Literature Review

# Endobronchial Tuberculosis: Diagnosis and Treatment Approach

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## Abstract

Endobronchial tuberculosis (EBTB) is defined as tuberculosis (TB)infection of the tracheobronchial tract. Tracheal and bronchial involvement from TB infection was first reported by Morten in 1698. Endobronchial tuberculosis is a form of TB that is difficult to diagnose because the lesions are frequently undetectable by sputum examination and chest X-ray alone. Endobronchial tuberculosis is present in 10-40% of active TB patients and more than 90% of cases are accompanied by bronchial stenosis of various degrees. The main goal of therapy in active EBTB is to eradicate *Mycobacterium tuberculosis* in the tracheobronchial tract and further prevent stenosis. Complications of EBTB apart from airway stenosis are atelectasis, haemoptysis and shortness of breath accompanied by wheezing even after administration of anti-tuberculosis drugs (ATD).

**Keywords:** atelectasis, EBTB, TB

## INTRODUCTION

Tuberculosis (TB) is still a global health issue, as well as the leading cause of death from infectious diseases. In 2019, there were 10 million new TB cases reported, with roughly 1.5 million fatalities from the disease.[1]

Endobronchial tuberculosis (EBTB) is defined as TB infection of the tracheobronchial tract. Tracheal and bronchial involvement from TB infection was first reported by Morten in 1698. Endobronchial tuberculosis is a form of TB that is difficult to diagnose because the lesions are frequently undetectable by sputum examination and chest X-ray alone. Even after the development of efficient TB therapy, EBTB remains a major health issue due to the frequently delayed diagnosis. Complications of EBTB are airway stenosis, atelectasis, haemoptysis and shortness of breath accompanied by wheezing even after administration of anti-tuberculosis (ATD) drugs.[2,3]

Endobronchial tuberculosis is present in 10-40% of active TB patients and more than 90% of cases are accompanied by bronchial stenosis of various degrees. The main goal of therapy in active EBTB is to eradicate *Mycobacterium tuberculosis* in the tracheobronchial tract and to further prevent stenosis. To prevent complications that can increase morbidity and mortality,

prompt diagnosis and therapy are needed. This literature review discusses the signs and symptoms, pathogenesis, diagnosis and therapy of EBTB [4,5]

## EPIDEMIOLOGY

The incidence of EBTB cannot be determined with certainty, especially since bronchoscopy is no longer a routine examination in pulmonary TB cases. In a 1943 investigation, it was discovered that the proportion of EBTB was 15% in pulmonary TB cases using rigid bronchoscopy and 40% in autopsy results.[4]

According to numerous research, the incidence of EBTB after the introduction of anti-tuberculosis therapy ranged from 6 to 40%. Su et al reported an incidence of EBTB, which was 23.9% of 1,442 pulmonary TB patients, with a higher proportion of females aged <50 years than males. EBTB cases are reported to occur more frequently in females, for reasons that are unknown with certainty, but it is possible that this is due to females tend to cough up less from preconceptions for socio-cultural and aesthetic reasons, allowing them to be exposed to tubercles containing mycobacteria for longer because the anatomical structure of the bronchial anatomy of females are narrower than that of males, allowing them to be exposed to tubercles containing mycobacteria for longer.[5–7]

EBTB is most common among people in their twenties. Aniwidyaningsih et al discovered that 86.7% of the 30 EBTB patients studied were females, with a mean age of 28 years.

## PATHOGENESIS

Although the exact pathogenesis of EBTB is unknown, five mechanisms are thought to play a role in its occurrence: (1) direct spread of the focus of infection in the lung parenchyma; (2) direct attachment of mycobacteria from infected sputum; (3) hematogenous spread; (4) erosion of lymph nodes into the bronchi; and (5) lymph flow from the parenchyma to the peribronchial region.[3,4,7,8]

Endobronchial tuberculosis can affect all bronchial branches, but the main location is the main bronchi, bilateral superior lobe and middle lobe. Since the left main bronchus is structurally more constricted by the aortic arch and mediastinal lymph nodes, infection in the lymph nodes spreads more rapidly to the left bronchus than to the right bronchus.[9] Endobronchial tuberculosis (EBTB) is classified as single if it is detected only in one location in the trachea, main bronchus, or lobar bronchus, multiple if it is found in two or more bronchial branches, and central if it affects the proximal part of the bronchus. This location is susceptible to stenosis.[7,8]

