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Manifestation and diagnosis of tuberculosis of the larynx at the Universitas Academic  
Hospital Bloemfontein

By

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Submitted in fulfilment of the academic requirements in respect of the Master's  
Degree MMed in the Department of Otorhinolaryngology Faculty of Health Science

At the

**UNIVERSITY OF FREE STATE**

**October 2018**

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**Manifestation and diagnosis of tuberculosis of the larynx  
at the Universitas Academic Hospital Bloemfontein**

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# Declaration

I, Dr Abongile Matimba declare that the coursework Master's Degree mini-dissertation that I herewith submit in a publishable manuscript format for the Master's Degree qualification Otorhinolaryngology at the University of the Free State is my independent work, and that I have not previously submitted it for a qualification at another institution of higher education.

# Acknowledgement

I would like to express my gratitude to my supervisors Professor RY Seedat, Dr M Moncho and Dr J Musoke, the HSREC of the University of the Free State, the Department of Health, consultants, fellow colleagues, nursing staff, administrative clerk in the otorhinolaryngology department, and for their support and contribution in making this study a success.

# Abbreviations

AFB: Acid fast Bacilli

CXR: Chest X-ray

ENT: Ear Nose and Throat

HIV: Human Immunodeficiency Virus

MC&S: Microscopy culture and sensitivity

MRI: Magnetic resonance imaging

MTBC: Mycobacterium tuberculosis complex

PCR: Polymerase chain reaction

PPD: Purified protein derivative test

PPI: Proton pump Inhibitor

PTB: Pulmonary TB

RHZE: R- Rifampicin

H- Isoniazid

Z- Pyrazinamide

E- Ethambutol

SA: South Africa

TB: Tuberculosis

WHO: World Health Organisation

# Chapter 1 – Literature Review

## 1.1 Introduction

Tuberculosis (TB) is the most frequent granulomatous disease involving the larynx, often secondary to pulmonary tuberculosis (PTB). However, PTB still remains a major global health problem. Laryngeal TB occurs in less than 2% of extra-pulmonary TB cases compared to 25% in the first decades of the 20th century<sup>1</sup>.

South Africa (SA) is one of the countries with the highest burdens of TB, with the World Health Organisation (WHO) reporting an incidence of 454,000 cases of active TB in 2016<sup>2</sup>. Out of the 454,000 TB incident cases in SA, it is estimated by WHO that about 258,000 [57%] people had Human Immunodeficiency Virus (HIV) co-infection and 127,000 [28%] had extra-pulmonary TB<sup>2</sup>.

Otolaryngologists should remain on high alert while dealing with unusual patterns of airway infection<sup>3</sup>. Early diagnosis relies on clinical suspicion. Several observational studies have found that clinical manifestations of laryngeal TB seem to differ from those described in the past, as clinical presentation of laryngeal TB was dominated by constitutional symptoms, misdiagnosis and incorrect treatment<sup>4</sup>.

## 1.2 Pathogenesis

Tuberculosis is a chronic bacterial infection caused by *Mycobacterium tuberculosis* complex (MTBC). Included in the MTBC is *Mycobacterium tuberculosis*, *Mycobacterium canettii*, *Mycobacterium bovis*, *Mycobacterium africanum* and other *non-tuberculous mycobacteria organisms*. Humans are believed to be the only host for infections with *Mycobacterium africanum* and *Mycobacterium tuberculosis*<sup>5</sup>.

Predisposing factors include smoking, alcohol, malnutrition and immunosuppression<sup>4</sup>.

Mycobacterial infections are usually classified into two groups:

- Infections caused by *Mycobacterium tuberculosis complex (MTBC)*.
- Infections caused by non-tuberculous mycobacterial (NTM).

The pathogenesis of laryngeal tuberculosis may be primary or secondary. Primary lesions occur in the absence of current pulmonary disease<sup>6</sup>. In a review of 60 cases, 15% of the study participants had primary laryngeal TB, 47% had active PTB and 33% had history of PTB as well as pulmonary changes on Chest X-ray (CXR)<sup>6</sup>.

The pathogenicity of TB in the larynx is mainly cell-mediated immunity also known as type 4 hypersensitivity, process whereby macrophage bactericidal mechanisms are activated followed by survival of the mycobacteria within the macrophage. Then there is proliferation within the macrophages inducing production of proinflammatory cytokines. The local inflammatory process induces the recruitment of several cell types including monocytes, neutrophils and dendritic cells and it forms a characteristic granuloma in the affected tissue.

