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Review

Bronchoscopic techniques in the management of patients with tuberculosis

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ABSTRACT

Tuberculosis (TB) is one of the leading causes of morbidity and mortality worldwide. Early diagnosis and treatment are key to prevent *Mycobacterium tuberculosis* transmission. Bronchoscopy can play a primary role in pulmonary TB diagnosis, particularly for suspected patients with scarce sputum or sputum smear negativity, and with endobronchial disease. Bronchoscopic needle aspiration techniques are accurate and safe means adopted to investigate hilar and mediastinal lymph nodes in cases of suspected TB lymphadenopathy. Tracheobronchial stenosis represents the worst complication of endobronchial tuberculosis. Bronchoscopic procedures are less invasive therapeutic strategies than conventional surgery to be adopted in the management of TB-related stenosis.

We conducted a non-systematic review aimed at describing the scientific literature on the role of bronchoscopic techniques in the diagnosis and therapy of patients with TB.

We focused on three main areas of interventions: bronchoscopic diagnosis of smear negative/sputum scarce TB patients, endobronchial TB diagnosis and treatment and needle aspiration techniques for intrathoracic TB lymphadenopathy. We described experiences on bronchoalveolar lavage, bronchial washing, and biopsy techniques for the diagnosis of patients with tracheobronchial and pulmonary TB; furthermore, we described the role played by conventional and ultrasound-guided transbronchial needle aspiration in the diagnosis of suspected hilar and mediastinal TB adenopathy. Finally, we assessed the role of the bronchoscopic therapy in the treatment of endobronchial TB and its complications, focusing on dilation techniques (such as balloon dilation and airway stenting) and ablative procedures (both heat and cold therapies).

Contents

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Introduction

Tuberculosis (TB) is one of the most important infectious diseases worldwide (World Health Organization, 2016). Its epidemiological burden is relevant in terms of morbidity and mortality. In particular, the last World Health Organization (WHO) Global Report on TB, published in 2016, highlighted an increased incidence (10.4 million) and mortality (1.4 million) in 2015 in comparison with the estimated figures reported in the previous year (World Health Organization, 2016). The new public health WHO strategy (World Health Organization, 2014; D'Ambrosio et al., 2014; Lönnroth et al., 2015; Sotgiu and Migliori, 2014), named End TB Strategy and aimed at eliminating TB, can achieve its goal by 2050 only if new cases of active disease are prevented (through vaccination and treatment of individuals with latent TB infection) or early detected and appropriately treated. The current diagnostic and therapeutic weapons are old and frequently ineffective (e.g., sputum smear negative patients, drug-resistant cases). Intensified research and development activities in the diagnostic, therapeutic, and preventive field could significantly address the current operational issues.

An appropriate therapeutic prescription strongly relies on microbiologic diagnosis of the collected biological specimen (*i.e.*, liquid or solid culture) (World Health Organization, 2006).

Several factors can hinder the collection of specimens and, then, the definitive diagnosis. In case of pulmonary TB, at least two sputum specimens are required; however, in some groups of patients (for instance, children, HIV-positive patients) the collection is difficult and alternative methods are necessary (World Health Organization, 2006; Dheda et al., 2004). Until now, observational and experimental studies have not provided sufficient scientific evidence to recommend one specific method more than another.

One of the medical interventions which could improve the clinical management of the TB patients is the bronchoscopy (Theron et al., 2013).

Aim of the present review is to describe the most important studies on bronchoscopy in the TB field and its potential recommendations.

Methods

We carried out a non-systematic, narrative literature review based on a Pubmed search until June 2017. We selected only epidemiological studies performed in adult human beings and written in English. Other filters, including those related to the aim of the study, were not used.