Pathologically, EBTB can affect the entire tracheobronchus layer, including the muscularis laminae and cartilage. Pathological alterations that develop include mucosal and submucosal TB infections, ulcers, granulomas, fibroplasia, and tracheobronchial stenosis. Pathological

changes begin with the occurrence of hyperemia in the mucosa and submucosa due to infiltration of inflammatory cells, especially lymphocytes, then followed by the formation of tubercles accompanied by caseous necrosis which in turn will cause ulcers in the mucosal lining of the bronchi. The ulcer develops on the lining of the tracheobronchus wall and the ulcer becomes deeper, resulting in the formation of polyps towards the bronchial lumen. At an advanced stage, hyperplasia, fibrosis, and contractures develop, eventually leading to tracheobronchial stenosis.[2,5,10]

## CLINICAL

Clinical signs and symptoms are typically nonspecific, such as a dry or productive cough, haemoptysis (rarely massive), sternal or parasternal chest discomfort, and shortness of breath due to pulmonary atelectasis. Persistent cough is one of the most common respiratory symptoms in 70-80% of EBTB patients.[11]

Systemic TB symptoms such as decreased appetite, weakness, and fever are not prominent in EBTB. Sud et al found that a persistent cough lasting 4 weeks in young females is a predictor of EBTB and tracheobronchial stenosis, hence a bronchoscopy should be performed right away.[6] Lung examination can reveal diminished breath sounds, isolated wheezing, and crackles.[5,6,12] Liu et al reported late EBTB cases with pleural effusion as a clinical symptom.[13]

## DIAGNOSIS

Because of its atypical signs and symptoms, EBTB is more difficult to diagnose than pulmonary TB. The clinical outcomes of EBTB will benefit substantially from early identification and adequate care. A sputum examination was performed first, followed by bronchoscopy and radiographic evaluation.

### Sputum Examination

Sputum examination is an important initial examination for the diagnosis of EBTB. Examination of Acid fast bacilli (AFB) sputum gives varying results ranging from 16-53%, but a negative result does not exclude the presence of EBTB. Sputum examination by molecular rapid test (is said to give better results than AFB sputum. Zhang et al[14] found that in 61 EBTB patients, the specificity of genXpert was 100% as compared to microscopic sputum, bronchial swab swabs, sputum, and tissue culture, which were 13.1%, 32.8%, and 68.9%, respectively.

### Bronchoscopy

A 22-year-old female with full-term pregnancy and asymptomatic COVID-19 was referred to Ulin Regional Hospital Banjarmasin for cesarean section surgery. BMI was 21 kg/m$^2$, and blood pressure was 110/70 mmHg. There was no abnormality in the physical lung examination. Chest x-ray was within normal limit. Laboratory test result was RBS 116 mg/dl, NLR 3.16%, ALC 1657/ul, CRP 4.2 mg/L, LDH 181 U/L, Ferritin 22.20 ng/mL, D-dimer 6.63 mg/L,

AST 25 U/L, ALT 11 U/L, Cholesterol 263 mg/dL, Triglyceride 114 mg/dL, LDL 244 mg/dL, and HDL 38 mg/dL. The patient was declared cured after 27 days of treatment.

Bronchoscopy is a critical tool for detecting EBTB as early as possible. Procedures in bronchoscopy such as biopsy, brushing, rinse, needle biopsy and endobronchial ultrasound (EBUS) can be used to make the diagnosis.[15] A biopsy can yield a positive result in the range of 30.35%-84%.[1,2,5,8] According to a Chinese study, bronchial brushing provided favorable effects up to 84.88%, while bronchial rinses had positive results ranging from 10 to 37.5%.[3] Bronchoscopy is also important to rule out several other disorders such as malignancy and diseases that show other granulomatosis features such as pulmonary mycosis and sarcoidosis.[16]

(A) Caseosaactive, looks hyperemic and the tracheobronchial walls covered with a yellowish-white cheese-like material, seen in 43% EBTB;
(B) Hyperemia-edema shows tracheobronchial mucosal features that are heavily edematous and hyperemic, occurring in 14% of EBTB;
(C) Fibrostenotic shows a narrow tracheobronchial lumen due to fibrosis hyperplasia and contracture, occurring in 10.5% EBTB;
(D) Tumorous showing an intraluminal mass image occurred in 10.5% EBTB;
(E) Granular shows a hyperemic tracheobronchial mucosal appearance and there are nodules that look like grains of rice (11%);
(F) Ulcerative shows an ulcerated tracheobronchial mucosa (3%);
(G) Nonspecific bronchitis in the form of tracheobronchial mucosal features with mild to moderate edema and/or accompanied by hyperemia (8%).

This picture is shown in Figure 1.

