

The role of bronchoscopy in the diagnosis and management of pediatric pulmonary tuberculosis

Pierre Goussard , Francois Retief , Jonathan Burke, Annemie Malherbe and Jacques Janson

Abstract: Bronchoscopy is useful as a diagnostic and therapeutic procedure in children with Tuberculosis (TB) disease complicated by airway obstruction. It is needed in children when surgical intervention may be required for airway compression, when drug resistance is suspected, and to rule out an alternative diagnosis for airway obstruction. Bronchoscopy with bronchoalveolar lavage (BAL) should be performed when other, less invasive samples cannot be collected, or when they fail to provide useful diagnostic information. BAL specimens collected at bronchoscopy can be tested using molecular TB assays and mycobacterial culture. The aim of this review is to evaluate the role of bronchoscopy in the diagnosis and management of pulmonary TB in children, and, specifically, to review the role of interventional bronchoscopy. A search of electronic databases was undertaken using the online databases PubMed, Ovid MEDLINE, EMBASE, Google Advanced Scholar, and Web of Science to identify relevant literature. The search was limited to pediatrics, pulmonology, bronchoscopy, and pediatric pulmonary tuberculosis for all articles published in English on pediatric bronchoscopy between 2010 and 2020. Recent advances in pediatric bronchoscopy was included, as well as recent research on improving the diagnosis with the use of interventional bronchoscopy. The role of bronchoscopy in pediatric pulmonary tuberculosis has changed during the last decade, from a simple method of collecting samples for bacteriological confirmation to a more sophisticated procedure. New methods are available for collecting samples, which includes the use of Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and also better methods of bacteriological confirmation. Interventions are now possible; not only to improve the diagnostic abilities of bronchoscopy but also to diagnose, manage, and follow-up upon airway-related complications. Bronchoscopy services remain limited in resource-limited countries due to the high cost of equipment.

Keywords: flexible bronchoscopy, interventional bronchoscopy, pulmonary tuberculosis, rigid bronchoscopy, Xpert MTB/RIF

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Introduction

Tuberculosis (TB) is the leading cause of death from a single infectious agent globally.^{1,2} Childhood TB (<15 years of age) accounts for 11% of all TB cases and 14% of the overall TB mortality burden worldwide.³ The high mortality in children may be attributed partly to diagnostic

challenges, which may cause a delay in treatment initiation.⁴ The majority of children started on TB treatment do not have bacteriological confirmation, despite increased access to rapid molecular tests in most countries. The most common manifestation of pulmonary TB (PTB) in children is uncomplicated intrathoracic lymph node

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disease. Diagnostic and treatment delays can lead to rapid TB progression, resulting in significant morbidity and mortality, particularly in young and immune-compromised children.⁵ Enlarging lymph nodes can cause external airway compression and occlusion. The caseating lymph nodes can herniate into the airways, resulting in bronchogenic and hematogenous spread.⁶ Parenchymal complications of airway obstruction include collapse, expansile pneumonia, ball-valve effect, necrotizing pneumonia, and liquefaction; with or without cavitation.⁷

The incidence of airway involvement in children due to primary TB in the chemotherapeutic era is unknown. The reported incidence of airway compression varied from 8% to 38% in children <15 years of age.^{3,4} Airway involvement is relatively common in children, especially young children, but is not often so severe that an intervention is required to relieve airway obstruction.

Due to limited resources, bronchoscopy is not frequently performed for TB in resource-limited settings.⁸ Bronchoscopy is useful as a diagnostic and therapeutic procedure in children with TB disease complicated by airway obstruction. Bronchoscopy is needed in children when surgical intervention may be required for airway compression, when drug resistance is suspected, and to rule out an alternative diagnosis for airway obstruction. Bronchoscopy with bronchoalveolar lavage (BAL) should be performed when other, less invasive samples cannot be collected or when they fail to provide useful diagnostic information. BAL specimens collected at bronchoscopy can be tested using molecular TB assays and mycobacterial culture.

The aim of this review is to evaluate the role of bronchoscopy in the diagnosis and management of pulmonary TB in children, and, specifically, to review the role of interventional bronchoscopy.

Method of the review

A search of electronic databases was undertaken using the online databases PubMed, Ovid MEDLINE, EMBASE, Google Advanced Scholar, and Web of Science to identify relevant literature. Search terms were limited to pediatrics, pulmonology, bronchoscopy, and pediatric pulmonary tuberculosis for all articles published in English on pediatric bronchoscopy between 2010 and 2020. The following key words were used: bronchoscopy,

PTB and flexible bronchoscopy, rigid bronchoscopy, interventional bronchoscopy and anesthetic considerations, SARS-COV-2, and pulmonary tuberculosis. Hand searches were also carried out on the reference lists of retrieved articles.

Original articles on the use of both rigid or flexible bronchoscopy in the diagnosis and management of PTB in children <13 years were included. Articles on interventional bronchoscopy in the diagnosis and management of pediatric PTB and studies comparing chest computed tomography (CT) scan finding with flexible bronchoscopy were also included. Between 2010 and 2020, 59 articles meeting these criteria were published.

Our study did not require ethical approval because it was a systematic review of published data; as a result, no new patients were included.

Indications for bronchoscopy in suspected & confirmed cases of TB in children (Table 1)

Bronchoscopy is the gold standard for assessing the degree of airway compression and obstruction in pediatric PTB. In the developed world, bronchoscopy is mostly used to collect diagnostic samples; in contrast, in the developing world, its value mainly lies in the management of complicated airway disease. The following are commonly used indications for bronchoscopy.⁹

- To collect BAL samples for Xpert *Mycobacterium tuberculosis* (*M tuberculosis*) (MTB)/resistance to rifampicin (RIF) and MTB culture. Additional samples include endobronchial tissue or transbronchial needle aspiration (TBNA) biopsy specimens for bacteriological conformation.
- To assess the degree of airway obstruction in children with clinically and/or radiologically significant airway obstruction.
- To determine the cause and degree of life-threatening airway obstruction.
- To perform endoscopic enucleation as an emergency treatment for critical airway obstruction in children with TB lymph nodes ulcerating into the airways.
- To determine the cause of clinical and/or radiological failure in children being treated for TB.
- To perform interventional bronchoscopy procedures both for diagnosis and management.

- To intraoperatively guide surgical decompression of lymph nodes.
- To determine the cause and manage hemoptysis due to PTB.