Bronchoscopy and diagnosis of sputum smear negative/sputum scarce TB patients

Sputum smear microscopy is the easiest and widespread tool adopted globally to diagnose cases of pulmonary TB; however, although it has been recommended since the first WHO global TB strategy (*i.e.*, DOTS), its sensitivity can be poor and affected by specimen processing methods and technical skills (World Health Organization, 2006; Steingart et al., 2006). Notably, more than one third of patients with pulmonary TB cannot produce sufficient sputum or is sputum smear negative (Theron et al., 2013; Hepple et al., 2012). Even though sputum induction is frequently used, it fails to provide a specimen of adequate volume or quality in up to 20% of the cases (Hepple et al., 2012). Moreover, it is not allowed to explore the airways and collect samples from the low respiratory tract (Theron et al., 2013). Bronchoscopy with bronchial washing (BW), bronchoalveolar lavage (BAL), and biopsy can play a key role in the collection of suitable samples for TB diagnosis (Lewinsohn et al., 2017).

Chest radiology (*i.e.*, chest X-ray and chest computed tomography) is helpful to plan and guide the collection of bronchoscopic samples; it can show parenchymal features (e.g., consolidations, cavitations, scattered nodules, etc.) and endobronchial involvements, as well as hilar and mediastinal lymph nodes enlargements (Beigelman et al., 2000; Skoura et al., 2015; Burrill et al., 2007). On the other side, F-FDG PET/CT (^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography) may help detect active TB (Skoura et al., 2015).

Bronchoscopic diagnosis of pulmonary TB traditionally relies on acid-fast bacilli smear microscopy, nucleic acid amplification techniques (NAATs), and *Mycobacterium tuberculosis* cultures (Theron et al., 2013; Jafari et al., 2011; Jafari et al., 2009; Jafari et al., 2006; Tueller et al., 2005; Mok et al., 2016; Tamura et al., 2010). Transbronchial needle aspiration (Reichenberger et al., 1999) and transbronchial biopsy (Theron et al., 2013; Chan et al., 2015; Jacomelli et al., 2012) may support the detection of cytological and histological TB findings (*i.e.*, necrotizing granulomatous inflammation), but a positive culture is associated with the highest diagnostic accuracy (Theron et al., 2013; World Health Organization, 2015). Indeed, mycobacterial culture could provide further information on drug sensitivity (World Health Organization, 2015).

However, the diagnostic delay related to a time to positivity ranging from 2 to 6 weeks (Theron et al., 2013; Mok et al., 2016; Dheda et al., 2009) increases the probability of a poor prognosis (morbidity, mortality, and economic burden) and of *Mycobacterium tuberculosis* transmission (Theron et al., 2013; Jafari et al., 2009; Tueller et al., 2005; Dheda et al., 2009; Le Palud et al., 2014). Smear microscopy for the identification of acid-fast bacilli is rapid (one-two days) and inexpensive (Mok et al., 2016), but its bacillary load-related sensitivity based on bronchoscopic specimens is low (Theron et al., 2013; Jafari et al., 2011; Jafari et al., 2009; Jafari et al., 2006; Tueller et al., 2005; Reichenberger et al., 1999; Chan et al., 2015; Jacomelli et al., 2012; Dheda et al., 2009; Le Palud et al., 2014; Barnard et al., 2015; Lee et al., 2013; Lin et al., 2010). NAAT, aimed to detect *Mycobacterium tuberculosis* nucleic acids, and histology have a good diagnostic yield, providing a response in a few days (Theron et al., 2013; Jafari et al., 2011; Jafari et al., 2009; Jafari et al., 2006; Tueller et al., 2005; Mok et al., 2016; Tamura et al., 2010; Chan et al., 2015; Jacomelli et al., 2012). The combination of those techniques may significantly increase the sensitivity of bronchoscopy for the early diagnosis of pulmonary TB (Theron et al., 2013; Tueller et al., 2005; Mok et al., 2016; Tamura et al., 2010; Jacomelli et al., 2012). The main shortcoming of those techniques using sputum and bronchoscopic materials can be the low specificity.