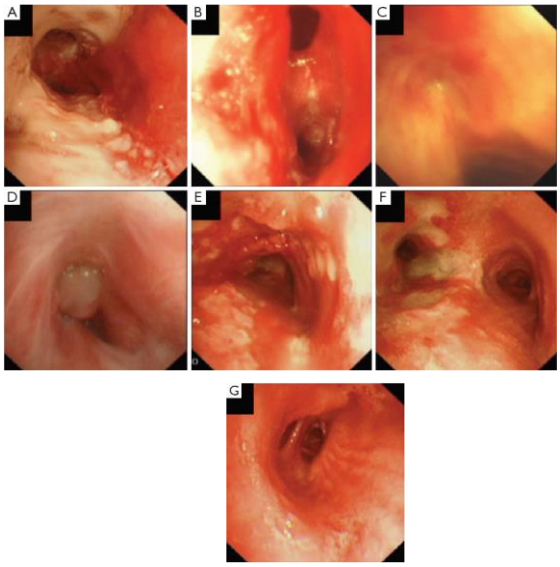


Figure 1. Bronchial mucosa EBTB on bronchoscopy A. caseosaactive; B. hyperemisedema; C. fibrostenotic; D. tumorous; E. Granular; F.ulserative; G. non-specific bronchitis[6]

The mucosal appearance on bronchoscopy can be used to determine the likelihood of stenosis. Despite 3 months of anti-tuberculosis therapy, edematous, hyperemic, fibrostenotic and tumorous mucosal features are more likely to develop bronchial stenosis or blockage. The granular subtype had the highest level of positivity for microscopic examination and M. tuberculosis culture based on the results of the bronchoalveolar lavage (BAL) examination, while the fibrostenotic and nonspecific types had more frequently negative results.[5,9,17,18]

Lymph nodes enlargement is often seen on bronchoscopic examination, appears in the form of a grayish yellow mass on the bronchial mucosa, Lymph nodes often appear to be ulcerated, bleeding and forming granulation fistulas.[4,10]

### Radiology

Approximately 10-20% of EBTB patients may show normal images on chest radiograph. Infiltrates in the lung parenchyma of the afflicted lobe are the most prevalent chest X-ray image in EBTB. Features of segmental or lobar collapse, as well as lobar hyperinflation, may also be present. Fibrotic, calcification, bronchiectasis, hillar lymphadenopathy, and pleural effusion are abnormalities that can be found.[2,8,13]

Chest Computed Tomography (CT) examination provides more detailed information than chest X-ray such as stenosis, nodules, cavities, pleural effusions and mediastinal lymphadenopathy. Ho et al[11] in their case report reported asymmetric hilar features that should be suspected as a sign of EBTB. Several studies have shown that 95-97% of EBTB can be seen on chest CT. Chest CT examination reveals a centrilobular asymmetric spot or nodule and tree in buds appearance. This features were distributed unilaterally as well as bilaterally. Bronchoscopy or microbiological testing must be performed on patients whose CT examination results indicate EBTB.[3,6,9,19]

## COMPLICATIONS

Bronchial stenosis and stricture are the most common complications of EBTB. This complication is irreversible despite adequate ATD administration. Bronchosthenosis occurs in about 60% of cases and affects the main bronchi. A poor clinical outcome may arise due to airway obstruction, which may also affect the trachea.[18,19]

Brochiectasis is also a frequent complication of EBTB, usually as a result of paracicatrial processes, destruction and pulmonary fibrosis. Bronchiectasis that occurs is often asymptomatic and usually found in the upper lobe of the lung and if there are complaints, haemoptysis is the most common complaint experienced by patients.[2,5]

## DIFFERENTIAL DIAGNOSIS

Lung cancer is the most important differential diagnosis that must be considered. Some of the other differential diagnoses are inflammation, sarcoidosis, asthma, atelectasis, foreign body aspiration, recurrent pneumonia and actinomycosis.[3,6,12,13]

Sarcoidosis is also a disorder that can affect endobronchial and has a clinical appearance very similar to EBTB. Bronchostenosis due to sarcoidosis is in some cases are very similar to EBTB and should be distinguished carefully. Patients with HIV AIDS should consider Kaposi's endobronchial sarcoma as the cause.[3,4]

## THERAPY

The stage of the disease must be considered in EBTB management. First, it must be determined whether the disease is active or in a fibrotic condition, which is quiescent but might develop bronchial stenosis. The goal of treatment during the active period is to eradicate *M. tuberculosis* and to prevent tracheobronchial stenosis. Tracheboronchial strictures can occur despite administration of ATD and intralesional silver nitrate administration. EBTB is treated in the same way as pulmonary TB, with first-line ATD (rifampin, isoniazid, ethambutol, pyrazinamide, and streptomycin) for 6 to 9 months.[4,5,20]