Contraindications include severe pulmonary hypertension and severe unresponsive hypoxia. Relative contraindications include a bleeding diathesis, significant hemodynamic cardiac lesions, significant upper airway pathology, superior vena cava syndrome, uncontrolled systemic hypertension, and increased intracranial pressure.¹⁰

Diagnostic features of airway involvement in children with pulmonary TB

The commonest bronchoscopic image in children with culture proven TB is lymph node compression of the airways. De Blic originally described that extrinsic compression of either the trachea or bronchus was the commonest visible abnormality, and that the airway compression was either the only visible abnormality or coexisted with obstructive caseating material, granulation tissue, and endobronchial mucosal inflammation of the airway.¹¹ Arlaud *et al.*¹² reported abnormalities in 49% of children with pulmonary TB. The most frequent abnormality was extrinsic compression of <50% of the bronchus lumen in 24.5% of cases and severe airway compression (>50%) in 18.9% of cases. Goussard *et al.*¹³ reported their findings of flexible bronchoscopy in a large series of infants and children ($n=250$) with clinical and radiological signs of airway obstruction. They reported that compression of the right bronchial tree (85%) was more common than left-sided compression (66%); whereas compression of both the right and left bronchial trees was seen in 53% of the cases. The most common airways compressed were the bronchus intermedius (BI) (72%) followed by the left main bronchus (LMB) (62%) and the trachea (57%).¹³ (Figure 1) The right main bronchus (RMB) was only compressed in 13% of cases. This differed from Bibi *et al.*,¹⁴ who reported that the right main bronchus was the most common airway involved. Large airway compression in children with symptomatic airway obstruction (trachea, BI, LMB) was always present, with smaller airway compression playing a lesser role. BI compression was visible in 95% of cases with clinically significant obstruction. Cakir reported airway involvement in 55% of children with TB ($n=197$) who had flexible bronchoscopy

Table 1. Indications for bronchoscopy.

Diagnostic findings for PTB on bronchoscopy
<ul style="list-style-type: none"> • Lymph node compression of airways • Endobronchial involvement • Complications of PTB e.g., broncho-oesophageal fistula
Collecting samples for bacterial conformation
<ul style="list-style-type: none"> • BAL: ZN, Xpert MTB/RIF, and culture • Endobronchial biopsy • TBNA • EBUS • EBUS-B-FNA
Interventional
<ul style="list-style-type: none"> • Endoscopic enucleation • Debulking of lymph nodes in airway • Dilation of bronchial stenosis • Closure of Broncho-oesophageal fistula • Closure of Broncho-pleural fistula • Management of hemoptysis
Role in management
<ul style="list-style-type: none"> • Determine need for corticosteroids • Monitor response to treatment • Determine need for surgical decompression • To intraoperatively guide surgical decompression of lymph nodes
BAL, bronchoalveolar lavage; EBUS, Endobronchial ultrasound-guided; EBUS-B-FNA, transesophageal bronchoscopic ultrasound guided fine needle aspiration; MTB/RIF; <i>Mycobacterium tuberculosis</i> /resistance to rifampicin; PTB, pulmonary tuberculosis; TBNA, transbronchial needle aspiration.

performed to determine the cause of treatment failure. Common findings included an obstructive endoluminal polypoidal mass (42%), extrinsic compression (24%) and obstructive caesium (22%), with less common findings being intraluminal granulation tissue (9%) and mucosal erosion with ulceration (3%).¹⁵ Cakir reported that the risk factor for developing airway compression was resistance to treatment ($p=0.002$) and that airway involvement was more common in young

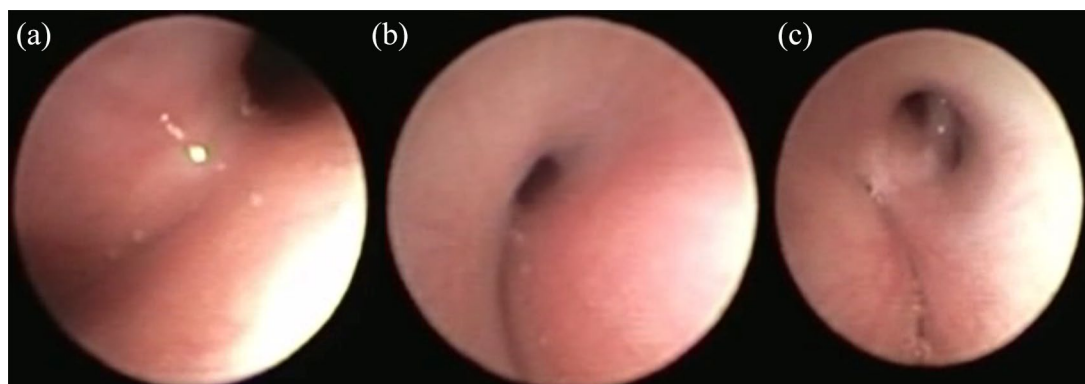


Figure 1. Bronchoscopy images: (a) swollen carina (b) severe compression of the left main bronchus (c) view from the opening of the right main bronchus demonstrating narrow bronchus intermedius due to compression from the subcarinal lymph nodes medial and right hilum lymph nodes from lateral.

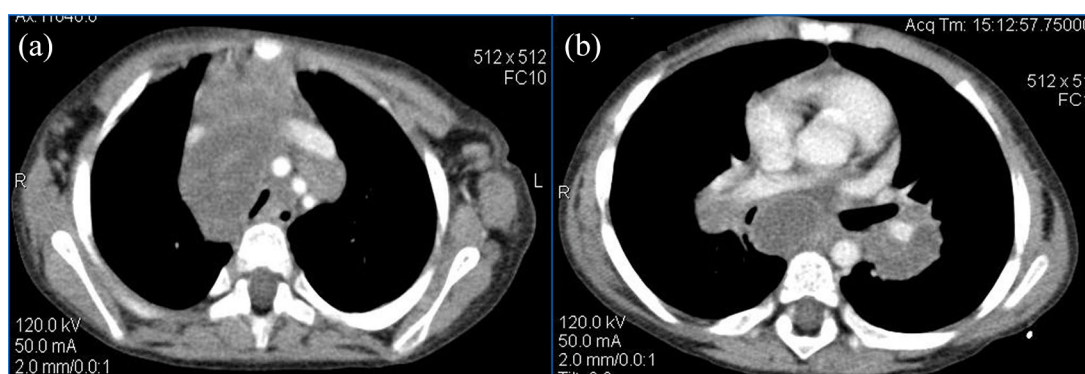


Figure 2. Chest CT-scan images. (a) Large right sided paratracheal lymph nodes causing significant tracheal compression from the right. (b) Large subcarinal lymph node with ring enhancement causing compression of both bronchus intermedius and the left main bronchus. CT, computed tomography.

children, primary TB, and parenchymal involvement, but this did not reach statistical significance.¹⁵

These findings are in keeping with a study by Lucas *et al.*¹⁶ on the chest CT scan findings of children with clinically significant airway compression caused by pulmonary TB. (Figure 2) The lymph nodes had ulcerated into the airways in 49% of cases, with the right side being involved in 64% and the BI (31%) the most common airway involved. They demonstrated a correlation between age and the severity of airway obstruction with children <24 months having statistically more severe airway obstruction. This is especially true for when the BI is >75% compressed.¹³ There is no reported difference seen in

the pattern or severity of airway obstruction in children who have drug-resistant TB and also TB in HIV positive children.¹³

Chest X-ray (CXR) findings do not necessarily reflect bronchoscopy findings. De Blic reported that bronchial involvement was found in 14 of 29 children in whom the enlarged lymph nodes was not seen on the CXR.¹¹ Chan *et al.*¹⁷ reported on 36 children, of whom 41.7% had endobronchial TB (ETB). The degree of airway involvement was underestimated on CXR, as 28% of the children had no clinical or radiological signs of ETB but at bronchoscopy had endobronchial involvement.