Rapid on-site evaluation (ROSE) of transbronchial needle aspirates is a well-known predictor of better yield in peripheral pulmonary lesions sampling (Mondoni et al., 2016a). Furthermore, for the diagnosis of endobronchial malignancies, parenchymal lesions and hilar/mediastinal lymphadenopathies, ROSE technique may allow bronchoscopists to interrupt the sampling procedure

when sufficient material has been collected, avoiding further needle passes and/or useless transbronchial biopsies or brushings (Mondoni et al., 2013; Mondoni et al., 2016a; Trisolini et al., 2011; Gasparini et al., 1995). In TB diagnosis ROSE may be useful to rapidly detect TB-related granulomas (Gasparini et al., 1995). Unfortunately, no methods are currently available for the immediate detection of mycobacteria in respiratory samples (Lewinsohn et al., 2017).

Bronchoalveolar lavage and bronchial washing aspirate

Smear microscopy shows a sensitivity ranging between 4.7% and 58.0% on BAL and BW (Theron et al., 2013; Jafari et al., 2009; Tueller et al., 2005; Dheda et al., 2009; Le Palud et al., 2014; Barnard et al., 2015; Lee et al., 2013; Lin et al., 2010; Ko et al., 2016; Agrawal et al., 2016; Khalil and Butt, 2015).

The NAAT sensitivity significantly varies when carried out on BW (51.9%-97.2%) (Tamura et al., 2010; Lee et al., 2011; Min et al., 2010; Wong et al., 1998; Chen et al., 2002; Boehme et al., 2010) and BAL (31.3-83.8%) (Jafari et al., 2011; Jafari et al., 2009; Tueller et al., 2005; Mondoni et al., 2016a; Chen et al., 2002), whereas the specificity is higher than 70% (73.2-100.0%) on BW (Tamura et al., 2010; Lee et al., 2011; Min et al., 2010; Wong et al., 1998; Chen et al., 2002) and 92.4-98.2% on BAL (Jafari et al., 2011; Jafari et al., 2009; Tueller et al., 2005; Dheda et al., 2009; Ko et al., 2016; Chen et al., 2002), respectively. The mismatch between sensitivity and specificity might be partially explained from the reference to different standards in the retrieved studies (single or combined use of microbiological, clinical and histological data) (Jafari et al., 2011; Jafari et al., 2009; Tueller et al., 2005; Tamura et al., 2010; Ko et al., 2016; Lee et al., 2011; Min et al., 2010; Wong et al., 1998; Chen et al., 2002).

Xpert®MTB/RIF (Cepheid Inc, Sunnyvale, California, USA) assay, a single cartridge-based NAAT, can simultaneously detect *Mycobacterium tuberculosis* nucleic acids and its genetic rifampicin (RMP) resistence within 2–3 hours (Boehme et al., 2010; World Health Organization, 2011). In comparison with the other commercially available NAATs, it is based on a fully-automated process (Theron et al., 2013; Le Palud et al., 2014; Boehme et al., 2010; World Health Organization, 2011; Sharma et al., 2015; Albert et al., 2016). Its diagnostic accuracy was widely confirmed on sputum specimens; however, in recent years its performance was successfully assessed on bronchoscopic specimens such as BW (Le Palud et al., 2014; Barnard et al., 2015; Lee et al., 2013; Ko et al., 2016; Sharma et al., 2015; Jo et al., 2016), BAL (Theron et al., 2013; Mok et al., 2016; Le Palud et al., 2014; Lee et al., 2013; Ko et al., 2016; Agrawal et al., 2016; Khalil and Butt, 2015; Sharma et al., 2015; Ullah et al., 2017), and endobronchial ultrasound guided-transbronchial needle aspiration (EBUS-TBNA) (Dhasmana et al., 2014; Dhooria et al., 2016a; Lee et al., 2017) (Table 1).