Another therapeutic modality used are corticosteroids. Corticosteroids have long been used as an adjuvant to EBTB treatment, but their use is debatable. Corticosteroids may be beneficial in the early stages of EBTB because hypersensitivity was the predominant at the time, but they have minimal effect in the advanced stages.[18]

Corticosteroids have also been tested intralesionally. Rikimaru[20] demonstrated that combining streptomycin 100 mg, dexamethasone 0.5 mg, and naphazoline 0.1 mg twice day with regular ATD resulted in faster healing of lesions and less bronchial stenosis. In another study, submucosal injection of methylprednisolone also showed resolution of EBTB. To date there has been no comprehensive and systematic evaluation of the use of cortiosteroids as adjunctive therapy in EBTB. Um et al[19] showed that age> 45 years, fibrostenotic subtype EBTB and duration of symptom with ATD administration of> 90 days were predictors of persistent tracheobronchial stenosis.

The complication of EBTB is bronchial stenosis which can lead to atelectasis and obstructive pneumonia. Usually, there are complaints of shortness of breath and wheezing. Because steroids cannot reverse bronchial stenosis, airway patency must be re-established through bronchoscopy or surgery. Bronchoscopy techniques include laser, argon coagulation, cryotherapy, and balloon bronchodilation.[1,8,9]

These strategies can be used separately or in tandem. The main indication for laser bronchoscopy is the presence of tracheal, main bronchial, and lobe obstruction, which results in decreased ventilation and severe symptoms such as shortness of breath, stridor, and haemoptysis. Bronchoscopy with balloon dilation is a minimally invasive and relatively safe procedure using flexible bronchoscopy. This is accomplished by inflating a balloon inside a bronchus with a stricture. This approach is better suited for circular cyclic stenosis and chronic stenosis than stenosis with active inflammation, calcification, and damaged cartilage (malacia).[21] The success rate of this procedure has been found to range between 6.3%-73%. If balloon dilation fails to resolve the stenosis, a stent should be inserted as soon as possible.

The stent used is usually made of silicon (Dumon stent). Metal stents (Ultraflex and Gianturco stents) should be

avoided because it is difficult to remove it again.[3]

Iwamoto et al[21] report the success of maintaining long-term airway patency with the use of Dumont stents. tubular and Y) in 6 EBTB patients. Iwamoto reported that the use of Ultraflex stents caused more granulation tissue than the use of click stents. The complications of bronchial stent placement are airway perforation, stent changing position and location, granuloma obstruction due to stents which can result in emphysema, pneumothorax, pneumomediastinum, mediastinitis, shortness of breath and haemoptysis.

Low et al[21] described immediate and long-term clinical recovery in 7/11 (63.6%) patients treated with Dumon stents. Similar successful findings were observed by Ryu et al[21] to 75 patients with tracheobronchial tuberculous stenosis. Independent factors such as granulation tissue expansion and tracheobronchial malacia indicate a bad prognosis in stent insertion.

A new technique has been described recently to prevent stenosis from recurring after dilation. Mitomycin-C, which is an antineoplastic agent that inhibits fibroblast proliferation and modulates wound healing and scar tissue, is administered topically with saturated serum applied by forceps biopsy (0.4-0.5 mg/ml) in some cases, as an adjunct therapy for bronchoscopy procedures. [21]

Other brnchoscopy interventions are ablative techniques including heat therapy (laser therapy, electrocautery, and argon plasma coagulation (APC)) and cyrotherapy. Laser resection is based on laser energy sent through a rigid and/or flexible bronchoscope. Direct laser therapy recommended for endobronchial malignant lesions but also for EBTB-related stenosis. Cavaliere et al[21] treating six patients with tracheobronchial stenosis TB: Normal bronchial patency was not fully achieved, but ventilation was significantly increased. The successful administration of Nd-YAG laser therapy was also described by Low et al[21] and Ryu et al[21] who cutting the fibrous band in 21 and 13 patients with TB stenosis, and by Lim et al[21] who treated 14 web-like stenosis before stent placement.

Bronchial stenting can serve as a temporary therapeutic intervention. This is followed by successful stent removal without the need for reintervention.[9] Bro Argon Plasma Coagulation is a safe method to be done in cases of tumorous EBTB to prevent luminal stenosis. Jin et al[21] describing the long-term outcomes of 41 patients with EBTB exposed to APC and TB drugs compared to a control group receiving antibiotics only. Cryotherapy, which results in cyclical and repeated cold-induced cell death is a safe approach to treating TB stenosis without the risk of airway fire or bronchial wall perforation. stenosis in 12 patients with post-TB stenosis.