There are two theories for the pathogenesis of laryngeal TB:

- The bronchogenic theory, which states that laryngeal involvement is secondary to pulmonary disease (direct spread).
- The haematogenous or lymphatic theory, which states that the larynx is infected from sites other than the lungs.

### **1.3 Clinical presentation of Laryngeal TB**

Common clinical symptoms include hoarseness of voice (80-100%), dysphagia and odynophagia (50- 67%), followed by cough (44-48%), dyspnoea (25%), haemoptysis (18-29%) and cervical lymphadenopathy (12%)<sup>7</sup>.

Constitutional symptoms such as night sweats, weight loss, fever and fatigue had previously been the major symptoms described, due to progressive PTB. Classic signs of laryngeal TB are localized oedema and granuloma which can be either ulcerative or exudative<sup>8</sup>.

Laryngeal TB may be categorized into four types based on laryngoscopic findings:

- Whitish ulcerative lesions (40.9%).
- Nonspecific inflammatory lesions (27.3%).
- Polypoid lesions (22.7%).
- Ulcerofungative mass lesion (9.1%)<sup>8</sup>

Classically, laryngeal TB involved the posterior half of the larynx because of pooling of the infected sputum. However, localization of laryngeal lesions in the anterior half of the larynx now occurs twice as often as in the posterior half, and vocal cords are the most commonly affected site with about 50 – 70% of laryngeal TB cases<sup>4</sup>. This is followed by false cords (40 – 50%), and epiglottis, aryepiglottic folds, arytenoids, posterior commissure and or subglottis (10 –15%) in certain cases<sup>4</sup>.

In a review of 738 cases of laryngeal TB , Gallas et al reported that 60.5% were localised to one region of the larynx, most frequently the vocal cords<sup>9</sup>.

Another change in the clinical pattern of laryngeal TB is in its appearance. The classical laryngeal TB lesions involved diffuse whitish edema or ulcerated lesions and chondritis. In the current era, an ulcerated larynx can still be encountered, information on the recent literature suggests that in most cases the lesions are hypertrophic or even exophytic<sup>4</sup>.

## **1.4 Diagnosis**

The usual TB diagnosis utilizes an approach which combines medical history, tuberculin skin test, CXR, as well as bacteriological examination<sup>9,10</sup>, due to TB not having specific clinical features<sup>11</sup>. Laboratory diagnosis includes microscopy, culture and molecular testing (Xpert MTB/RIF (Cepheid, Sunnyvale, CA, United States)) as well as histology morphology and Ziehl-Neelsen stain from laryngeal tissue specimens, which show acid-fast bacilli as suggestive of TB infection<sup>8</sup>. Complementary sputum microscopy, culture and sensitivity may also help to diagnose PTB as it may be the source of the laryngeal TB<sup>12</sup>. CXR and sputum examinations are however good for screening PTB<sup>13</sup>.

Computerized tomography and magnetic resonance imaging scan can show typical signs, such as mucosal lesions without infiltration of cartilaginous or prelaryngeal areas and paralaryngeal fat<sup>10</sup>.

Other differential diagnostic considerations of laryngeal lesions include syphilis, sarcoidosis, Wegener's granulomatosis, fungal infections, actinomycosis, leprosy, systemic lupus erythematosus, rheumatoid arthritis, relapsing polychondritis and amyloidosis. Both TB and malignancy may coexist in the same patient or laryngeal TB may mimic laryngeal cancer<sup>9</sup>. Furthermore, it is important to note that patients with malignant tumours of the larynx, may also have concomitant TB, because of impaired cell mediated immunity<sup>4</sup>.

However, the cornerstone of the laboratory diagnosis of laryngeal TB is by histopathological examination of a biopsy specimen, as well as microbiological confirmation by microscopy, culture and PCR specifically for MTB<sup>7</sup>. Epithelioid granulomas with Langerhans type giant cell, granulomatous inflammation and caseating granuloma formation are characteristic features of this form of TB.

