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Bronchoscopic valve therapy for tuberculosis: a scoping review

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Abstract

The management of tuberculosis (TB) presents significant challenges, particularly in the context of multidrug-resistant TB (MDR-TB) and TB-HIV co-infection. Traditional surgical interventions, such as lung resection and pneumothorax induction, have largely been phased out with the advent of modern antibiotic regimens. However, emerging evidence suggests that endobronchial interventions, specifically the use of unidirectional valves, have potential in supporting the treatment of MDR-TB.

The objective of this review is to demonstrate the feasibility of closure of tubercular cavities using endobronchial valves, resulting in improved clinical outcomes and sputum smear conversion. PubMed was searched from inception to September 2024.

The small studies reviewed here demonstrate the feasibility of tubercular cavity closure using endobronchial valves, resulting in improved clinical outcomes and sputum smear conversion. Yet, limited access to Food and Drug Administration-approved valves and funding challenges hinders large-scale trials. To address these limitations, further evidence is needed within improved international collaboration.

We suggest that international prospective trials and innovation are needed. Such collaborative efforts would clarify the role of valves in TB treatment and hopefully lead to the development of simpler and more affordable occlusive devices that would benefit patients with MDR-TB, particularly in low-income countries.

Key words: multidrug-resistant tuberculosis, endobronchial valves, TB-HIV co-infection, innovative treatment strategies, international collaboration in tuberculosis research.

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Introduction

Tuberculosis (TB) remains a global health concern, with an estimated 10.6 million people falling ill and 1.6 million losing their lives to this disease in 2021 [1]. Prior to the development of effective chemotherapy for TB, surgery was used to reduce mortality and morbidity. Today, the World Health Organization (WHO) recommends that partial lung resection may be used alongside drug treatment for some patients with RR/multidrug-resistant TB (MDR-TB) [1]. During the era when TB surgery was more widely used, thoracic surgeons performed procedures such as iatrogenic pneumothorax, intrapleural insertion of ping-pong balls, thoracoplasty, and excision surgery of cavernous areas with the aims of collapse lung and to limit oxygen exposure to the mycobacterium – *M. tuberculosis* is an aerobic organism and the reduction of oxygen induced by these interventions reduces the speed of mycobacteria replication [2]. The advent of effective antibiotic treatments in the late 20th century obviated the need for surgical interventions, which are now often limited to specific scenarios (*e.g.*, life-threatening haemoptysis, tension pneumothorax, cavitary disease progressing despite optimal chemotherapy) [3].

Until recently, drug treatment for fully sensitive TB was standardised, with a 6-month regimen used for all individuals independent of disease burden. This regimen was derived from trials conducted on patients with smear positive TB; however, it is increasingly recognised that TB exists on a spectrum including latent infection and subclinical disease to extensive, cavitating disease [4]. Recent trials have shown success using 2-month treatment regimens for people with drug-susceptible disease [5], and the WHO now recommends several 6- and 9-month options for people with drug-resistant disease, with excellent outcomes for an increasing majority of patients [6]. There has been less research interest, however, at the other end of the spectrum (*e.g.*, what interventions might improve treatment outcomes for those with cavitating, multibacillary disease?). Globally, for patients with fully susceptible disease treated in 2021, the success rate was 86% (71-92%), and for those treated for MDR/RR-TB in 2019, the success rate was 60% (57-72%), demonstrating that there is still ample room to improve overall outcomes. It is recognised that treatment failure is more common in people with MDR/RR-TB and those living with HIV [7]. Cavitating disease is a risk for treatment failure, possibly due to inadequate penetration of antibiotics into affected areas.

Historically used surgical interventions are not readily

amenable to large, randomized studies for several reasons, making it challenging to establish evidence-based guidelines. The complexity and infrequency of the surgery and the lack of clear definitions for indication, timing, procedural approaches, and patient selection, further hinders their effective implementation [8]. Bronchoscopic techniques seeking to mimic effects of thoracic surgery (*e.g.*, cavity closure) may be safer and easier, and we sought to review their role in the management of TB.

Methods

This scoping review systematically evaluated the available literature on the use of endobronchial valves (EBV) for TB management, focusing on their role in closing tubercular cavities and improving treatment outcomes for patients with multi-drug-resistant and extensively drug-resistant tuberculosis.

