

## Endobronchial Tuberculosis in Serbia over a 20 Year Period: Analysis and Review of Current Literature

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### Abstract

**Setting:** Endobronchial tuberculosis (EBTB) is a chronic, often unrecognized form of the disease with a complicated clinical course and significant airway complications.

**Objective:** The aim of this study was to evaluate common clinical features amongst individuals with bronchoscopic biopsy proven EBTB during a 20 year period in Serbia.

**Design:** An observational study of 212 patients with bronchoscopic biopsy proven EBTB between January 1993 and December 2012. Retrospective case note review was undertaken, including all clinical, microbiological and radiological evidence, at the University Hospital of Pulmonology, Belgrade.

**Results:** All patients were caucasian and HIV-negative, with a male to female ratio of 1.28:1. Every patient had an abnormal chest X-ray. The most common endoscopic features were oedematous hypereamic (39.2%) and non-specific bronchitis (35.8%). Microbiological culture rate was 64.6%. Sputum culture was positive in 55.2%, bronchial washing culture positive in 36.8%, and both in 27.4%.

**Conclusion:** Most patients with EBTB have concurrent pulmonary lesions. Bronchoscopy is an essential diagnostic tool for EBTB. Early diagnosis and early onset of therapy is of crucial importance to prevent the development of bronchostenosis.

**Keywords:** EBTB; Epidemiology; Clinical; Treatment

### Introduction

Endobronchial tuberculosis (EBTB) is a chronic, progressive form of the infection with bronchial mucosal infiltration, which is characterized by hyperaemia, oedema, formation of granulation tissue and potentially ulceration and bronchostenosis, secondary to scar tissue forming in the bronchial lumen [1-3].

EBTB is present in up to 40% of patients with active tuberculosis, frequently with a complicated clinical course including bronchostenosis. However, EBTB often presents a diagnostic challenge with variable symptoms at presentation, and a low rate of sputum smear positivity. Some patients can have a normal chest X-ray, even though the sputum sample is smear positive. The diagnosis of EBTB is often delayed until after the onset of serious bronchial stenosis [4,5].

TB incidence in Serbia has been 32-36 per 100,000 population for several decades, but in recent years it has decreased to below 20 per 100,000 [6,7]. There are very limited data on EBTB from countries in the Balcan region, and in a caucasian HIV-negative population as well.

The aim of this study was to evaluate clinical features and outcomes in a group of patients with bronchoscopy proven EBTB in one Serbian hospital over a 20 year period. We also describe the current international literature for this subgroup of patients with endobronchial TB.

### Study Population and Methods

An observational study of patients with endobronchial TB (EBTB) was conducted at the Institute of Pulmonary diseases Clinical Center of Serbia, in Belgrade from January 1993 to December 2012. We reviewed their clinical features, radiologic, mycobacterial and bronchoscopic

findings at the time of diagnosis; and the treatment outcomes with a follow up period of at least 5 years after completion of anti-tuberculosis treatment.

Bronchoscopies were performed for different reasons; firstly in order to confirm the diagnosis of TB in cases with suggestive radiology but negative sputum smear, and to exclude malignancy. Endoscopic abnormalities were classified according to Chung and Lee 2000, into seven subtypes [3].

For each patient the following data were collected using a targeted questionnaire: basic demographics, past medical history, physical examination, chest X-ray, bronchoscopy (histology and microbiology results), and mycobacterial analysis of sputum samples at the time of diagnosis. During the follow-up period, results of a physical examination, chest X-ray with/without CT scan of the thorax, mycobacterial analysis of sputum samples and at least one control bronchoscopy with mycobacterial analysis were also recorded.

The data collected on this patient group were analyzed using SPSS version 15 for Windows (SPSSCo.Ltd). Statistical differences were

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evaluated using the chi-square test and t-test. The correlation between different endoscopic findings, radiological and microbiological results was correlated by calculating the Phi correlation coefficient.

The Institutional Ethics Committee approved the study.

## Results

### Clinical features

Between January 1993 and December 2012 two hundred and twelve consecutive cases of bronchoscopic biopsy confirmed endobronchial tuberculosis were identified. This accounted for 3% of all the cases of TB at the Institute of Pulmonary Diseases, Belgrade. The male to female ratio was 1.28:1 (119:93). The mean age was 45.6 years (range 16-82 years). Nearly twenty percent of patients were in the sixth decade as well as in the fifth decade. Data regarding smoking habits were available for 126 patients, while missing for 86 patients; among males 56.9% (41 out of 72) were smokers, and among females 29.6% (16 out of 54). Eighteen patients (8.5%) had reactivated TB. The clinical presentation of EBTB varied (Table 1A and 1B). Seven patients (3.3%) were asymptomatic. The most common symptom was cough, followed by fatigue, fever and weight loss. Few had haemoptysis. In addition, some patients described chest pain (29%), sweating (9%), dyspnoea (8%), and a hoarse voice (3%).