Theron et al. firstly demonstrated the high diagnostic accuracy of Xpert®MTB/RIF on BAL (Theron et al., 2013). In a high TB incidence country (South Africa), the Authors prospectively enrolled 160 sputum scarce or smear-negative patients with suspected pulmonary TB, who underwent bronchoscopy with BAL. Out of 27 patients with BAL culture positive for *Mycobacterium tuberculosis*, Xpert®MTB/RIF showed a sensitivity of 97%, significantly higher than that of smear microscopy performed on the same specimen (58%). Definite diagnosis was done in more than 80% of sputum smear negative patients. HIV/TB co-infection (35% of patients) did not affect sensitivity and specificity (Theron et al., 2013). In contrast with the findings of Ko et al. (Ko et al., 2016), they failed to demonstrate a significantly shorter treatment delay in patients with positive BAL Xpert.

Similar findings were shown by other Authors (Barnard et al., 2015; Lee et al., 2013; Agrawal et al., 2016; Khalil and Butt, 2015; Sharma et al., 2015; Jo et al., 2016; Ullah et al., 2017) who retrospectively demonstrated a high sensitivity (81-100%) of Xpert®MTB/RIF in both BW and BAL (Table 1).

Interestingly, Le Palud et al. (2014) confirmed a high sensitivity (80%) of the assay also in a low TB incidence country (France), enrolling 23 culture-positive patients who underwent bronchoscopy with BAL and BW for suspected pulmonary TB.

However, Barnard et al. (2015) reported on a lower specificity (87.7%): 9 patients resulted Xpert positive and culture negative (with a very low cycle threshold value), with three of them previously treated for pulmonary TB and one infected by *Mycobacterium avium intracellulare*. They highlight the importance of culture confirmation, as well as the medical history of a previous

Table 1
Summary of studies evaluating the diagnostic performance of Xpert®MTB/RIF on bronchoscopic specimens.

Author/year	Country	Study design	Patients number	Bronchoscopic specimen	Sensitivity	Specificity	Reference standard
Theron et al. (2013)	South Africa	PCS	27	BAL	92.6%	96%	Culture
Lee et al. (2013)	Republic of Korea	RCS	38	BAL and BW	81.6%	100%	Culture
Le Palud et al. (2014)	France	RCS	23	BAL and BW	80%	98.6%	Culture
Dhasmana et al. (2014)	Great Britain	RCS	84	EBUS-TBNA	72.6%	NR	Culture
Barnard et al. (2015)	South Africa	RCS	39	BW	92.3%	87.7%	Culture
Khalil and Butt (2015)	Pakistan	RCS	85	BAL	91.8%	71.4%	Culture
Agrawal et al. (2016)	India	RCS	27	BAL	81.4%	93.4%	Culture
Ko et al. (2016)	Republic of Korea	RCS	105	BAL and BW	92.4%	91.7%	Culture
Sharma et al. (2015)	India	PCS	BAL: 127 BW: 4	BAL and BW	BAL: 90% BW: 100%	BAL: 100% BW: 100%	Culture
Mok et al. (2016)	Singapore	RCS	44	BAL	68%	98%	Culture
Jo et al. (2016)	Republic of Korea	RCS	64	BW	92.2.4%	81.6%	Culture
Dhooria et al. (2016a)	India	RCS	53	EBUS-TBNA	49.1%	97.9%	AFB microscopy or culture or histology and clinico-radiological presentation and responses to treatment
Lee et al. (2017)	Republic of Korea	RCS	10	EBUS-TBNA	100%	NR	Culture or histology or NAAT (Xpert)
Ullah et al. (2017)	Pakistan	PCS	98	BAL	80%	87.5%	Culture

PCS: prospective cohort study; RCS: retrospective cohort study; TB: tuberculosis; BAL: bronchoalveolar lavage; BW: bronchial washing; EBUS-TBNA: endobronchial ultrasounds-transbronchial needle aspiration; NR: not reported.