The pattern of airway obstruction seen at bronchoscopy can make the diagnosis of pulmonary

TB very likely. Involvement of the BI is the most common presentation, but if both the main bronchus and trachea are involved, the diagnose of TB is more likely. The BI is compressed from both the medial and lateral side as a result of the fact that it gets caught between the enlarged subcarinal and right hilar lymph nodes. The specificity of diagnosis is increased if lymph nodes have ulcerated into the airways. (Figure 3)

Bronchoscopic diagnostic procedures

Broncho-alveolar lavage

The collection of samples for confirming the diagnosis of PTB has remained the main indication for bronchoscopy in children with PTB. Previous reports have demonstrated that the culture yield from BAL is significantly less than that from gastric washings (GWs). The reported yield from culture from BAL samples varies between 2.4% and 44%, while that from GWs is between 14% and 47%.^{11,14,18–22} Cakir *et al.*¹⁸ reported that the cumulative yield of BAL and GWs is increased to 20% compared to the GWs and BAL yield of 19% and 12.8%, respectively. Both Somu *et al.*²¹ and Abadco *et al.*¹⁹ have shown that combining the two procedures increased the yield to 34% and 50%, respectively. Cakir *et al.*¹⁵ reported that the diagnostic yield increased to 41.9% if both BAL (32.6%) and GWs (28.7%) were conducted. Higher yields from BAL compared to GW have been rarely reported with the exception by Menon *et al.*,²² who reported a yield of BAL of 30.8% and GWs of 21.2%. Endobronchial lesions can be seen in 47% of culture positive patients.¹⁸ Goussard *et al.*¹³ demonstrated a higher culture yield in children with complicated PTB. In this study, 44% of children were culture positive on BAL, with 82% already on TB treatment for a mean duration of 30 days at time of bronchoscopy. There was a higher yield in children who had pneumonic consolidation on CXR. Based on these findings, it is advisable to conduct BAL from the most affected lobe.¹³

The highest yield report for culture on BAL was 61.4% achieved in a group of children with complicated PTB. Overall, bacteriological confirmation was achieved in 78.7% from all samples.²³

Bronchoscopy is unlikely to be; indeed, should not be, the first investigation used to identify the

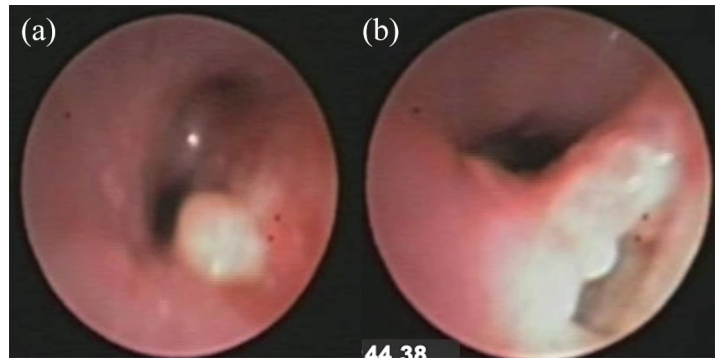


Figure 3. Bronchoscopy images of the right main bronchus. (a) Granuloma visible at the opening of the right main bronchus. (b) Images demonstrating a mediastinal defect where the lymph node has ruptured in the airway.

organism. This is especially true in the developing world, which is impacted by limited resources.

Xpert MTB/RIF on BAL

In 2011, the World Health Organization (WHO) recommended the Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA) for the diagnosis of PTB and the detection of rifampicin resistance. The Xpert MTB/RIF assay is an automated, single-cartridge-based, nucleic acid amplification test that is able to simultaneously detect MTB and rifampicin resistance within 2–3 h.

Children with severe forms of intrathoracic TB have higher culture yields which may be indicative of higher bacillary loads.

A limited number of studies have reported on the yield of Xpert MTB/RIF on BAL in pediatrics.

Walters *et al.*⁷ have reported in a pilot study that TB was confirmed by either culture or Xpert from any sample in 11/14 (78%) children with 9/14 (64%) cases confirmed by culture and BAL Xpert was positive in 7 (78% sensitivity). Xpert confirmed 2 cases who had negative culture (14% additional diagnostic yield). Saini *et al.*²⁴ report on BAL Xpert in 41 children with probable PTB with a negative smear and Xpert on induced sputum/gastric aspirate. They found that 24 (58.5%) had Xpert positive in BAL fluid and 11 (26.8%) had culture confirmed tuberculosis (BAL fluid, 10; sputum, 1). The sensitivity of Xpert in BAL fluid among probable and culture confirmed tuberculosis cases was 58.5% (24/41) and 81.8% (9/11), respectively.

Yin *et al.*²⁵ reported that Xpert MTB/RIF assay on BAL could detect 33.9% of cases with negative MTB culture, and 48.7% of cases with negative AFB microscopy. Younger age (<3 years), absence of Bacille Calmerre Guerin scar, and contact with TB patient were significantly associated with a positive result of Xpert MTB/RIF assay.

Goussard *et al.* have demonstrated that radiological features (pneumonia, expansile pneumonia, and airway compression) were associated with bacteriological confirmation on BAL on univariate analysis, but only the presence of lymph nodes observed in the airway during bronchoscopy was associated with bacteriological confirmation on BAL on multivariate logistic regression. Of the 146 children in the study, 101 were confirmed on BAL, 62 (61.4%) were positive by both Xpert and culture, 35 (34.7%) only by Xpert, and 4 (4.0%) only by culture. Antituberculosis treatment status did not affect the overall confirmation rate in this study, with 70.5% *versus* 64.7% overall positivity among those with and without treatment, respectively ($p=0.52$). Of the 41 children who had been on treatment for >2 weeks, 10 (24.4%) had a positive culture and 32 (78.0%) had a positive Xpert. The median duration of treatment was significantly different for children with a positive culture compared with those with a negative culture (7 *versus* 14.5 days, $p<0.001$); in contrast, there was no difference among children with a positive *versus* a negative Xpert (11 *versus* 8 days, $p=0.36$).²³

Most pediatric studies have shown that Xpert MTB/RIF has identified additional cases on BAL compared to culture and where other routine samples could not confirm the diagnosis. Except for confirming the diagnosis bacteriologically, bronchoscopy has the additional value of assessing the severity of airway obstruction, which can lead to the addition of corticosteroids to the TB treatment and to referral for surgical decompression. In cases of potential drug resistance, BAL Xpert MTB/RIF can be formed as drug resistant TB needs specific therapy with potential significant side effects. We would suggest that bronchoscopy be conducted when routine samples fail to confirm TB and also in cases with clinically and radiological severe airway obstruction; in these cases, severity and cause needs to be urgently established to determine the correct treatment and management.