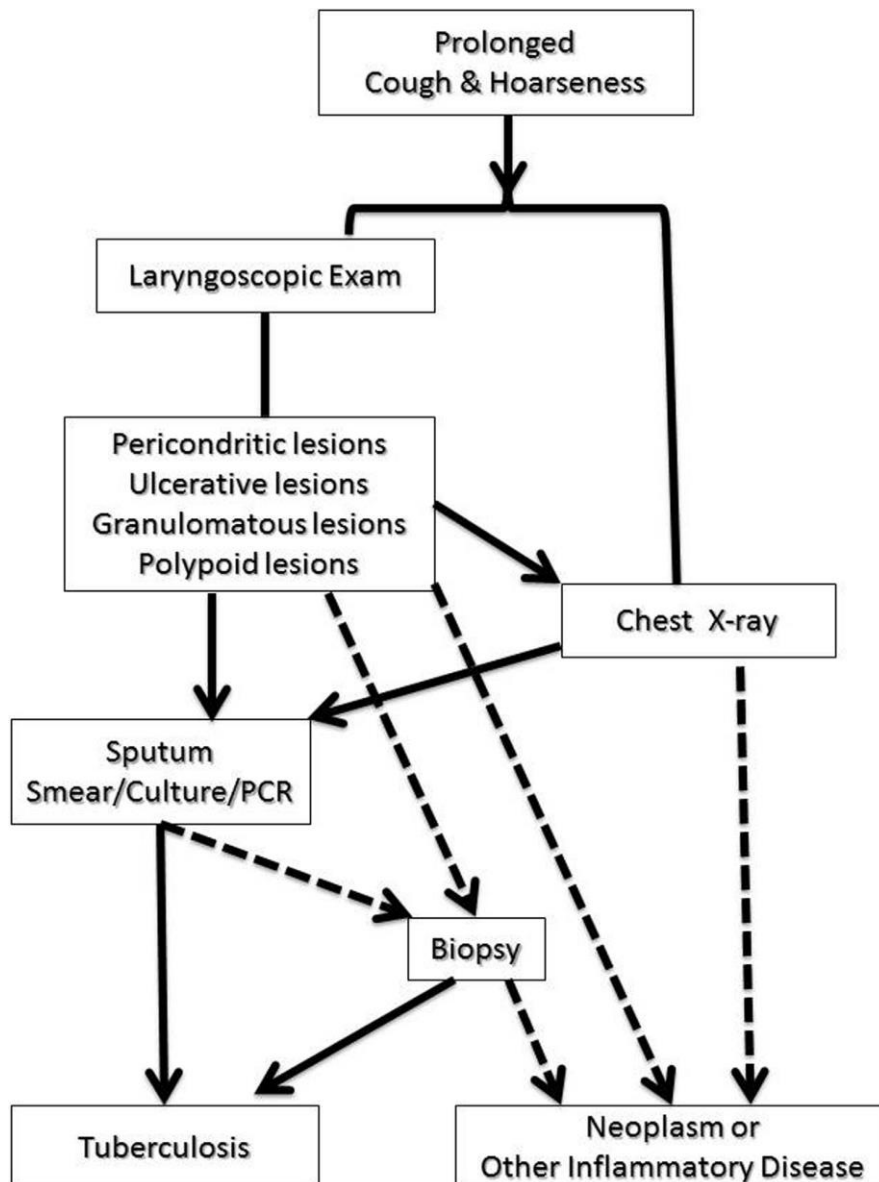
## **1.5 Treatment**

Laryngeal TB therapy consists of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol (RHZE) for susceptible mycobacterium strain, offers a good prognosis generally curing the laryngeal disease without any sequela<sup>7</sup>. Laryngeal TB is a form of extra-pulmonary TB. Therefore, treatment is instituted for six to nine months with an intensive phase of two months (RHZE) followed by continuation phase of four to seven months with Rifampicin and Isoniazid (RH)<sup>2,14</sup>.

Complete resolution of laryngeal symptoms mainly occurs within two to nine months<sup>6</sup>. Patients usually have a good response to chemotherapy and the lesions disappear. Voice quality also improves within three months of treatment<sup>13</sup>.

If not treated early, laryngeal TB could cause posterior glottic stenosis, subglottic stenosis, muscular involvement, and vocal cord paralysis when the cricoarytenoid joint or recurrent laryngeal nerve are invaded<sup>6</sup>. The prognosis of the disease is optimistic with early diagnosis and proper medical treatment<sup>8</sup>.

The clinical approach to laryngeal TB is usually straight forward as depicted in Figure1.



**Figure 1: Approach to laryngeal TB diagnosis**

Continuous arrow: positive findings, dashed arrow: negative findings<sup>12</sup>

# Chapter 2 – Publishable Article

## Manifestation and diagnosis of tuberculosis of the larynx at the Universitas Academic Hospital Bloemfontein

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### 2.1 Abstract

**Introduction and Aim:** Tuberculosis (TB) is the most frequent granulomatous disease involving the larynx. However, the incidence is unknown at Bloemfontein. Hence, the aim of this study was to determine the incidence, clinical presentation and optimal diagnostic methods for laryngeal TB in patients presenting with laryngeal lesions to Universitas academic hospital in Bloemfontein.