TB diagnosis and treatment (Barnard et al., 2015; Ko et al., 2016; Khalil and Butt, 2015).

Ko et al. compared the accuracy of Xpert®MTB/RIF with AdvanSure™, a conventional real-time polymerase chain reaction (PCR) in 105 culture-confirmed pulmonary TB patients for whom both PCR techniques were available on BAL and BW. Xpert®MTB/RIF sensitivity was significantly higher than that of the conventional assay (92.4% vs. 83.8%, respectively) in smear negative patients, without any significant differences in smear positive subjects (Ko et al., 2016). Similar findings were also demonstrated by Jo et al. (2016).

Several studies demonstrated a high sensitivity (83.3-100.0%) and specificity (97.7-100.0%) of Xpert in diagnosing RMP resistance on both BAL and BW (Theron et al., 2013; Barnard et al., 2015; Lee et al., 2013; Sharma et al., 2015; Ullah et al., 2017).

Interferon-gamma release assays (IGRAs) are being used increasingly for the detection of an immune response against *Mycobacterium tuberculosis* antigens. However, their diagnostic accuracy (sub-optimal sensitivity and low specificity) for active TB has been disappointing when performed on blood specimens, especially in high TB incidence areas (Sester et al., 2011; Cattamanchi et al., 2012). The identification of a TB-specific immune response at the site of disease (*i.e.* the lungs) might improve IGRA performance, favouring an early diagnosis in AFB smear negative/sputum scarce patients (Sester et al., 2011; Cattamanchi et al., 2012).

Only a few studies have assessed the IGRAs on BAL specimens: the first ones, performed in low TB burden countries (Europe) with a lowest HIV infection prevalence, demonostrated a sensitivity and a specificity ranging from 91.0 to 100.0% and from 80.0-100.0%, respectively, with a low rate of indeterminate results (5-9%) (Jafari et al., 2011; Jafari et al., 2009; Jafari et al., 2006). Studies performed in high HIV/TB incidence countries showed a lower accuracy and a higher rate of indeterminate results (up to 34%) (Dheda et al., 2009; Cattamanchi et al., 2012; Jafari et al., 2013). To date, its suboptimal accuracy in BAL is limiting its scale-up (Sester et al., 2011; Cattamanchi et al., 2012; Jafari et al., 2013).

Transbronchial biopsy techniques

Fluoroscopy-guided transbronchial forceps biopsy (TBB) has long been used in diagnosing pulmonary TB in sputum-scarce or smear negative patients with peripheral pulmonary lesions (Figure 1). The histological feature of necrotizing granulomas on transbronchial samples in adjunction with AFB examination can shorten the TB diagnostic delay (Mok et al., 2016; Tamura et al., 2010; Chan et al., 2015; Jacomelli et al., 2012; Willcox et al., 1982). In case of missing contraindications, it was recommended by several Authors to add on TBB to BAL in order to increase bronchoscopy sensitivity (Mok et al., 2016; Tamura et al., 2010; Jacomelli et al., 2012; Lin et al., 2010; Charoenratanakul et al., 1995).

Several studies showed a TBB sensitivity of 16-77% in association with a good safety profile. Pneumothorax and bleeding are the most frequently reported complications (Theron et al., 2013; Mok et al., 2016; Tamura et al., 2010; Chan et al., 2015; Jacomelli et al., 2012; Willcox et al., 1982; Charoenratanakul et al., 1995; Wallace et al., 1981; Willcox et al., 1986; Danek and Bower, 1979; Stenson et al., 1983; Lai et al., 1996).

The wide inter-study variability of the diagnostic accuracy might be explained by the heterogeneous TB diagnostic criteria (*i.e.*, histology, bacteriology, or their combination), lesions size, and radiological features of the parenchymal lesions (Theron et al., 2013; Mok et al., 2016; Tamura et al., 2010; Chan et al., 2015; Jacomelli et al., 2012; Willcox et al., 1982; Charoenratanakul et al., 1995; Wallace et al., 1981; Willcox et al., 1986; Danek and Bower, 1979; Stenson et al., 1983; Lai et al., 1996), with lesions sized >2 cm (Lai et al., 1996) and miliary TB (Willcox et al., 1986; Burk et al., 1978) associated with an improved yield.