Comorbid condition was noted in 79 patients (37.3%), with 2 or more comorbidities in 7 patients (3.3%), and most frequently registered diabetes (71 patients-33.5%), arterial hypertension (16 patients-7.5%), chronic aethylismus (11 patients-5.2%), chronic gastritis/ulcer disease (10 patients-4.7%).

### Radiological findings

The results of the chest X-ray findings are recorded (Table 2). Bilateral TB lesions were more frequent (120 patients, 56.6%) than unilateral (92 patents, 43.4%). The upper lobes were most commonly affected (127 patients, 59.9) and 70.3% (149 patients) had cavitating lesions, a significantly higher rate than in pulmonary TB as a whole [7]. Major parenchymal lesions (more than one lobe massive involvement or/and significant cavitations) were registered in 72 (34.0%) patients, and were significantly more frequent in patients older than 40 years

( $p=0.04$ ). Twelve patients (5.7%) had miliary disease and 31 (14.6%) had lower lobe disease.

### Bronchoscopic findings

Oedematous-hyperemia was the most common finding at initial bronchoscopy, followed by non-specific bronchitis (39.2% and 35.8% respectively). Only two patients (0.9%) had ulcerous lesions and seven patients (3.3%) had granular subtype (Figure 1). Fibrostenotic and tumorous subtype were significantly more frequent in older patients, with a mean age:  $57.4 \pm 14.1$  and  $57.1 \pm 20.9$  years respectively ( $p=0.0001$  and  $p=0.043$  respectively). Non-specific bronchitis was significantly more common in younger patients (mean age  $41.0 \pm 15.0$  years) ( $p<0.001$ ). Endobronchial lesions were diffused in all cases, except in cases of tumorous form of EBTB which were mainly located in segmental orifices of upper lobar bronchi. In the vast majority of cases the site of EBTB lesions was trachea or main or lobar bronchi, with no correlation of with the prognosis, and no significant difference based on age or sex. There was no significant difference in distribution of endoscopic EBTB subtypes based on sex, with the exception of tumorous subtype, which was significantly more frequent in females ( $p=0.007$ ). No significant difference was found between the distribution of bronchoscopic findings and the extent of disease radiologically ( $p=0.504$ ), nor regarding bronchoscopic finding in patients with recurrent TB compared to newly diagnosed TB patients.

### Microbiological features

As shown in Table 2, 136 patients (64.2%) had positive culture confirmation of TB; sputum culture was positive for Mycobacterium tuberculosis in 117 patients, and an additional 19 patients were confirmed on bronchial wash. A minority of patients were smear positive for acid/alkali fast bacilli, 62 (29.2) from sputum and 26 (12.3) from bronchial wash (Table 2). In the subgroup of patients with radiological finding of TB major parenchymal lesions (more than one lobe massive involvement or/and significant cavitations), there was a significantly higher rate of smear positivity in both sputum and bronchial wash samples compared to the subgroup of patients with TB minor parenchymal lesions (38.9% vs 24.3% and 18.1% vs 9.3% respectively,  $p=0.047$  and  $p=0.021$  respectively), while similar rate of

Age	Gender		Females*		Total	
	Males					
	Number	%	Number	%	Number	%
≤ 29	18	15,1	22	23,7	40	18,9
30-39	18	15,1	18	19,3	36	17,0
40-49	32	26,9	9	9,7	41	19,3
50-59	27	22,7	15	16,1	42	19,8
60-69	16	13,5	17	18,3	33	15,6
≥ 70	8	6,7	12	12,9	20	9,4
<b>Total</b>	<b>119</b>	<b>100,0</b>	<b>93</b>	<b>100,0</b>	<b>212</b>	<b>100,0</b>

\*Females more likely to be younger than 40 years ( $\chi^2=12,3$  DF=5  $p=0,03$ )

Table 1A: Age and gender distribution in 212 patients with EBTB.