Endobronchial biopsy

There is limited information on the value of endobronchial biopsy in the diagnosis of PTB in children.²⁶ Because the lymph nodes ulcerate into the airway it is possible to obtain material for diagnosis. The size of biopsy is limited in young children due to the small working channel of the bronchoscopy. We have not found the culture yield from endobronchial tissue biopsy to be higher than BAL. We add the biopsy material with the BAL samples for bacteriological confirmation. The value of endobronchial tissue biopsy requires further investigation to determine its value in the diagnosis of pulmonary TB in children.

Transbronchial biopsy

Transbronchial biopsy (TBB) has a limited role in the diagnosis of pulmonary TB in children, as TB seldom involves alveoli adjacent to the large bronchi. TBB may have a role in the diagnosis of miliary TB or in human immunodeficiency virus (HIV)-positive children to distinguish miliary TB from lymphocytic interstitial pneumonia.²⁶ Prior to TBB, a complete blood count, including platelets, and coagulation should be performed. TBB is always performed under general anesthesia and fluoroscopic monitoring in young children. This helps to correctly align the forceps, avoid positioning too close to pleura, and allow immediate monitoring of any possible pneumothorax. Potential risks of TBB include pneumothorax and bleeding.²⁷ This remains a theoretical possibility, as there are no studies published on the use of TBB in the diagnosis of childhood TB.

Transbronchial needle aspiration

Transbronchial needle aspiration (TBNA) has been safely used in adult patients; mostly to diagnose lung malignancy.^{28–33} The risk of pneumothorax or pneumomediastinum with TBNA is very small compared to TBB. The risk of air leaks is reduced because only central mediastinal lymph nodes are aspirated. TBNA was always limited in children due to the size of the bronchoscope and more importantly due to the limited size of the working channels. The aspiration needle needs to be passed through at least a 2 mm working channel. (Figure 4) The newer generation pediatric bronchoscopes have larger working channels, and this enables one to do TBNA safely. The Olympus 4.0 mm and 4.9 mm videoscope with 2.0 mm working channel allows TBNA to be done in

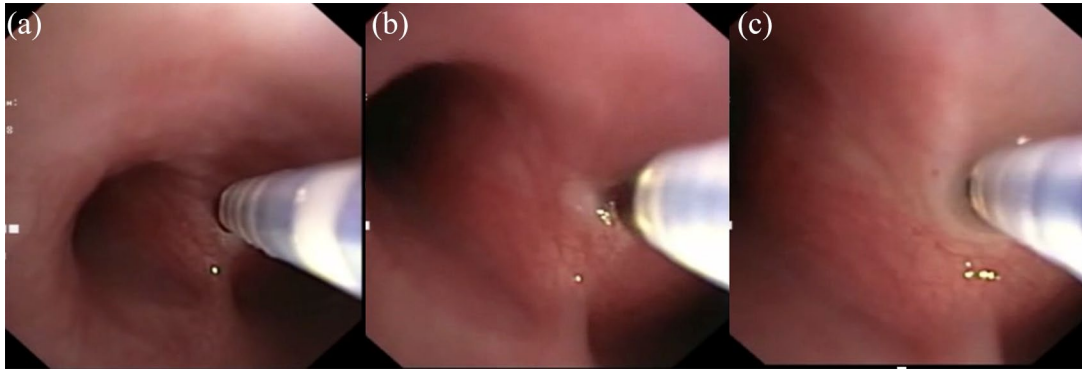


Figure 4. Bronchoscopy images demonstrating TBNA of the subcarinal lymph node. TBNA, transbronchial needle aspiration.

children as young as 1 year. A size 2 or bigger laryngeal mask airway (LMA) allows for ventilation during the procedure. TBNA can be done *via* an endotracheal tube (ETT), but a 4.0 mm scope can only be passed through size 5.0 mm ET or bigger. To ensure that the procedure is performed safely, a preceding chest CT scan is performed. This is needed to identify the mediastinal lymph nodes that need to be biopsied and their relationship to the airways.

Younger children may only be suitable for subcarinal sampling, with a diagnostic yield of approximately 50%.³⁴ Older children (aged ≥ 12 years) may be amenable to either right paratracheal, bronchial, or hilar node sampling, as a result increasing the diagnostic yield to $>80\%$.³⁵

The technique described by Wang for use in adults has been adapted for children.^{28,33} The cytologist should be in the theatre to immediately assess the adequacy of the sample. This is described as the Rapid On-Site Evaluation (ROSE) method. The advantage of this method is that the cytologist can inform the bronchoscopist if the aspiration contains tissue and not only bronchial mucosa. It is also possible for the cytologist to give an opinion if malignant cells are present or in the case of TB, identify ZN positive organisms with the correct stains. Separate specimens can be collected for cytology as well as fungal and MTB culture and GeneXpert. The reported complication rate is low, with only a small amount of self-limiting bleeding visible at the site of the TBNA.³⁴ In small children or children with significant airway compression, especially of the trachea, there is risk of hypoxia and hypercapnia as the bronchoscope may completely

obstruct the airway. It is advisable to do short, repeated passes to limit the time of complete airway obstruction. Although this is a rare complication, the left atrium can be punctured during the procedure.³⁴

The advantage of TBNA is that it provides a safe and rapid diagnosis based on histology and culture without performing an open thoracotomy. TBNA also provides an additional method of obtaining tissue for GeneXpert. This is especially important in areas with high incidence of TB and of drug resistance. It has been reported that TBNA is valuable in the workup of HIV-positive children, as well as those infected with drug-resistant TB.³⁴ It may be of value to repeat the BAL for culture and GeneXpert after TBNA, as this may potentially increase the yield; however, this remains unproven.

In a series of 30 children, a definitive diagnosis was made using TBNA in 54% of patients with a median age of 41 months (range 9–168 months); the diagnoses made were MTB lymph node enlargement ($n=13$), metastatic nephroblastoma ($n=1$), and fibrosing mediastinitis ($n=1$). In 25% of these cases, the TBNA was the sole source of the specimens from which the diagnosis was made. No serious complications were reported.³⁴

Endobronchial ultrasound-guided transbronchial needle aspiration and transesophageal bronchoscopic ultrasound guided fine needle aspiration

Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) in adults is a

well-established tool in investigating mediastinal and hilar lymphadenopathy. It is part of the diagnostic and staging algorithm for lung cancer, as well as the diagnosis of other malignancies, lymphoma, and non-malignant granulomatous conditions, such as sarcoidosis and tuberculosis.³⁶ Because the diagnostic yield is comparable to open biopsy, along with decreased complications, this method has reduced the requirement for previously standard surgical biopsy sampling.^{37,38}

Convex probe-EBUS offers real-time, ultrasound-guided performance of TBNA *via* the EBUS puncture scope. This puncture scope is a specially designed bronchoscope equipped with a distally located convex ultrasound probe. It is designed with a modified bronchoscopic viewing angle (30 degree, compared to 0 degree viewing with a standard flexible bronchoscope) but more importantly, provides a real-time ultrasound image of the area of interest. The EBUS puncture scope also utilizes specifically designed 21- and 22-gauge TBNA needles. As a result of the different viewing angle and unique needle system, specialized training is required in order to obtain proficiency in the use of Convex probe-EBUS.