Chan et al. described the highest sensitivity of TBB (77%) with the guidance of radial probe endobronchial ultrasounds (Chan et al., 2015), whereas Lin et al. showed that EBUS-guided TBB is associated with a higher sensitivity than conventional fluoroscopically-guided samples (32.9% vs. 4.2%). Furthermore, in the subgroup of lesions detected with EBUS probes, AFB smears and

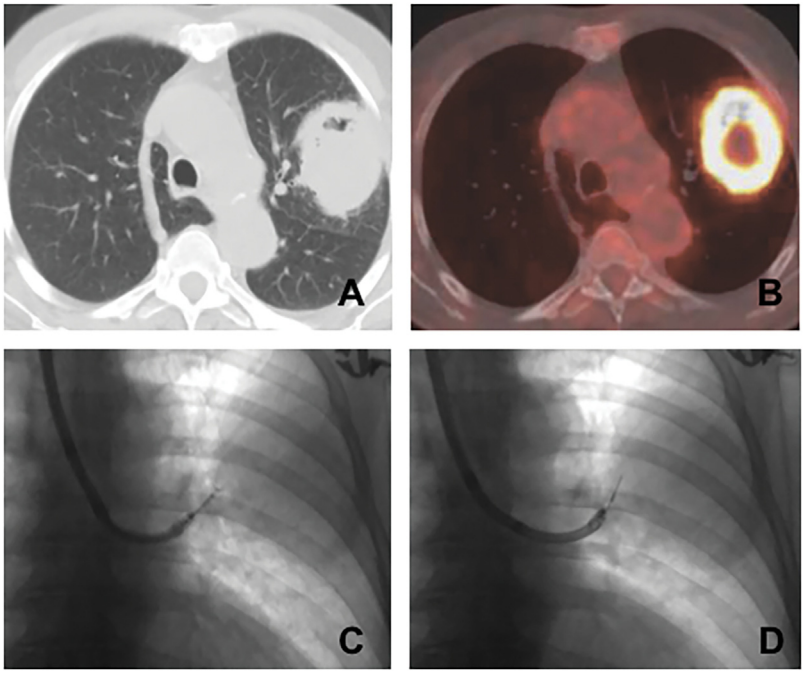

Figure 1. Chest computed tomography (A) and PET/CT scan (B) of a cavitated lesion in a patient with tuberculosis; conventional fluoroscopy-guided transbronchial biopsy (C) and needle aspiration (D) of the lesion.

Table 2
Factors potentially affecting the sensitivity of transbronchial biopsy in diagnosing pulmonary tuberculosis.

Lesion size
Presence of miliary tuberculosis
Radial probe endobronchial ultrasounds-guidance

cultures on BAL showed a higher sensitivity than in the control group (Lin et al., 2010) (Table 2).

More recently, Mok et al. reported on the results of an observational, retrospective study conducted in a tertiary hospital in Singapore, where the diagnostic role of BAL Xpert on sputum scarce and smear negative patients with pulmonary TB was assessed (Mok et al., 2016). They confirmed the good sensitivity of Xpert assay on BAL (68%) and stated that when Xpert® assay is added to routine BAL analysis TBLB did not significantly increase early and overall diagnostic yield. However, TBLB has a higher yield than BAL in diagnosing both interstitial lung diseases and pulmonary cancers, *i.e.* in cases showing clinical and radiological features that can closely resemble pulmonary TB. This technical characteristic may be relevant in countries with a low TB incidence, where the diagnosis of interstitial and malignant diseases is more frequent than TB. Then, the replacement of TBLB might lead to underdiagnosis of rapidly progressive and life-threatening medical conditions (Mok et al., 2016; Jacomelli et al., 2012; Lin et al., 2010; Mondoni et al., 2016b).