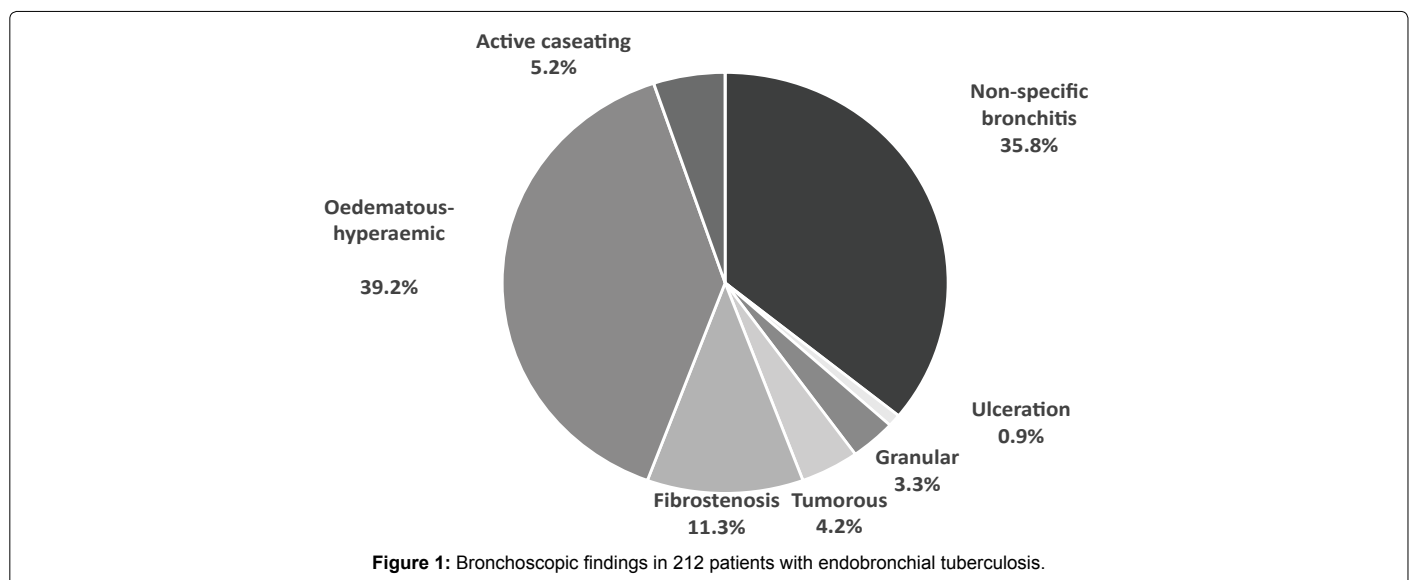
Symptoms	Number (%)	Median (SD) (days)	Min-Max (days)
Cough	155 (73.1)	102.3 (117.6)	10-730
Haemoptysis	27 (12.7)	49.6 (91.5)	1-365
Fever	106 (50.0)	52.4 (48.8)	2-365
Fatigue	116 (54.7)	99.1 (110.2)	10-730
Weight loss	92 (43.4)	93.8 (87.7)	10-450

Table 1B: Frequency and duration of symptoms in 212 patients with EBTB.

Radiology features		Number (%)
Laterality	Unilateral	92 (43.4)
	Bilateral	120 (56.6)
Specific features	Major parenchymal damage*	72 (34.0)
	Minor parenchymal damage	140 (66.0)
	Upper lung fields involved	127 (59.9)
	Atypical TB localization	31 (14.6)
	Cavitation	149 (70.3)
	Miliary TB lesions	12 (5.7)
Microbiology features		
Sputum	Smear positive	62 (29.2)
	Smear negative	143 (67.5)
	Missing data	7 (3.3)
	Culture positive	117 (55.2)
	Culture negative	68 (30.1)
	Missing data	27 (12.7)
Bronchial wash	Smear positive	26 (12.3)
	Smear negative	109 (51.4)
	Missing data	77 (36.3)
	Culture positive	79 (37.3)
	Culture negative	51 (24.1)
	Missing data	82 (38.7)
Sputum and bronchial wash culture positive		60 (28.3)
Positive TB culture from either sample*		136 (64.2)

%-percentage  
 Major parenchymal damage: more than one lobe massive involvement and/or significant cavitation  
 Minor parenchymal damage:  
 \*Sputum culture only positive in 117 patients, and additional 19 patients in whom bronchial wash culture only positive (out of 79 patients bronchial wash culture positive).

