32]. Today,

the usage of molecular techniques like sequencing and nucleic amplification tests (NAATs) is very important in TB diagnostics. Also XDR-TB is describ as resistance to a second-line injectable drug and fluoroquinolones [33]. Now, we are facing MDR/XDR TB cases. Fortunately to date no study of involving MDR-TBE or XDR-TBE published. According to the latest WHO Guidelines for DR TB, the best treatment regimen for patients with MDR TB is the use of the All-Oral regimen. According to this, the use of group A drugs, Bedaquiline, Linezolid, and levofloxacin, in combination with group B drugs, Clofazimine, Cycloserine or Terizidone can reduce the duration of treatment from eighteen months to twelve months. A noteworthy point in the new All-Oral regimen is the elimination of injectable drugs of the aminoglycoside family. Therefore, the side effects of Amikacin, Capreomycin, Kanamycin, or streptomycin are reduced. In addition to the All-Oral regimen, the suggestion of using a (BpaL) regimen, Bedaquiline, Pretomanid, and Linezolid has been considered. The use of Delamanid is still debated and may be added to group A. Interestingly, according to this guideline, cases that are resistant to all antibiotics in the fluoroquinolone family along with one of the group A drugs are called XDR TB. In the previous guideline, resistance to injectable Aminoglycoside drugs was considered [34].

8. New treatment strategy

Today, due to the rise of antibiotic resistant strains, researchers have succeeded in treating human and animal infections using lytic bacteriophages [35]. Bacteriophage therapy has been used as a suitable and alternative method for treating infections such as dysentery, Skin infection, and pulmonary infection [36]. The usage of lytic bacteriophages in the treatment of infections associated with the device, such as urinary catheters, has prevented the spread of drug-resistant bacteria [37]. Carson et al. reported that the use of catheters coated with lytic bacteriophages prevented the biofilm formation by E.coli and Proteus [38]. Studies related to phage therapy in cardiovascular operation are limited. Rubalskii et al. in 2020 reported 8 immunosuppressed patients with MDR *E. coli, K. pneumoniae, P. aeruginosa, E. faecium,* and *S. aureus*, infections after cardiovascular implant. Usage of phage applied orally, locally, and inhalation with antibiotics, resulted in the eradication of infection in seven patients [39]. Aslam et al. used IV bacteriophage therapy (BT) in a 65-year-old man with non-ischemic cardiomyopathy who performed the left ventricular assist device (LVAD) implantation surgery [40]. Mulzer et al. presented a patient with mechanical mitral valve replacement with fever and inflammation. The result of CT showed an abscess that was positive for MSSA. Bacteriophages that were obtained from the Eliava Institute, every 8 h were applied on the skin in the surgical site. The patient didn't have other side effects [41].

9. Nontuberculous Mycobacteria (NTM) endocarditis

According to studies, TBE is rare, and not only tuberculosis can cause endocarditis, but the causative bacteria are also mostly the rapidly growing mycobacteria (RGM). There is a remarkable predilection of non-tuberculous mycobacteria (NTM) compared to tuberculous mycobacteria. NTM are divided into four separate groups, based on Runyon classification [42]. RGM including *M. abscessus, M. chelonae, M. fortuitum, M. chimaera, M. mageritense* can also lead to IE and It is estimated to account for 68% of the isolates [43-47]. According to a systematic study by Yuan et al., Which described 50 patients with mycobacterial endocarditis who had symptoms such as cardiac murmur, fever, and chest pain. The most commonly affected sites were the aortic valve, mitral, and tricuspid valves 29.7%, 26.6%, and 10.9%, respectively [48]. The distribution of mycobacteria was determined based on four predisposing risk factors that cardiac surgery was associated with more *M. chelonae, M. fortuitum, and M. chimera*, and implants with *M. fortuitum* [48]. Wallace et al. reported that the occurrence of mycobacterial endocarditis was 33.3% out of *M. fortuitum* and *M. chelonae* [49]. In the study of Olalla et al. 15 cases of *M. fortuitum* and *M. chelonae*, that were prosthetic or valve replacement and were performed in 8 patients with mortality [50]. Strabelli et al described 13 patients with *M. chelonae* endocarditis whit valve replacement and the mortality rate was including 1early and 2 late deaths. In any case, Mycobacterial endocarditis is dreadful, and (RGM) are predominant pathogens that *M. chelonae* is the most common [51].

10. Development of diagnosing

In the early 1980s, patients who had TBE were died and were diagnosed after autopsy [16, 52]. Diagnosed of patients with TBE evolved with the improvement of cardiovascular imaging [53]. The trans-esophageal echocardiography (TEE) method is invasive than the transthoracic echocardiography (TTE) method and is better in performance and spatial resolution [52]. Definitive diagnosis of TBE due to the presence of non-specific symptoms was difficult [25]. Early studies instead of describing clinical symptoms of the valvular disease showed the symptoms of TB such as Fever, weight loss, and lethargy [16, 54]. Histopathological assays are necessary for a definitive diagnosis but it is difficult because of the slow growth of the TB [11, 55]. The GeneXpert MTB/RIF assay is a rapid test for the diagnosis of extra-pulmonary TB [56]. The real-time polymerase chain reaction (RT PCR) that shows DNA on vegetation tissue, is more sensitive than Gene Expert MTB/RIF [56]. In the previous study, RT-PCR consisted of the IS6110 insertion element and related to the detection of MTB complex on the vegetation tissue, was performed, and confirmed with the pyrosequencing [22]. Next-Generation sequencing (NGS) is a method of diagnostic that is of interest. NGS can give information from definite diagnosis and surveillance of MDR-TB. The WHO recently published guidelines for better interpretation of genetic information, the use of NGS in population-based research, and utilization in low-income countries. Nevertheless, NGS needs rules to facilitate its implementation in routine diagnoses [57]. The Sass et al. study presented a 14-month-old patient with disseminated tuberculosis, tuberculous endocarditis, and intracardiac tuberculomas. The results of the transthoracic demonstrated mitral valve vegetations. In this report, liquid

chromatography-tandem mass spectrometry (LC-MS/MS) of cardiac mass was performed to evaluate the composition of tuberculosis endocarditis. More than eighty proteins were identified in the cardiac vegetation by (LC-MS/MS). Also, bone marrow biopsy and vegetation PCR were positive for the M tuberculosis complex [58].

11. Conclusion

TB is a major health challenge. TBE is very rare and it is given its nonspecific symptoms difficult to clinically diagnose and also it requires pathology and microbiological confirmation simultaneously. Rapid diagnosis is very crucial and decreases the mortality rate of TBE. Both immunocompromised individuals and immunocompetent can be infected. Today with the emergence of MDR/XDR TB cases necessitates the development of new strategies for treating infections. Using alternative methods such as the usage of lytic bacteriophages in the face of MDR/XDR TB and also prosthetic valves coated with lytic bacteriophages to prevent contamination, are recommended.

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Conflict of interest

The authors declare no conflicts of interest.

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