Other Authors reported on the utility of cytological specimens containing typical granulomas collected through fluoroscopically-guided brushing and transbronchial needle aspiration in the diagnosis of TB-related peripheral pulmonary nodules and masses (Tamura et al., 2010; Reichenberger et al., 1999; Gasparini et al., 1995; Jafari et al., 2013; Franzen et al., 2016) (Figure 1). Franzen et al., who carried out a randomized controlled trial in a high TB incidence country, failed to demonstrate a higher yield of brushing and TBLB performed with an ultrathin bronchocope versus samplings obtained with a standard bronchoscope (Franzen et al., 2016).

To date only one case report has described the utility and safety of transbronchial cryoprobes in diagnosing pulmonary TB and discriminating it from other diffuse lung diseases (such as sarcoidosis) in a high TB incidence setting (Dhooria et al., 2016b). Cryoprobes might further enhance the diagnostic performance of bronchoscopy in early and overall diagnosis of TB and diseases closely resembling TB (Mondoni et al., 2016b; Dhooria et al., 2016b) but future, controlled studies are needed.

Bronchoscopy and endobronchial tuberculosis

Endobonchial TB (EBTB) is a TB form involving the tracheobronchial tree (microbiological and histopathological evidence), regardless of a parenchymal involvement (Kashyap and Solanki, 2014; Sahin and Yildiz, 2013). The estimated incidence of EBTB was equal to 5.8%-50% (Altin et al., 1997; Chung and Lee, 2000; Lee et al., 2010; Kurasawa et al., 1992; Jung et al., 2015) among all pulmonary TB cases. However, since bronchoscopy is not routinely performed in all TB patients, its true incidence is likely underestimated (Kashyap and Solanki, 2014; Ozkaya et al., 2012). Bronchoscopy can be relevant for its diagnosis. In this context the role of endoscopy is complementary to chest CT, which evaluates the bronchial involvement length and peribronchial thickness, as well as the luminal patency. Furthermore, CT scans may detect indirect signs of bronchial stenosis (*i.e.*, atelectasis, cavities, hyperinflation, obstructive pneumonias) and predict patient outcome after bronchoscopic re-expansion procedures (Beigelman et al., 2000; Skoura et al., 2015; Burrill et al., 2007; Kashyap and Solanki, 2014; Chung and Lee, 2000; Lee and Chung, 2000). Since severe complications have been described in patients with EBTB, bronchoscopic examination of the tracheobronchial wall should be prompt in case of persistent cough, haemoptysis, clinical signs of bronchostenosis (such as wheezing and stridor), and radiological suspicion of endobronchial micobacterial invasion (Kashyap and Solanki, 2014; Lee et al., 2010; Hou et al., 2014).

On the basis of the bronchoscopic characteristics, endobronchial TB may be classified into seven categories, which are closely related to pathological changes (Chung and Lee, 2000; Xue et al., 2011) (Table 3).

Edematous-hyperemic, granular, and actively caseating subtypes are the most frequently detected (Sahin and Yildiz, 2013; Chung and Lee, 2000; Ozkaya et al., 2012; Qingliang and Jianxin, 2010; Um et al., 2008) but different subtypes may coexist in the same patient and one subtype may change into another (Chung and Lee, 2000; Xue et al., 2011). Bronchoscopic follow-up studies demonstrated that the evolution of EBTB depends on initial findings, which are closely related to the formation of granulation tissue (Chung and Lee, 2000; Kim et al., 1993; Lee et al., 1992). Fibrostenotic, actively caseating, edematous-hyperemic and tumorous EBTB are associated with the worst prognosis (Figure 2); however, while the fibrostenotic subtype is not associated with a worsening of the bronchial narrowing until complete fibrotic bronchial obstruction, the other three subtypes result in fibrostenosis in the majority of the patients (Kashyap and Solanki, 2014; Chung and Lee, 2000; Shim, 1996). Furthermore, because changes