**Methods:** This was a prospective study conducted over one year from 1 May 2017 to 30 April 2018. All patients (n=80) undergoing direct laryngoscopy under general anaesthesia were included and a biopsy was sent for histopathological examination, Xpert MTB/RIF and TB microscopy, culture and sensitivity.

**Results:** Of the 80 patients, five (6,25%) were diagnosed with laryngeal TB. The median age at presentation was 56,0 years (range 18.1- 83.5 years) with the majority 64 (80%) being males. The most common symptom was dysphonia in all five patients with laryngeal TB. The most frequent endoscopic presentation was a granulomatous like lesion, present in three patients, followed by tumour and ulcerofungative lesion in one patient each. Three patients with laryngeal TB patients had active pulmonary lesions (cavities in the upper lobes) and (hilar lymph nodes) and two had inactive pulmonary lesions (upper lobe fibrosis) on CXR. The diagnosis of laryngeal TB was based on histology alone in two patients, histology, together with a positive tissue Xpert MTB/RIF in another patient and on positive tissue TB cultures in the last two

patients. None of the biopsy specimens submitted to histology or microbiology were positive on direct microscopy for AFB.

**Conclusion:** We diagnosed TB in 6.25% (5/80) of patients who presented with laryngeal lesions. The diagnosis of laryngeal TB required a combination of histopathology, culture and PCR. The successful management of patients with laryngeal TB requires a high clinical index of suspicion, prompt diagnosis and early initiation of anti-tuberculosis chemotherapy.

## 2.2 Introduction

South Africa has the highest burden of tuberculosis/human immunodeficiency virus (TB/HIV) co-infection in the world. While significant progress has been made in improving the diagnosis of pulmonary tuberculosis (PTB), the diagnosis of extra-pulmonary TB remains a significant challenge in resource-constrained settings<sup>2</sup>.

Laryngeal tuberculosis (TB) is one of the most common extra-pulmonary manifestations of tuberculosis. The incidence of laryngeal TB has significantly declined to <2% in the last fifty years due to availability of anti-TB drugs in the public health system<sup>15</sup>. When patients present with laryngeal symptoms, including cough, hoarseness, haemoptysis, dysphagia, odynophagia and stridor laryngeal TB should be considered as the differential diagnosis.

Predisposing factors for laryngeal TB include smoking, alcohol, malnutrition and immunosuppression<sup>3</sup>. Previously, laryngeal TB was shown to affect the posterior larynx in most patients, since it spread directly along the airway<sup>6</sup>. Recent reports indicate that there has been a shift in clinical presentation as it affects any part of the larynx and shows various clinical manifestations<sup>6</sup>. Evidence suggests that the larynx is infected by *Mycobacterium tuberculosis* from bronchogenic or hematogenous routes and that patients with laryngeal TB could present with or without PTB<sup>16</sup>.

On laryngoscopy, laryngeal lesions vary from erythema to ulceration and exophytic masses. These laryngoscopic appearances may mimic other causes of laryngeal lesions such as neoplasm<sup>16,17</sup>. Laryngeal TB is usually diagnosed on characteristic histologic findings of chronic granulomatous inflammation with caseous necrosis<sup>13</sup>.

Laboratory diagnosis includes microscopy, culture and molecular testing (Xpert MTB/RIF (Cepheid, Sunnyvale, CA, United States) as well as histology morphology and Ziehl-Neelsen stain from laryngeal tissue specimens which show acid-fast bacilli as suggestive of TB infection<sup>8</sup>. CXR and sputum examinations are however good for screening for PTB<sup>13</sup>. Screening for PTB in SA is by performing Xpert MTB/RIF on sputum, which is also done on extra pulmonary specimens such as tissues<sup>15</sup>. Culture is the WHO recommended gold standard for the diagnosis of TB disease<sup>2</sup>.

Laryngeal TB is often misdiagnosed, thus delaying the initiation of appropriate anti-TB treatment<sup>12</sup>. The treatment of laryngeal TB is therapy by anti-tuberculosis drugs and the prognosis of laryngeal TB is optimistic with early diagnosis and proper medical treatment<sup>16</sup>.

## **2.3 Aim**

The aim of this study was to determine the incidence, clinical presentation and optimal diagnostic methods for laryngeal tuberculosis in patients presenting with laryngeal lesions to a large tertiary hospital in Bloemfontein.