Recently, Mu et al[21] found that bronchoscopic cryotherapy could increase granular EBTB and prevent progressive stenosis. They evaluated 38 patients treated with flexible instrument cryotherapy and anti-TB drugs compared with 38 patients who received only anti-TB drugs. Treatment success rate is 100% in

cryotherapy arm affected by a mean of 4 applications per patient vs. 78.9% in those treated only with anti-TB drugs. Recovery time was faster in the cryotherapy-treated sections and there were no reports of severe side effects. Cryosurgery is another safer option than balloon and laser dilatation. The risk of bronchial perforation in cryosurgery is smaller than other procedures but this procedure requires repeated procedures so it can take longer. Li et al[14] reported successful bronchoplasty in 8 EBTB patients who experienced pulmonary atelectasis due to EBTB even though they had been given OAT for a long time. The success of the bronchoplasty performed by Li et al shown in Figure 2.

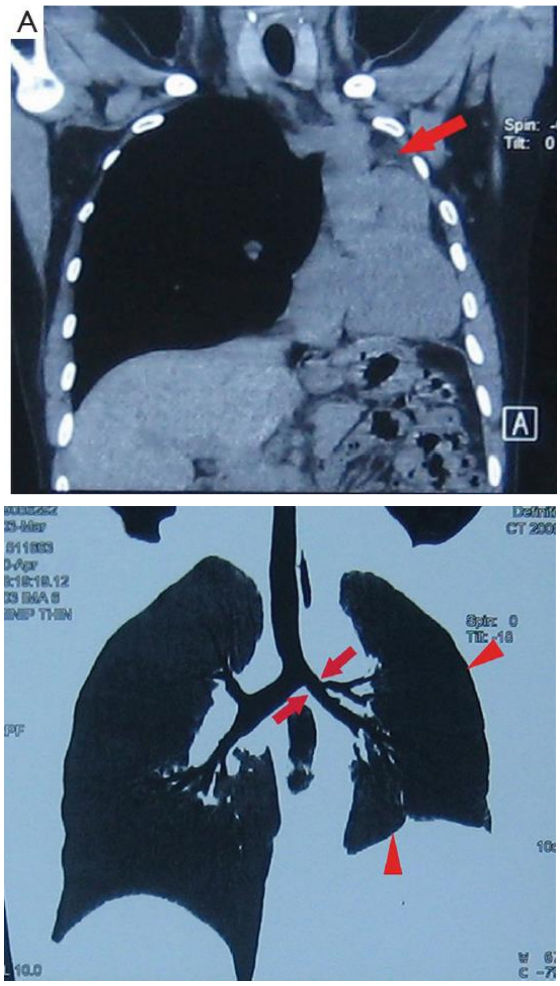


Figure 2. Pre and Post bronkoplasti[14]

Severe tracheobronchial stenosis that causes lung collapse, pulmonary infection and recurrent haemoptysis requires surgery such as pneumonectomy or lobectomy.[22] A study conducted by Lei et al[22] showed that of 25 EBTB patients who underwent surgery, almost all were females, young with the fibrostentotic type. Cough was the most common complaint. Surgery is an option for EBTB patients with severe bronchostenosis. The most common surgical methods are lobectomy or multilobectomy followed by pneumonectomy and bronchial sleeve resection.[2,5,7]

The final method was performed on strictures in the main bronchus near the upper lobe. There was no postoperative death, but found atelectasis, atrial fibrillation, empyema as postoperative complications. Several different studies conducted showed that post-lobectomy and pneumonectomy complications ranged from 15.3-23.8%. A dangerous post-resection complication is bronchopleural fistula with a mortality rate of up to 40% and the main causative factor is active local infection, therfore one way to prevent complications of bronchopleural fistula is to delay surgery as long as there are signs of acute infection in the bronchi.

## CONCLUSION

Endobronchial tuberculosis is a rare form of TB. It is more common among young females, and the cause is unknown. Because of the atypical clinical symptoms of TB, the diagnosis of EBTB is sometimes

delayed until the development of complications from severe bronchial stenosis. Bronchoscopy is the main diagnostic approach combined with radiological, microbiological and histopathological examinations. ATD is administered along with single or recurrent bronchial dilatation, and is frequently combined with laser, argon plasma coagulation, cryotherapy, and balloon bronchoplasty performed by bronchoscopy. If the stenosis is severe, surgical procedures such as lobectomy or pneumonectomy are undertaken.

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