Search strategy

A comprehensive search was conducted on PubMed from inception until September 2024. The search terms included "Multidrug-Resistant Tuberculosis", "Endobronchial Valves", "TB-HIV Co-Infection", "Bronchoscopic Interventions", and "Tuberculosis Treatment Innovations".

We included studies that evaluated the efficacy and safety of EBV in TB management and included primary data on clinical outcomes such as cavity closure, sputum smear conversion, and treatment duration (Table 1). Case reports, case series, and clinical trials were included, while editorials, commentary, articles without available full text, and review articles were excluded. Language filters were not applied, with translation services used for articles in languages not understood by the reviewers.

Results and Discussion

Bronchoscopic intervention as an alternative to surgery

Bronchoscopic lung volume reduction (BLVR) with EBV is a technique developed over the last few decades, initially to restore lung function to patients affected by chronic obstructive pulmonary disease (COPD) with hyperinflation [9].

The principle underlying EBV is to seal the drainage bronchus through a one-way valve so that the air can exit but not enter, promoting the volume reduction of the corresponding lung tissue without affecting the secretion drainage. The safety of BLVR in patients with severe emphysema inspired the use of unidirectional valves in emulating the physiological outcomes of surgical procedures for TB. These proposed bronchoscopic interventions aim to induce absorptive atelectasis and collapse of the tubercular lung, leading to cavity closure and, perhaps, improved penetration of TB medications. The use of EBV for COPD has gained considerable attention and in 2018 the Zephyr® Endobronchial valve (Pulmonx, Redwood City, California, USA) was approved for use by the Food and Drug Administration (FDA) in the USA following a large, randomised trial [10]. The systematic application of these valves in patients with TB remains largely unexplored, but a small body of literature has emerged, offering evidence supporting the safety and effectiveness of EBV use as an alternative management approach for the closure of tubercular cavities.

Corbetta *et al*. reported a case series that included four patients between 2010-2015 with various difficult-to-treat forms of TB and one with atypical mycobacterial infection [11]. Complete cavity collapses were observed in four out of five patients after the insertion of a Zephyr valve, accompanied by clinical improvement and nega-

Table 1. Summary and characteristics of studies included in the final analysis.

Author	Year	Country	Study design	N. and features	Intervention	Outcomes
Corbetta *et al.* [11]	2016	Italy	Case series	4 patients with difficult to treat forms of TB and 1 atypical mycobacterial infection, with cavities each	Insertion of Zephyr valves	Complete or partial cavity collapses, clinical improvement and negative sputum smears within 3-5 months in all the patients
Levin *et al.* [12]	2016	Russia	Randomized controlled trial	102 patients with destructive MDR-TB	49 patients received EBV placement associated to chemotherapy. 53 received chemotherapy only	The presence of EBV implicate a higher rate of bacteriological conversion in 3 months and higher rate of cure at 3 years, compared to patients with only chemotherapy. ($p<0.0001$)
An *et al.* [13]	2022	China	Single-arm study	35 patients with cavitating, pulmonary MDR-TB and positive sputum cultures	EBV placement in addition to individualized chemotherapy	Reduction of cavity size with complete closure in 68.8%. Sputum culture conversion
Popova *et al.* [14]	2018	Russia	Randomized control trial	74 patients with cavitary pulmonary TB.	Assessment of pulmonary function after the placement of locally designed endobronchial valves	Improvements in pulmonary function in those with abnormal lung function

TB, tuberculosis; MDR-TB, multidrug-resistant tuberculosis; EBV, endobronchial valve.

tive sputum smears within 3-5 months. Notably, no severe short- or long-term complications were reported, and the valves were successfully removed in three patients after an average of 8 months, without any relapse during a 15-month follow-up period.

In 2016, Levin *et al.* reported on a study on MDR-TB patients comparing the efficacy of EBV placement to conventional second-line chemotherapy alone. A total of 102 patients with destructive MDR-TB were enrolled, with 49 receiving EBV and chemotherapy and 53 receiving chemotherapy only. The addition of EBV placement resulted in a significantly higher rate of bacteriological conversion at 3 months (95.9% *vs.* 37.7%, p<0.0001) and a higher rate of cure at 3 years (80.5% *vs.* 25.0%) [12].