**Table 2:** Radiological and microbiological features in 212 patients with EBTB.



culture positivity in sputum and bronchial wash samples (Table 3). There was no significant difference neither in size and extent of the endobronchial lesions nor in the microbial culture findings between patients with reactivated TB and those with newly diagnosed TB.

### Treatment outcome

Standard anti-tuberculosis treatment was given as per WHO recommendations. Eighteen patients with miliary TB or massive parenchymal lesions received the 9-month regimen. Nine patients

received streptomycin as well. With few exceptions, no additional drugs such as steroids were given. None of these patients have shown any resistance to anti-tuberculous drugs. Four patients died two of them due to devastating fibrotic TB lung disease with the advanced COPD comorbidity and subsequent severe respiratory insufficiency, 7 months and 1 year following completion of anti-TB treatment respectively; the other two patients with extensive miliary disease, which failed to respond to anti-tuberculous treatment, in the 2<sup>nd</sup> and 4<sup>th</sup> month of treatment respectively (Table 4).

Extent of Pulmonary TB lesions	Sputum smears positive Number (%)	Sputum culture positive Number (%)	Bronchial washing smear positive Number (%)	Bronchial washing culture positive Number (%)
Major parenchymal damage, 72 patients (100%)	28 (38.9)	41 (60.0)	13 (18.1)	24 (33.3)
Minor parenchymal damage, 140 patients (100%)	34 (24.3)	76 (54.3)	13 (9.3)	55 (39.3)
<b>Total</b>	<b>62</b>	<b>117</b>	<b>26</b>	<b>79</b>
<b>p-value</b>	0.047	0.432	0.021	0.723

**Table 3:** Relationship between microbiological features and the extent of TB parenchymal damage.

6-months anti-tuberculous treatment regimen	9-months anti-tuberculous treatment regimen	1 <sup>st</sup> line anti-tuberculous drugs Resistance	Treatment outcome		Total Number of patients
			Successful	Failed (Lethal**)	
Number of patients (%)	Number of patients* (%)				
194 (91.5%)	18 (8.5%)	None	208 (95.7)	4 (4.3%)	212 (100.0%)

\* Nine patients received streptomycin as well.  
 \*\* Four patients died, two due to devastating lung disease with severe respiratory insufficiency, and the other two with miliary disease, which failed to respond to anti-tuberculous treatment.

**Table 4:** Anti-tuberculous drugs treatment outcome.

	Lee et al. [8]	Chung et al. [3]	Park et al. [10]	An et al. [11]	Morrone et al. [26]	Kim et al. [16]	Qingliang et al. [27]	Ozkaya et al. [14]	Kim et al. [19]	Sahin et al. [12]	Jung et al. [9]	This study
Number of patients	81	114	280	234	75	22	22	23	156	16	233	212
Ethnicity	Asian	Asian	Asian	Asian	Race mixed	Asian	Asian	Turkish	Asian	Turkish	Asian	Caucasian
HIV status	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Negative	Not tested	Unknown	Not tested	Negative	Negative
Radiographic parenchymal lesions	Unknown	Unknown	91%	100%	87% cavitating	100%	95%	100%	58% infiltration	100%	100%	100%
<b>Bronchoscopy finding (%)</b>												
AC	41.9	43	31.4	33.3	0	27.3	9.1	17.3	49.3	37.5	48.9	5.2
OH	13.6	14	27.1	36.7	28.6	68.2	9.1	34.7	21.1	12.5	37.3	39.2
FS	8.6	10.5	19.6	10.2	9.0	0	13.6	4.3	2.6	12.4		10.4
TUM	12.3	10.5		3	1.0	4.5	13.6	21.7	3.8	12.5		4.7
GRAN	13.6	11.4		7.7	1.0	0	31.8	17.3	1.3	18.7	12.8	3.8
ULC	2.4	2.7	1.2	2.6	2.5	0	4.5	0	20	0		0.9
NSB	7.4	7.9		6.4	48	0	18.2	34.3	1.9	0		35.8
Normal					9.0							
Mixed									30.5			

**Legend:** AC=actively caseating, OH=oedematous hyperaemia, FS=fibrostenosis, TUM=tumorous, GRAN=granular, ULC=ulcerating, NSB=non-specific bronchitis.