The problem with EBUS scopes is that they have an external diameter of 6.7–6.9 mm which is significantly larger than pediatric bronchoscopes (2.8–4.9 mm).³⁹ This limits the use of EBUS in younger children due to inadequate ventilation and restricted movement of the scope. Intermittent ventilation is less of an option than during TBNA, since the procedure takes longer.

There is limited data on the use Convex Probe (linear) EBUS in pediatric populations involving mostly older children.^{39,40}

In children, linear probe EBUS TBNA is suitable for investigation of mediastinal or hilar lesions to diagnose leukaemia,⁴¹ lymphoma,⁴¹ sarcoidosis,⁴² and tuberculosis.⁴³

Gilbert *et al.*⁴⁴ reported in a multicentre North American study on 21 pediatric patients undergoing EBUS-TBNA 95% adequacy with 48% of cases providing diagnostic material and obviating the need for invasive surgical biopsy in 62% of cases, with no significant complications. Dhooira *et al.*⁴⁵ in India reported on 55 pediatric EBUS-TBNA patients, mostly with suspected TB. They reported

92% adequacy, with diagnostic material in 57%, no major complications, and a 78% positive culture rate.

Gulla *et al.*⁴⁶ reported that the diagnostic yield of EBUSTBNA was 36.6%.⁴⁶ The mediastinal lymph nodes were biopsied through the esophageal wall using the EBUS scope, with no risk of airway obstruction during the procedure.⁴⁶

Al-Najjar *et al.* reported on 40 patients ≤ 18 years undergoing EBUS-TBNA for mediastinal or hilar abnormalities. TB (either cultured or clinically confirmed) in 67.5% ($n=27$), reactive lymphadenopathy in 17.5% ($n=7$), exclusion of TB recurrence in 7.5% ($n=3$), hematological malignancy in 5% ($n=2$), and neurofibroma with granulomatous reaction in 2.5% ($n=1$) of cases was seen. Cytology had a sensitivity of 96% [confidence interval (CI) 81–100%] for TB and a negative predictive value of 88% (CI 47–100%). Culture compared with cytology had a positive predictive value of 63% (CI 42–81%).⁴⁷ The final diagnosis was changed from initial clinical suspicion by sampling, in 23.5% of those with suspected TB, and 67% of those with suspected lymphoma.⁴⁷

Transesophageal bronchoscopic ultrasound guided fine needle aspiration (EUS-B-FNA) in children has recently been described. The EBUS bronchoscope can be introduced into the esophagus for the purpose of mediastinal evaluation and sampling. Madan *et al.*⁴⁸ reported about a 3-year-old child with subcarinal lymph nodes where EUS-FNA was done usefully under conscious sedation with no complications. The advantage of EUS-B-FNA is that it is not necessary to enter the small pediatric airways with a large EBUS scope. It is also much less irritating to the airway than bronchoscopy; therefore, it can be conducted under sedation with spontaneous breathing and oxygen insufflation.

Madan reported on a systematic search on the use of EBUS-TBNA/EUS-B-FNA in children (<18 years of age). They included 164 patients and found that the pooled sampling adequacy and combined diagnostic yield of EBUS TBNA/EUS-B-FNA were 98% (95% CI, 92–100%) and 61% (95% CI, 43–77%), respectively.⁴⁸ This diagnostic yield in children approximates the diagnostic yield of EBUS-TBNA found in adults.⁴⁹ In adults, the complication rate was 0.05%, but

EUS-B-FNA had a small risk (0.02%) of esophageal perforation due to the fact that the needle transverses the esophageal wall. Madan concluded that EBUS-TBNA and EBUS-B-FNA is safe in children with mediastinal lymphadenopathy; it may be considered as the first-line diagnostic modality.⁵⁰

Radial probe EBUS employs a flexible catheter housing a rotating ultrasound transducer, which produces a 360-degree ('radial') ultrasound image and was first used to guide TBLB by Herth *et al.*⁵¹ These radial probes are compatible with channel diameters from 2.0 mm to 2.8 mm. They can be inserted directly through the working channel or used with a guide sheath.

The radial probe EBUS is suitable for localization and sampling of peripheral lesions, including pulmonary nodules. This is done by passing a 1.4-mm diameter EBUS probe with a 1.9-mm outer plastic guide sheath through the working channel of the bronchoscope. The EBUS is then advanced into subsegments until the pathological area is identified. The probe is withdrawn, leaving the sheath in place, through which the biopsy forceps or brush is then passed, and samples can be taken.⁵¹ The 4.0-mm bronchoscope is the smallest suitable bronchoscope for use with the radial probe EBUS. It has been used to diagnose lung cancer and other conditions causing peripheral lung nodules, including mycobacterial infection. A meta-analysis reported a diagnostic yield of 70%. Complications are rare, but a pneumothorax rate of 1.5% was reported.⁵¹

The advantages of the radial probe EBUS *versus* Convex Probe (linear) EBUS is that it can be used in much younger children and with less airway compromise. It also gives precise real time confirmation of the lesion location and gives a 360-degree view. The real-time ultrasound image enables direct visualization of the exact position of the lesion for sampling. At the moment, there is limited data on its use in children; most existing data is focused on its use in peripheral lung lesions.

Role of bronchoscopy in management of pulmonary tuberculosis

Bronchoscopy is important to determining the severity of airway obstruction and in deciding

which patients can be treated medically and which patients require surgery. Children with airway obstruction of <50% can be treated medically.

The indications for surgery are the following:

- Severe, life-threatening airway obstruction on presentation requiring ventilation.
- Critical airway obstruction as accessed at the initial bronchoscopy, where the airway obstruction of both the main bronchi was >90%.
- Severe airway obstruction treated with anti-TB drugs and oral prednisone for one month, where at bronchoscopy re-evaluation the airway obstruction of one or both main bronchi remained >75%.
- Persistent collapse of a lobe due to airway compression.

The use of corticosteroids in ETB as an adjunct to anti-TB drugs has always been controversial. Studies indicate that adding corticosteroids to anti-TB drugs is beneficial in treating children with airway compression due to lymph node enlargement in pulmonary TB.⁵²⁻⁵⁴

Children with significant airway compression will need repeat bronchoscopy to determine their response to therapy. In non-life-threatening airway compression, this can be conducted after one month of anti-TB therapy and corticosteroids.