In 2022, An *et al.* reported on a single-arm study which enrolled 35 patients with cavitating, pulmonary MDR-TB and positive sputum cultures to receive treatment with EBV in addition to individualized chemotherapy. In all patients EBV implantation resulted in a reduction in cavity size with complete closure in 68.8%. Sputum culture conversion occurred in all individuals, and no severe adverse events associated with EBV implantation were reported [13].

Several studies on endobronchial device closure in patients with TB were found published in Russian medical journals. Popova *et al.* assessed the impact of a locally designed EBV on lung function in 74 patients with cavitary pulmonary TB [14]. They found EBV placement may cause "functional worsening" in patients with normal lung function at baseline, but improvements in those with abnormal lung function at baseline. A second study by the same group describe "endoscopic valve bronchomalacia" with the aim of preserving functioning lung tissue in patients with significant lung damage after thoracic surgery [15].

Togo *et al.* report the case of a 48-year-old diagnosed with extensive, clarithromycin-resistant *Mycobacterium avium* complex pulmonary disease, who achieved a good outcome with lobectomy and bronchial occlusion using an endobronchial Watanabe Spigot, avoiding the need for pneumonectomy [16].

EBV devices have also been studied for indications other than cavity closure. One study used EBV for the treatment of bronchopleural fistula, and some of the patients had TB [17]. Good outcomes were reported, although it was not possible to disaggregate the results for patients with TB. Additionally, EBV have been used for a patient with TB and intractable hemoptysis, and broncho-cutaneous fistula [18,19]

Collectively, these studies provide intriguing preliminary evidence that endobronchial device closure may be a valuable adjunct in the management of tubercular cavities. The rapid closure of cavities may reduce the risk of acquired drug resistance and potentially reduce the duration of time a person is infectious with public health implications if performed early. Additionally, bronchoscopy may be feasible in patients too unwell for thoracic surgery. The concept has garnered interest from the interventional pulmonology community and experts in the field are involved in further development of EBV interventions [20]. The quality of the evidence base to date is limited, and further research with larger, controlled studies are needed to establish the long-term effectiveness, safety, and cost-effectiveness of endobronchial closure in TB management.

Challenges of bronchoscopic interventions trials for multidrug-resistant tuberculosis

A major obstacle in the development of future clinical trials is the limited access to FDA-approved endoscopic valves for the use in patients with TB. As already discussed, the evidence base for EBV in TB is weak and there are no guidelines or recommendations regarding their use. Valve-manufacturing companies are predominantly small and have responsibilities to their stakeholders for the development of treatment for emphysema, and shifting their focus to support TB research would be challenging. Efforts should be directed towards simplifying the regulatory environment – potentially including 3D-printed devices, ensuring that necessary approvals and certifications are accessible in a timely and efficient manner.

A further challenge concerns the device itself. It is not known whether the characteristics in currently available EBV devices, built for closing emphysematous bullae, are optimized for use in tubercular cavities. Additionally, investment in the manufacturing process may help develop EBV with simpler designs, that are easier to manufacture, more cost-effective, and easy to insert and remove.

Furthermore, the development of an adequately powered trial for EBV in TB would be challenging. It is imagined that bronchoscopic EBV placement would remain a highly specialized intervention, and the population of suitable patients likely small outside of highly endemic settings.

We believe that addressing these limitations requires a coordinated international collaboration. By bringing together researchers, policymakers, manufacturers, and funding agencies in a collaborative network, it may be possible to enhance access to, and use of, EBV for TB research and prioritize the development of simpler, cost-effective occlusive devices.

Conclusions

The use of EBV placement to induce lung collapse in patients with TB may shorten time to cavity closure and improve rates of sputum culture conversion. Bronchoscopic interventions may be easier and safer than major thoracic surgery and may have a role as an adjunct in TB treatment – especially for patients with advanced disease or MDR-TB. The current evidence base is weak and access to devices limited. These challenges may be overcome with the development of a network alliance bringing together clinicians, researchers, and manufactures, to advance the knowledge base for this potentially important intervention.

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