## **2.4 Methods**

### **Study design**

We conducted a prospective, descriptive study in adults admitted for laryngoscopy and biopsy in the Department of Otorhinolaryngology, Universitas academic hospital, Bloemfontein, during the period 1st May 2017 to 30th April 2018.

### **Study sample**

All patients 18 years and older, with laryngeal symptoms and lesions, who underwent laryngoscopy and biopsy were included. Eighty patients fulfilled these criteria. No patients were incidentally excluded.

## **Measurement**

Data collected (Appendix A).

Histopathological and microbiological investigations (MC&S, Xpert MTB/RIF) were performed from laryngeal specimens to diagnose laryngeal TB as part of patient routine management. CXR was performed in all cases and sputum MC&S were performed on patients diagnosed with laryngeal TB. The age, symptoms duration, laryngoscopy findings were analysed in this study and disease prevalence reported.

## **Pilot study**

A pilot study was performed using the records of the first ten patients. These patients were included in the study.

## **Statistical Analysis**

Statistical analysis was performed by the Department of Biostatistics. Descriptive statistics, namely frequencies and percentages for categorical data, medians and percentiles for continuous data, were calculated.

## **Implementation of findings**

This study reports on the presentation and treatment of patients with laryngeal TB at Universitas Hospital and compare our patient profile, treatment and outcomes with that reported in the current literature. This may provide insight about patients diagnosed with laryngeal TB and guide their management.

## **Ethical considerations**

The study was approved by the Health Sciences Research Ethics Committee of the University of the Free State (HSREC 35/2017) (Appendix C). Permission to perform the study was obtained from the Free State Department of Health (Appendix D). Consent (Appendix B) was obtained from all participants. Confidentiality was maintained by keeping patient information on the dataform or spreadsheet anonymous.

## 2.5 Results

### Demographics

Eighty patients were included in this study. The median age of the patients at presentation was 56,0 years (range of 18,1- 83,5 years) with 64 males (80%) and 16 females (20%).

The diagnosis obtained on histological examination of the laryngeal tissue is indicated in Table 1.

**Table1 - Laryngeal tissue diagnoses (n=80)**

Diagnosis	Number of patients (%)
Laryngeal Tuberculosis	5 (6,25%)
Laryngeal cancer	45 (56,3%)
Chronic laryngitis	12 (15%)
Singer's nodule	10 (12,5%)
Dysplasia	5 (6,25%)
Laryngeal papilloma	3 (3,8%)

Five of the 80 (6,25%) study patients were diagnosed with laryngeal TB. with two (40%) of these patients having laryngeal TB concurrent with PTB. One( 20%) [1/5]had both Xpert MTB/RIF positive and granulomas positive on the laryngeal biopsy results, two (40%) had granulomas on tissue histology, two (40%) had positive microbiology tissue culture results. None of the patients had positive tissue Ziehl-Neelsen stain on histology results.

On the CXR, 43 (53,4%) had a normal CXR, 32 (40%) had features of inactive/old PTB.

Five (6,25%) of the study patients[5/80] had positive sputum TB MC&S results. Of these five, two (40%) had concurrent laryngeal TB, one (20%) had the clinical appearance suspicious of laryngeal TB but with negative tissue histology, tissue TB culture and Xpert MTB/RIF. Two (40%) had laryngeal squamous cell carcinoma concurrent with PTB. Both these patients were HIV positive.

### **Five laryngeal TB patients**

All five (100%) patients diagnosed with laryngeal TB were males. Their median age was 54,8 years (range 39,3-60,9 years). All five patients were smokers and four (80%) of the patients were alcohol users. Two of the patients were HIV positive, while three were HIV negative.

Five patients with laryngeal TB are depicted in Table 2.

**Table 2- Presenting symptoms in 5 patients with Laryngeal TB**

<b>Symptom</b>	<b>Number of patients (%)</b>	<b>Median duration (months)</b>
Dysphonia	5 (100%)	4
Cough	3 (60%)	4
Odynophagia	3 (60%)	3
Dyspnea	3 (60%)	2
Dysphagia	1 (20%)	3
Weight loss	1 (20%)	2

The common endoscopic appearance was granulomatous lesions in three (60%) patients (Table 3). Three (60%) of the five patients had active pulmonary TB (cavities in the upper lobes and hilar lymph nodes) on CXR. Two (40%) had inactive TB (upper lobe fibrosis), but did not report current or previous PTB treatment.