Children may experience worsening airway obstruction after the initiation of anti-TB treatment due to a hypersensitivity reaction.^{55,56} Follow-up bronchoscopy may be needed to evaluate if decompression of the mediastinal lymph nodes may be required. Complicated PTB with airway compression is treated with four first-line TB drugs, to which methylprednisolone (2 mg/kg/day) is added for the first 28 days. The corticosteroids are weaned over the next month. If children are asymptomatic, repeated bronchoscopy is not indicated. The reported mean time before improvement on CXR is 5.3 ± 2.7 months, whereas bronchoscopy improvement closely follows (5.5 ± 2.7 months).¹⁸ De Blic reported that airway compression resolved in <100 days (range 14-98 days) in 11 of 20 children.¹¹ Of the remaining cases, in five children, the improvement took up to 120 days. Of the five children with delayed

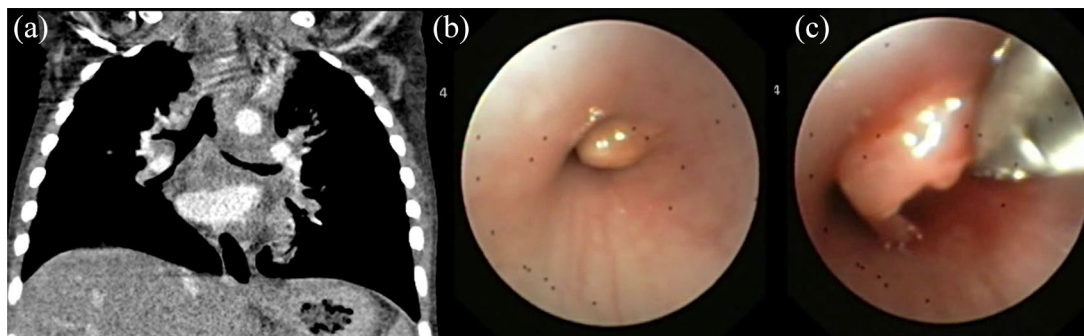


Figure 5. (a) Chest CT-scan MPR reconstruction demonstrating compression of the left main bronchus with lymph node that have herniated in the airway. (b) Bronchoscopy image demonstrating lymph nodes in the left main bronchus. (c) Bronchoscopy image of endoscopic enucleation. CT, computed tomography; MPR, multiplanar reformation.

improvement, four developed bronchial stenosis. De Blic also reported that endobronchial tissue in the airway took between 3 and 10 weeks to resolve.¹¹ Arlaud *et al.*¹² have reported the results of follow-up bronchoscopy done after a mean time of 28.5 days in 12 children. They reported that in nine cases the abnormalities had resolved, two had stable lesions, and in one case the lesions had worsened. Early detection and treatment are important to prevent the long-term complications of bronchiectasis and bronchial stenosis. Bronchial stenosis, said to be a complication of endobronchial TB in children, has been rarely reported. De Blic described four cases that developed bronchial stenosis, having both severe compression and marked inflammation of the airway visible at bronchoscopy.¹¹ Although TB is the most common cause of endobronchial obstruction in a developing world setting, other causes of airway obstruction must be considered.⁵⁷ Kut *et al.* have reported on a series of 2555 flexible bronchoscopy procedures with the following causes of endobronchial obstruction: foreign bodies (35.9%, $n=92$), endobronchial TB (31.6%, $n=81$), mucous plugs (16.7%, $n=43$), granulation scars (6%, $n=16$), hydatid cysts ($n=5$), hemangiomas ($n=5$), tumors ($n=5$), submucosal nodules ($n=5$), and polyps ($n=4$). They reported that the most common areas of airway obstruction were the right bronchus 51% ($n=130$), left bronchus 33% ($n=85$), and trachea 8% ($n=20$). Obstruction of both bronchi occurred in 8% ($n=21$) of cases.⁵⁸

Interventional bronchoscopy procedures

Pediatric bronchoscopy has evolved from a primarily diagnostic procedure to include

interventional bronchoscopy. This is possible due to the development of new and smaller instruments and devices which include biopsy forceps and alligator forceps. The biggest development is the availability of a 4.0mm video bronchoscope with a 2mm working channel. Advanced therapeutic techniques such as laser treatment, balloon dilation, and stent placement are used in children in specialized centres, with an expanding number of applications and indications.^{59,60}

There is limited reporting on the use of interventional procedures in children with PTB. Endoscopic enucleations have been used in children with life threatening airway obstructions, with debulking of the lymph nodes that have herniated into the large airways. (Figure 5) The airways mostly affected are the bronchus intermedius, the left main bronchus, or the trachea or combinations thereof. The aim with endoscopic enucleation is to create an airway without removing too much caseating tissue; the goal is to avoid going through the bronchial wall and creating bronchopleural fistula. Endoscopic enucleation can be conducted by both flexible and rigid bronchoscopy. Rigid bronchoscopy has the advantage of effective ventilation during the procedure and the use of larger instruments, but vision is limited, especially through the smaller size scopes. Flexible bronchoscope interventions are limited by the small working channels, however these procedures can be conducted under vision which is important to prevent creating air leaks.

Goussard *et al.*¹³ reported that 9% of children with severe airway obstruction ($n=250$) caused by TB lymph nodes needed endoscopic enucleation.

Bronchial stenosis in pediatric PTB is a rare complication that may be amendable to balloon dilatation. It is important to determine the size, length, and thickness of the stenosis before dilatation. A chest CT-scan is needed to determine these parameters.

Fibrin glue have been used to close acquired broncho-esophageal fistulas (BOF) resulting from TB; they are instilled into the fistula through the channel of a flexible bronchoscope. Goussard *et al.*²⁶ have reported that there were no complications related to the use of fibrin glue in these children.

Role of bronchoscopy in the diagnosis and management of unusual forms of pulmonary TB

Expansile pneumonia

Expansile pneumonia is a radiological diagnosis that is characterized by an increased volume of the affected lobe or segment resulting in bulging fissures. Goussard *et al.*⁵⁵ described expansile pneumonia caused by MTB. The upper lobes are most often involved. Severe airway compression (>75%) is seen in 83% of the cases, where TB is the cause of expansile pneumonia. In 13% of cases, endoscopic enucleation was required to re-establish airway patency. The value of bronchoscopy in the evaluation of expansile pneumonia in children is that the etiology can be rapidly established, especially with Xpert MTB/RIF, and if required, endoscopic enucleation can be performed. Most children with expansile pneumonia due to TB will have either airway compression or lymph nodes that have herniated into the airway compared to the absence of these findings in other causes.

Tuberculosis of the upper airways

Tuberculosis of the larynx is rare and not often considered as a cause of laryngeal involvement in children. In the early part of the 20th century, the larynx was thought to be involved in 25% of all cases of TB, but this has decreased to 1% following the introduction of TB treatment.⁶¹ MTB affects the posterior and the glottic larynx, probably due to direct spread of infected sputum. Although laryngeal TB is rare in children, in high prevalence areas it should be included

in the differential diagnosis of upper airway obstruction.⁶² Recently acute epiglottitis due to MTB in a child has been described.⁶³ Bronchoscopy is essential to confirm the diagnosis and determine the extent of the involvement.