**Table 5:** Comparison of EBTB features across the studies 2000-2015.

Follow-up bronchoscopy was performed within 4 months of completing treatment in 149 (70.3%) patients in order to assess for bronchostenosis. Significant fibrostenosis was identified in 6 patients who required interventional procedures. All 6 patients had less grade stenosis (mainly active caseating and tumorous form of EBTB) on initial bronchoscopy. Despite all treatment applied, they developed significant fibrostenosis of trachea and main bronchi (defined as 50% and more of the lumen obstructed) that was treated with mechanical recanalization and cryotherapy in all 6 patients, and in one patient silicone stent was placed in trachea because of long complex stenosis. In 2 patients with tumorous form of EBTB resistant to therapy (located in anterior segmental bronchus of right upper lobe), cryorecanalisation and electrocautery were performed with subsequent cryotherapy as well.

The endobronchial findings in our cohort are compared with 11 published studies from 2000 onwards where bronchoscopic findings are reported (Table 5) [3,8,9]. Almost all these studies were in Asian or Turkish populations, and the number of cases varied from 16 to 280, with our cohort comparing favorably in size. All relevant comparison findings are given in discussion.

## Discussion

### Main findings

Despite significant progress in the last 20 years, the incidence of pulmonary tuberculosis is still increasing in many regions of the world, due to the impact of HIV, multidrug-resistant strains, poverty, migration and failings in TB control systems. The incidence of EBTB is also rising [1,5] and we found 32% of patients with TB had evidence of endobronchial involvement at bronchoscopy. Almost all our patients had symptoms, but the duration of these prior to diagnosis, was relatively short. This will reflect the relative ease with which individuals in Belgrade can access a respiratory physician and the high level of clinical suspicion regarding both TB and lung cancer, resulting in rapid access to bronchoscopy.

Our results demonstrate a high level of microbiological confirmation of infection. Only 29% had a positive sputum smear reflecting a lower rate of infectivity than one might estimate based on the high proportion with cavitating lesions on chest X-ray (70.3%). Despite evidence of disease at bronchoscopy, the standard six month

regime of combination antibiotics was adequate in the vast majority of patients. We report only four deaths, and in the 149 patients who underwent follow-up bronchoscopy after treatment, six patients were found to need interventional procedures to correct the endobronchial sequelae. We found no evidence of drug resistance, and none of our cohort was HIV positive.

### Strengths and weaknesses

This is the largest series of cases with endobronchial TB in a Caucasian HIV-negative population from a high TB incident region at the time of the endobronchial TB diagnosis and treatment [6,7]. Compared with the eleven other international studies, only three studies reported cohorts larger than 200 patients (Table 5) [9-11]. Despite being a retrospective case series, this study includes detailed clinical features, with radiology, microbiology and endobronchial biopsy results. Follow up data is comprehensive and includes a control bronchoscopy after treatment in 70% of the cohort.

### Comparison with published literature

In our study, men were more likely than women to be affected which is in contrast with the majority of published data [3,4,9,11-13]. These studies are in Asian populations where the high rates of EBTB in women have been attributed to small calibre airways [14], or sociocultural restrictions on coughing, and the lower rates of tobacco smoking amongst women. Nevertheless, there are reports with a sex ratio similar to ours [13,15], which may relate in part to the higher rate of TB amongst men in Serbia as a whole.

Our results demonstrate an almost equal distribution of EBTB with increasing age, with only a quarter being more than 60 years at diagnosis, in contrast to some reports. There is a peak of EBTB in the elderly, thought to be driven by increasing co-morbidity and reduced immune status, leading to the reactivation of dormant infection [1,16]. Given Serbia has been a high incidence country for many years, reactivation of dormant bacilli is believed to account for 85% of cases [7]. We also noted an association between age and sex, with females more likely to be younger than 40 years ( $p=0.03$ ), in keeping with published data [3,10,12,16,17]. In our series, there was no significant difference in the site of EBTB based on age unlike published data, where lobar and segmental bronchial invasion is more common in the elderly, and trachea and main bronchi are more common in younger adults [12,18].

Only 3% of our patients were asymptomatic, which fits with the lower limit of published data, 3% [23] to 24% [4]. Cough was the most common symptom (73%) as is the experience of other authors [15,18]. Fever and weight loss were recorded at slightly lower rates compared with published data. The average time to diagnosis in our cohort was 6-14 weeks which is significantly shorter than published literature (11 to 26 weeks).