**Table 3 – Profile of 5 Patients with Laryngeal TB**

Patient	Age	TB history	Sites affected	Endoscopic appearance	CXR findings	Microbiology Tests			Histology
						Xpert MTB/RIF tissue	Sputum TB culture	Tissue TB culture	
1	60	None	True cords	Granulomatous lesion	Inactive	Negative	Negative	Negative	TB granuloma
2	39	PTB and contact with TB	False cords	Granulomatous lesion	Active	Negative	Positive	Negative	TB granuloma
3	43	None	False cords & aryepiglottic fold	Tumour	Inactive	Negative	Negative	Positive	Squamous cell carcinoma
4	54	Contact with TB	All sites except interarytenoid region	Ulcerofungative	Active	MTB detected	Positive	Negative	TB granuloma
5	56	Contact with TB	True & false cords and interarytenoid region	Granulomatous lesion	Active	Negative	Negative	Positive	Dense chronic inflammation

The five patients diagnosed with laryngeal TB were treated with a RHZE TB regimen. The patients with primary laryngeal TB were treated for six months, while the patients with laryngeal TB patients with concurrent PTB and patient with concurrent laryngeal carcinoma were treated for nine months. There is no specific reason why the primary health practitioners decided to treat the two groups differently. All patients showed complete regression in symptoms and endolaryngeal lesion during follow up examination sessions.

## 2.6 Discussion

Laryngeal TB commonly occurs in male adults aged between 40 and 50 years, with the median age of 51.4 years<sup>12,13</sup>. Similarly, the median age in our study is 54,8 years with all five patients being male.

Dysphonia is the most common laryngeal symptom<sup>9,13,18</sup>, but odynophagia and dyspnoea can also be presenting symptoms. The chief symptom of laryngeal TB is dysphonia (96,6%), followed by odynophagia (67%) and cough (51%), with constitutional symptoms such as weight loss being rare<sup>6,7</sup>. Our findings are similar to that reported in the literature with all five patients presenting with dysphonia, followed by cough, odynophagia and dyspnea which were observed in three patients.

Lifestyle risk factors reported in laryngeal TB include smoking, alcohol, immunosuppression and malnutrition. Topak et al reported that about 94% of laryngeal TB patients have a history of tobacco use and only 2% have a history of alcohol use<sup>15,8</sup>. A study in Iran showed that 32% of laryngeal TB patients were heavy smokers<sup>16</sup>. In our study all five (100%) were heavy smokers and four (80%) had a history of alcohol use.

Additional risk factors identified in patients with laryngeal TB are diabetes mellitus, malnutrition and immunodeficiency<sup>4</sup>. Of the five positive laryngeal TB patients, one had previous PTB, two had contact with a TB patient and one was diagnosed with PTB prior to the study. In our study none had diabetes mellitus and two were HIV positive.

Kurokawa et al described that infected subsites were true cord 94%, arytenoids 35%, false cords 23,5% and epiglottis 23,5% , other authors reported that affected sites were vocal folds, vestibular folds, epiglottis, arytenoids, aryepiglottic folds and interarytenoid region<sup>12,17,18</sup>. A different picture to Kurokuwa et al was observed in this study where of the five laryngeal TB patients, the most common affected laryngeal sites were the false cords four, followed by true cords, aryepiglottic folds and epiglottis three and the least affected sites being epiglottis and arytenoids in two patients.

Laryngeal TB lesions reported in literature have different presentations such as, whitish ulcerative lesions, nonspecific inflammatory lesions, polypoid lesions,

ulcerofungative lesions and granulomatous lesions which can either be ulcerative or exudative<sup>8,19</sup>.

The most frequent endoscopic presentation in our study was a granulomatous like appearance in three (60%) patients, followed by ulcerofungative and tumour laryngeal lesions in one (20%) of each patient.

The CXR is an important adjunctive test, since images suggestive of PTB in individuals with laryngeal lesions raise the suspicion of laryngeal TB<sup>20</sup>. In our study three patients with laryngeal TB had active lesions with cavities in the upper lobes and enlarged hilar lymph nodes and two had inactive lesions with upper lobe fibrosis on CXR.

El Ayoubi et al described that laryngeal biopsies for histopathological and bacteriological examination were carried out to diagnose laryngeal TB, histology results for laryngeal TB were giant cell granuloma, caseous necrosis and giant Langerhans cells<sup>8,21</sup>. Bacteriological examination consisted of positive TB tissue culture and PCR<sup>8,14,16</sup>. Similar diagnostic results were observed in our study. Of the five laryngeal TB patients, two (40%) were diagnosed based on tissue histology (necrotising epithelioid granulomas with giant Langerhans cell), one (20%) on both tissue Xpert MTB/RIF and tissue histology (caseating epithelioid granulomas with giant cells), none had positive Ziehl-Neelsen stain on histology and two (40%) were diagnosed on tissue TB culture.