Phrenic nerve palsy

Phrenic nerve palsy is a rare complication of complicated intrathoracic pulmonary TB with all described cases involving the left phrenic nerve.^{55,64–67} The value of bronchoscopy is that lymph node compression of the LMB is visible in 63% of cases and samples can be collected.⁶⁷

Broncho-esophageal fistula

Broncho-esophageal fistula (BOF) is a rare complication of MTB.^{68–75} TB-associated BOF presents either as acute respiratory failure, aspiration pneumonia, or as a complication of surgical decompression of thoracic lymph nodes. BOF due to TB is mostly only left-sided. Bronchoscopy is used in the diagnosis of BOF. Most of these fistulas are seen at the opening of the LMB on the medial side, as a slit-like opening. Sometimes, it may be difficult to visualize because it is located in the caseating materials. Bubbles can be seen with installed fluid and abdominal distension may be seen during assisted ventilation. Ideally, spontaneous ventilation should be maintained until the lesion is sealed. Bronchoscopy can be used to aid the placement of an ETT into the RMB to decrease the leak in ventilated children.

Methylene blue or rifampicin can be instilled into the esophagus *via* a nasogastric tube to demonstrate the connection between the esophagus and bronchus at bronchoscopy.⁷⁵

Glandular compression of the large airways was seen in 56% of patients with BOF at bronchoscopy with the most common sites of airway compression at the LMB and BI.⁷⁵

Esophageal stent placement has been used to successfully seal the leak in the acute presentation. After placement of the stent, the airways need to be evaluated to ensure that it does not cause severe airway compression.^{74,75}

BOF may close spontaneously, but the majority require some form of surgical intervention to seal.

Bronchoscopy is important in the management of BOF to determine if the fistula have closed spontaneously or if surgical interventions have been successful. The use of fibrin glue, instilled into the fistula, may be an attractive bronchoscopic alternative.⁷⁵

Complications of bronchoscopy in children with pulmonary TB

Bronchoscopy has the potential for significant morbidity and even mortality if not done correctly in appropriate facilities and with correct monitoring. Complications of flexible bronchoscopy in children have rarely been reported. The potential risk factors for complications include young age, significant airway disease especially with tracheal involvement, bilateral main bronchi obstruction, and significant parenchymal disease. There is a small risk for bleeding during endobronchial biopsy or enucleation. The risk of bleeding is higher with biopsy of granulation tissue than of caseating material. Goussard *et al.*¹³ reported a complication rate of 3.2% during bronchoscopy for severe airway obstruction in children. The reported complications of TBNA includes mild bleeding at the biopsy site and a small risk for pneumothorax. A CXR must be done after the intervention to exclude this complication.²⁹ Complications in children with life-threatening airway obstruction can be minimized by performing the bronchoscopy in the thoracic surgery theatre so that transthoracic lymph node enucleation can immediately follow the bronchoscopy.

Anesthetic and oxygenation considerations in bronchoscopy for complicated pulmonary tuberculosis

Excellent team communication and coordination between the bronchoscopist and anesthetist, and insight into each other's roles and concerns, are vital while sharing the airway during bronchoscopy, as emphasized by Londino and Jagannathan in an extensive review discussing various anesthetic principles for pediatric bronchoscopy.⁷⁶

Infants and small children have increased oxygen consumption (VO_2), with fixed functional residual capacity and tidal volumes. PTB lymph node airway obstruction is common; there is the potential for bronchopulmonary fistula (BPF). These physiological and pathophysiological characteristics combined with periods of apnea, hypoventilation, and V/Q mismatch under anesthesia significantly

increases the risk for hypoxemia and hypercarbia; this may result in bradycardia and arrest. Anesthesia optimizes dynamic examination and treatment of the airways, while insuring adequate ventilation and oxygenation.

Several anesthesia and oxygenation options are available during bronchoscopy. Sevoflurane induction and a short acting opioid like alfentanil $10\ \mu\text{g}/\text{kg}$ before placement of a supraglottic airway (SGA) are commonly used.^{76,77} The larger internal diameter provided by SGAs facilitate the use of larger diameter flexible bronchoscopes and visualization of the larynx and supraglottic area.⁷⁸ Lignocaine 1–4% is sprayed onto the vocal cords *via* the working channel of FB, maximum dose $6\ \text{mg}/\text{kg}$, but considering factors like age and protein binding effecting the risk for local anesthetic toxicity.⁷⁶

The SGA position is continuously optimized and held by the anesthetist, aiming to maintain spontaneous ventilation and assist access for the bronchoscopist. An adapter like the Rusch Mainz Universal Adapter inserted between the SGA and anesthetic breathing circuit provides a sealed channel for both FB and ventilation. (Figure 6) Should positive pressure ventilation be required, it is gently done by hand to reduce the potential of leaks, aerosol generation, and inflation of the stomach.

In cases where inhaled sevoflurane sedation is not possible, intravenous agents such as propofol or ketamine is added to reduce airway reflexes such as cough. However, it may increase wake-up time.⁷⁹ Other agents, such as remifentanyl, fentanyl, midazolam, and dexmedetomidine have been used successfully.

Neuromuscular blocking agents are rarely used during FB for PTB procedures due to the risk of hypoxemia by altering ventilation dynamics; they may be beneficial during complex rigid bronchoscopy procedures where patient movement is to be avoided.⁷⁶

Alternative options for oxygenation in spontaneously breathing children are oxygen insufflation *via* nasal cannula or nasal endotracheal tube placed above the glottis, to allow access for larger/bulkier equipment.⁷⁸ HFNO is a newer approach used in spontaneously-breathing children, where humidified oxygen is administered through nasal cannulas

at flow rates in excess of the peak inspiratory flow. This reduces the effective anatomical dead space, thereby increasing oxygen delivery and possibly the removal of carbon dioxide. It also provides continuous positive pressure, which helps to maintain lung volume and oxygenation.^{80–83}

In small babies where the bronchoscope obstructs the airway, or during procedures like tracheal balloon dilatation where ventilation is not possible, intermittent ventilation may be utilized. The predicted safe apnea time for the specific patients and the uninterrupted time intervals needed for the procedure must be discussed beforehand. Maintaining lung volume and providing full pre-oxygenation allows longer apnea time. This can be accomplished between periods of apnea by gentle assisted mask ventilation or by HFNO as above.⁸⁴

It is important to recognise that a decrease in oxygen saturation will only be recognized when the desaturated blood reaches the site of the pulse oximeter probe, e.g., the finger or toe. Recognition of hypoxemia may be delayed even more if accompanied by bradycardia, slowing the circulation to peripheral tissue. Therefore, more central measurement sites, e.g., the ear or nose, are appropriate and, at the first sight of decreased SpO₂ or lowering of heart rate, the procedure must be interrupted, and the scope removed to allow for effective ventilation. In higher risk cases, the anesthesiologist may estimate the safe apnea time and the procedure be interrupted regularly for repeated recruitment and preoxygenation.