Most EBTB patients have concurrent pulmonary lesions evident on chest X-ray, although a normal chest X-ray is reported in 10-20% of cases [4,8-10,15,19-21] which can cause diagnostic delay [22]. None of our patients had a normal chest X-ray, and non-specific atypical radiographic features were noted in only 15% unlike published literature reporting between 42-90% [11,23]. Cavitating lesions were present in two-thirds of our cohort which is significantly higher than in the pulmonary TB population as a whole, and similar to some studies of EBTB, whilst in contrast to others [15,24].

The endobronchial findings in our cohort are compared with 11 published studies from 2000 onwards where bronchoscopic findings are reported (Table 5) [3,8-12]; almost all these studies were in Asian or Turkish populations, and the number of cases varied from 16 to 280. The predominance of oedematous hyperemic (39%) and non-specific bronchitis (36%) in our cohort is a significant finding compared with these studies where active caseation was much more common [3,8-13,19].

The bronchoscopic findings in our cohort, of a high proportion of non-specific bronchitis were similar to the study of Ozkaya [25] and Morrone [26], but quite different to the other 9 papers used for the international comparison. These differences might be explained in part by the shorter duration of symptoms prior to diagnosis, around two months in half of our patients, resulting in the higher proportion of early stage disease. Active caseating endobronchial lesions were only present in 5% of our cohort compared with more than 40% patients in three Asian studies [8,16,26]. Both studies amongst Turkish patients reported a high level of tumorous disease, 13 and 22%, compared with only 5% in our cohort [12,27].

However, racial and genetic differences seem to play an important role in the clinical presentation, course and prognosis of EBTB. Tracheobronchial stenosis is uncommon in the West but is prevalent in many Asian countries. The incidence in Hong Kong is reported to be 18% in patients with parenchymal TB [28], but can reach 68% during the first 6 months of the disease [4].

There is some evidence to suggest different outcomes based on the nature of the endobronchial disease. A study conducted by Um et al. [17], revealed that pure or combined fibrostenotic subtype was an independent risk factor for bronchial stenosis. Six of our patients developed significant fibrostenosis and required interventional procedures. Evidence of fibrostenotic and tumorous subtypes at diagnosis were significantly linked with older age in our study, while non-specific bronchitis was significantly more common in younger patients. There are scarce published data comparing age and EBTB subtypes, but the study by Um et al. [17], which analysed 67 patients; reported age over 45 years was one of three independent predictors of persistent airway stenosis. The other two were pure or combined fibrostenotic lesions, and duration of symptoms prior to treatment greater than 90 days. A paper from Beijing in 2014, reported the need for surgical intervention in 1% of patients with endobronchial TB, which is similar to the 3% reported here [29].

Published data varies greatly on the infectivity of individuals with EBTB. Sputum smear positivity was reported between 52%-91% in three studies [3,26,30]; whilst two other studies reported much lower levels of 9 and 17% [4,15]. One study reported no positive sputum smear results [12]. Our results confirm sputum smear positivity in nearly one third of the patients, while sputum cultures were positive in over half of cases, which is consistent with reported results [3]. EBTB in our cohort was not highly contagious, despite coexisting parenchymal lesions in all of our cases of which two thirds showed cavitation. However, the studies are not directly comparable. In our cohort, as in others, bronchoscopy was performed on the basis of abnormal chest X-ray and clinical suspicion of TB and lung cancer, regardless of sputum smear result [31,32]. In contrast, Morrone et al. [26] studied only sputum smear positive patients. In our series, there was a positive correlation between active caseation within the bronchial tree and a positive bronchial wash smear. This is a direct result of the tuberculous granulomas formed on the bronchial mucosal surface. Kim et al report higher sputum smear positivity with ulcerative and actively caseating

EBTB, rather than oedematous or fibrostenotic [33]. However, in our study microbiological findings reflect predominantly the severity and type of pulmonary lesions, as well as the endobronchial features.

Little is known about the relationship between EBTB and HIV infection, as the published literature rarely documents HIV status. All the patients in our cohort were HIV negative.

## Conclusion

In spite of the developments in diagnosis, therapy and prevention in the past several decades, the incidence of pulmonary tuberculosis, and endobronchial TB, is still increasing in many regions of the world. The symptoms and signs of EBTB are not unique, and the majority of patients will have concurrent lung parenchymal lesions. Bronchoscopy is an essential diagnostic tool for EBTB and should be performed early in the course of the disease. Repeat bronchoscopy after treatment should be considered in order to prevent and treat tracheal or bronchial stenosis. Early diagnosis and early onset of therapy is vital in order to prevent the development of unwanted sequelae such as bronchostenosis. Consideration should be given to a nine month treatment course.

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