It is believed that laryngeal TB is as a result of the hematogenous spread from a primary focus (hematogenous theory) or by direct spread of bacilli in bronchial secretions (bronchial theory)<sup>6</sup>. A pulmonary focus in 97,2% of laryngeal TB supports the direct spread from a bronchial focus<sup>7,20</sup>. A different picture is observed. Five patients [5/80] had positive TB sputum MC&S and of these, two had PTB concurrent with laryngeal TB, one had clinical presentation suggestive of PTB and an endoscopic appearance of laryngeal TB (suspected laryngeal TB) but negative tissue histology, tissue TB culture and Xpert MTB/RIF diagnostic tests with concurrent PTB. Moreover, two patients had PTB concurrent with laryngeal cancer.

The knowledge concerning the clinical features and the most common endoscopic characteristics of laryngeal TB may guide physicians to continue the diagnostic investigation for laryngeal TB<sup>22,23</sup>. This may be through laryngeal biopsies and

histopathological studies<sup>22,24</sup>. It should be kept in mind that both TB and malignancy may coexist in the same patient<sup>7</sup>.

Laryngeal TB mimics laryngeal cancer hence the two need to be differentiated<sup>19,22</sup>. Two of the five patients diagnosed with laryngeal TB had concurrent PTB (secondary laryngeal TB) and three (60%) had primary laryngeal TB.

Treatment consist of anti-tuberculosis chemotherapy for six to nine months with two months of RHZE, followed by four to seven months of RH. Cure without sequelae was obtained in of cases<sup>8</sup>. According to the literature, most lesions disappear over a two to four months period<sup>7,25-28</sup>. All patients in the study who were treated for laryngeal TB showed complete regression of symptoms and endolaryngeal lesion within four months of follow up.

### **Limitations of study**

Limitations of this study included a very small sample size of only 5 patients with laryngeal TB. Other pitfalls included patients who were diagnosed with active PTB on presentation and had to be postponed to approximately six weeks while on TB treatment before laryngeal biopsies could be taken. This could have resulted in these patients having negative TB diagnostic tests from the laryngeal tissue specimen.

## **2.7 Conclusion and Recommendations**

We diagnosed TB in 6.25% (5/80) of patients who presented with laryngeal lesions. The diagnosis of laryngeal TB required a combination of histopathology, culture and PCR whereas literature reports TB culture as the gold standard test. The successful management of patients with laryngeal TB requires a high clinical index of suspicion, prompt diagnosis and early initiation of anti-tuberculosis chemotherapy.

Primary laryngeal TB is not as rare as generally considered from literature. Although this series is of a small number, it does provide some insight towards clinical features, endoscopic appearance and management of laryngeal TB. In some cases, TB of the larynx occurs concurrently with PTB (secondary laryngeal tuberculosis).

We recommend that for all patients with laryngeal lesions, tissue specimen should be sent for TB MC&S because laryngeal carcinoma may co-exist with laryngeal TB.

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# Appendices

## Appendix A - Dataform

### Manifestations and diagnosis of TB of the larynx at Universitas Academic Hospital Bloemfontein

#### ENT Dataform

##### General Data

Date of presentation.: \_\_\_\_\_

Date of birth:(dd/mm/yyyy) \_\_\_\_\_

Gender:(M/F) \_\_\_\_\_

1-3		
4-11		
12-19		
20		

##### Clinical Presentation

	Yes	No	Duration(Mon)
Dysphonia			
Cough			
Odynophagia			
Dyspnea			
Dysphagia			
Weight loss			

	21		22-:
	24		25-:
	27		28-:
	30		31-:
	33		34-:
	36		37-:

Smoking History

Yes	No
-----	----

Alcohol history

Yes	No
-----	----

##### Past Medical history

	Yes	No	
Any TB ?			
Diabetes Mellitus			
Contact with TB			
On TB treatment			
HIV status	Pos	Neg	Unknown

	41
	42
	43
	44
	45

##### Affected laryngeal Sites

Epiglottis	
Interarytenoid region	

	46
	47

	Left	Right
Arytenoid region		
Aryepiglottic fold		
False cord		
True Cord		

	48-49
	50-51
	52-53
	54-55

##### Endoscopic appearance

	Yes
Granulomatous lesion	
Non specific inflammatory	
Ulcerofungative lesion	
Polypoid lesion	
Tumour	