Risk of transmission of disease during bronchoscopy for pulmonary tuberculosis and the COVID-19 pandemic

One of the major drawbacks of bronchoscopy in children with PTB is the risk of transmission of disease, including resistant MTB species and coexisting infections. The emergence and rapid global spread of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-COV-2) has been well documented and has drawn renewed attention to this matter.

Both MTB and SARS-COV-2 are predominantly transmitted through respiratory droplets, but aerosol transmission may also occur.^{85–88} The greatest risk for transmission is the performance of aerosol generating procedure (AGPs), including bronchoscopy and anesthetic airway management.⁸⁹

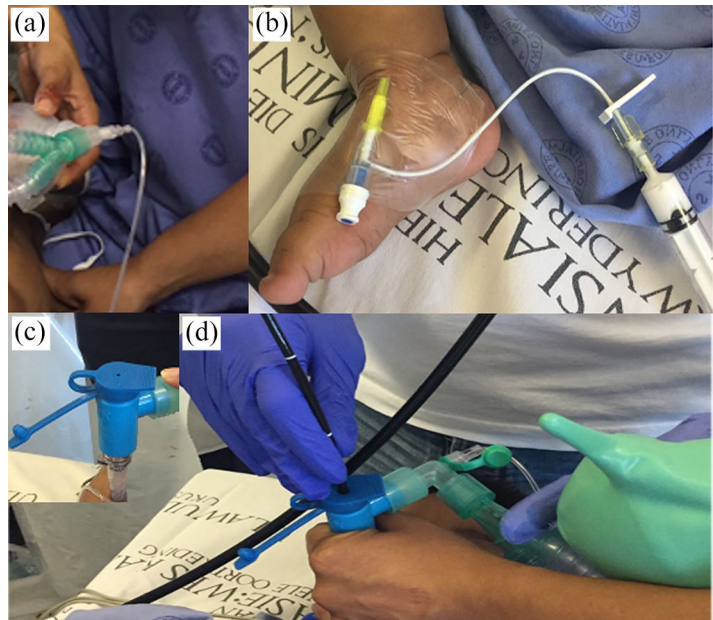


Figure 6. Anesthesia for bronchoscopy in children with complicated tuberculosis (a) Gas induction on mother's lap. (b) IV access great saphenous vein. (c) LMA with Rüsch Universal adapter. (d) Manual optimization of LMA for insertion of flexible bronchoscopy. IV, intravenous; LMA, laryngeal mask airway.

These are associated with an increased risk of patient-to-healthcare worker transmission, due to aerosolized particles which may be inhaled and also result in environmental contamination of surfaces.^{90–93}

Bronchoscopy has a limited role in the management of COVID-19 positive children but children with TB may be co-infected with SARS-COV-2. TB airway obstruction in children with co-infection with SARS-COV-2 has been described. Some of these children had significant airway obstruction.^{77,94} Bronchoscopy in children with TB and COVID-19 must only be done if there is life threatening airway obstruction or massive hemoptysis needing urgent intervention.^{95–97} This includes large airway obstruction with both external and or intraluminal obstruction or where there is airway obstruction present, with TB not confirmed, to rule out other causes of large airway obstruction including foreign body aspiration or malignancy. Children may be asymptomatic and in an emergency the SARS-COV-2 test may not be available. In these cases, the children should be managed as if they are SARS-COV-2 positive. Rigid bronchoscopy should be avoided when

possible due to the increased risk of droplet spread during the COVID-19 pandemic.^{95,96}

During bronchoscopy, full Personal Protective Equipment (PPE) should be worn by all staff involved. This includes a tight-fitting N95 mask and protective clothing. Currently, there are no specific pediatric COVID-19-related guidelines published for bronchoscopy.^{97,98} Bronchoscopy in children infected with SARS-COV-2 and TB has been reported in small case series.^{77,94} None of the HCW got infected. They used an adapted modified full-face snorkel masks (FFSMs) as an alternative to N95 respirators. Modifications entail the removal of the snorkel and addition of a 3D printed or molded adaptor and a heat and moisture exchange (HME) filter meeting N95 protective standards.⁷⁷

Children who are deemed infective should be booked at the end of the list and be allowed into theatre only when all preparations are complete, wearing a face mask for protection of healthcare providers. The child should be kept calm to prevent crying and coughing during induction, e.g., by inhalation induction on the parent's lap and by using appropriate premedication if needed. Caregiver anxiety plays an important role and should also be actively managed.⁹⁹

Anesthetic technique can be adapted to decrease the risk of droplet spread and aerosolization. Deep sevoflurane sedation is recommended before the intravenous line is placed. Airway reflexes are suppressed by short-acting opioids and lignocaine sprayed onto the vocal cords. The LMA is connected to the universal adaptor and an N95 filter before placement, to minimize the need for further disconnections. If disconnections are needed, they are coordinated with end of expiration. The use of a universal adaptor between the anesthetic breathing circuit and the LMA is advocated to ensure a sealed channel for both bronchoscopy and ventilation, while minimizing the risk for aerosolization. Spontaneous breathing is maintained as far as possible to minimize leaks. The LMA should be removed under deep sevoflurane anesthesia to reduce the risk of coughing.^{77,95,96}

Equipment and surfaces should be cleaned appropriately after the procedure. The bronchoscope should be inserted into a 75% alcohol bottle afterwards for negative pressure suction to

clean and sterilize the suction tube of the bronchoscope. The surface of the bronchoscope should be wiped with 75% alcohol, and then send to sterilization after sealing the bronchoscope with a sealed bag.

Glutaraldehyde can be used to sterilize the flexible bronchoscope by leaving it immersed for 20 min. The bronchoscopy theatre should be cleaned, and surfaces wiped off.⁹⁶ Anesthesia equipment should be cleaned and breathing circuits replaced.

Single-use disposable bronchoscopes have been used in adults with SARS-COV-2 but are not routinely used in children, with limited data available.¹⁰⁰ Most children with TB reside in the poorer parts of the world where single-used disposable bronchoscopes would be too expensive.

Conclusion

The role of bronchoscopy in pediatric PTB has changed during the last decade from a simple method of collecting samples to an more sophisticated procedure. New methods are available for collecting samples, which include the use of EBUS and also better methods of bacteriological conformation. Interventions are now possible; not only to improve the diagnostic abilities of bronchoscopy but also to diagnose, manage, and follow-up airway-related complications. The challenge remains the availability of this expensive technology in resource-limited countries with the highest incidence of PTB. Furthermore, the pediatric pulmonologist needs to be trained in these procedures by providing good affordable training courses.

Author contributions

All authors were responsible for writing and reviewing the manuscript.

Prof Pierre Goussard was responsible for the bronchoscopy review.

Dr Jonathan Burke, Dr Francois Retief, and Dr Annemie Malherbe was responsible for the anesthesiology review. Prof Jacques Janson was responsible for the surgical review.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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