 56

CXR TB pathology

Active	
Inactive	
Normal	

 57

**Diagnosis**

TB Gene xpert

TB	No TB
<input type="checkbox"/>	<input type="checkbox"/>

58

Histology- Granuloma & Z-N stain

TB	No TB
<input type="checkbox"/>	<input type="checkbox"/>

59

Tissue Culture & Sensitivity

TB	No TB
<input type="checkbox"/>	<input type="checkbox"/>

60

MC & S sputum

Positive	Negative	Not Done
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

61

**Treatment**

Standard TB Regimen

Yes	No
<input type="checkbox"/>	<input type="checkbox"/>

62

## Appendix B – Consent

### CONSENT TO PARTICIPATE IN RESEARCH

**PROJECT TITLE: Manifestation and diagnosis of tuberculosis of the larynx at the Universitas Academic Hospital Bloemfontein**

You have been asked to participate in a research study.

You have been informed about the study by Dr A Matimba, Department of Ear Nose & Throat, Faculty of Health science, University of Free State.

You may contact Dr A Matimba at 051 4053344 any time if you have questions about the research.

You may contact the Secretariat of the Ethics Committee of the Faculty of Health Sciences, UFS at telephone number (051) 4052812 if you have questions about your rights as a research subject.

Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to terminate participation.

If you agree to participate, you will be given a signed copy of this document as well as the participant information sheet, which is a written summary of the research.

The research study, including the above information has been verbally described to me. I understand what my involvement in the study means and I voluntarily agree to participate.

\_\_\_\_\_  
**Signature of Participant**

\_\_\_\_\_  
**Date**

\_\_\_\_\_  
**Signature of Witness**  
*(Where applicable)*

\_\_\_\_\_  
**Date**

\_\_\_\_\_  
**Signature of Translator**  
*(Where applicable)*

\_\_\_\_\_  
**Date**

# Appendix C – Ethics Approval



IRB nr 00006240  
REC Reference nr 230408-011  
IORG0005187  
FWA00012784

04 May 2017

DR A MATIMBA  
DEPT OF OTORHINOLARYNGOLOGY  
FACULTY OF HEALTH SCIENCES  
UFS

Dear Dr Matimba

**HSREC 35/2017 (UFS-HSD2017/0161)**

**PROJECT TITLE: MANIFESTATION AND DIAGNOSIS OF TUBERCULOSIS OF THE LARYNX AT THE UNIVERSITAS ACADEMIC HOSPITAL BLOEMFONTEIN**

1. You are hereby kindly informed that the Health Sciences Research Ethics Committee (HSREC) approved this protocol after all conditions were met. This decision will be ratified at the next meeting to be held on 30 May 2017.
2. The Committee must be informed of any serious adverse event and/or termination of the study.
3. Any amendment, extension or other modifications to the protocol must be submitted to the HSREC for approval.
4. A progress report should be submitted within one year of approval and annually for long term studies.
5. A final report should be submitted at the completion of the study.
6. Kindly use the **HSREC NR** as reference in correspondence to the HSREC Secretariat.
7. The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

Yours faithfully

  
.....  
PROF WJ STEINBERG  
VICE CHAIR: HEALTH SCIENCES RESEARCH ETHICS COMMITTEE  
Cc: R Seedat



# Appendix D – Free State Department of Health Approval



health

Department of  
Health  
FREE STATE PROVINCE

26 April 2017

Dr A Matimba  
Dept. of Otorhinolaryngology  
Faculty of Health Science  
UFS

Dear Dr A Matimba

**Subject: Manifestation and diagnosis of tuberculosis of the larynx at the Universitas Academic Hospital Bloemfontein.**

- Please ensure that you read the whole document, Permission is hereby granted for the above – mentioned research on the following conditions:
- Participation in the study must be voluntary.
- A written consent by each participants must be obtained
- Serious adverse events to be reported and/or termination of the study.
- Ascertain that your data collection exercise neither interferes with the day to day running of Universitas Hospital nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of the University of Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to [sebeelats@fshealth.gov.za](mailto:sebeelats@fshealth.gov.za) before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- Please discuss your study with the institution managers/CEOs on commencement for logistical arrangements
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future research will only be granted permission if correct procedures are followed see <http://mhrd.hst.org.za>

Trust you find the above in order.

Kind Regards

  
Dr D Motau

HEAD: HEALTH

Date: 27/05/17

Head : Health  
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[www.fs.gov.za](http://www.fs.gov.za)