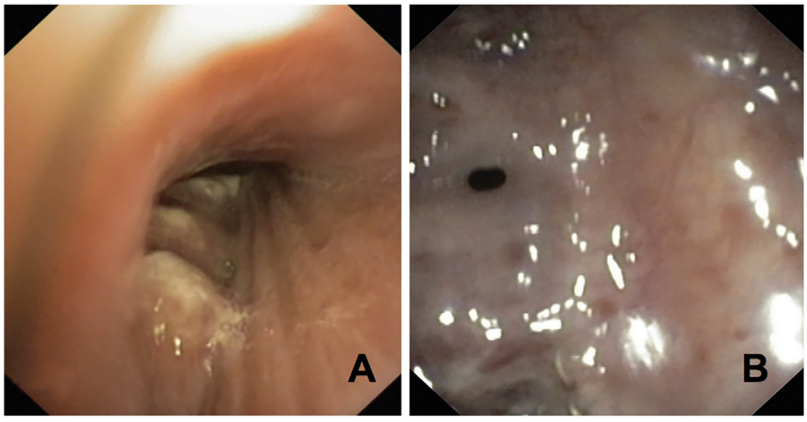

Figure 2. Tumorous endobronchial tuberculosis: endobronchial lesions covered with caseous material (A); fibrostenotic endobronchial tuberculosis: severe pinpoint lobar stenosis (B).

Table 3
Bronchoscopic features of endobronchial tuberculosis (EBTB) subtypes according to Chung classification (Chung and Lee, 2000).

EBTB Subtype	Bronchoscopic features
Non specific bronchitic	mildly swollen and/or hyperemic mucosa
Edematous-hyperemic	severely swollen and hyperemic mucosal surface
Actively caseating	edematous and hyperemic tracheobronchial mucosa covered with a large amount of whitish cheese-like material. Usual luminal narrowing.
Granular	severely inflamed mucosa with scattered rice-like nodules on the surface
Tumorous	endobronchial mass whose surface is often covered with caseous material and may totally occlude the bronchial lumen
Ulcerative	ulcerate tracheobronchial mucosa
Fibrostenotic	tracheobronchial narrowing of the bronchial lumen due to fibrosis

of endoscopic findings can occur within the first three months of treatment without any further significant variations, therapeutic outcomes can be estimated by follow-up bronchoscopy performed during the first three months of therapy, with the only exception of the *tumourous* type. This group of lesions, which is mainly due to an intrathoracic tuberculous lymph node erosion and protrusion into the bronchus (Figure 3), deserves a close and long-term follow-up because its evolution may be unpredictable and bronchial stenosis may occur in a late phase of the disease (Chung and Lee, 2000; Kim et al., 1993; Lee et al., 1992). Unfortunately, antibiotics play a limited role in preventing bronchostenosis (Um et al., 2008). Therefore, prompt diagnosis and mechanical treatment are of paramount importance in EBTB, in order to minimize the resultant bronchial strictures (Chung and Lee, 2000).

Bronchoscopic diagnostic techniques for patients with endobronchial tuberculosis

Bronchoscopy may provide support for bacteriological and histological diagnosis of EBTB, since sputum examinations show a low diagnostic yield in the majority of the cases (Sahin and Yildiz, 2013; Chung and Lee, 2000; Hou et al., 2014; Kim et al., 1993; Lee et al., 1992; Aggarwal et al., 1999). Furthermore, because endobronchial tuberculosis may mimic endobronchial neoplasms, in this context endoscopy plays a key role to rule out the presence of malignancies (Altin et al., 1997; Ozkaya et al., 2012; Shim, 1996).

Endobronchial biopsy (EBB) is the most reliable sampling method for EBTB diagnosis, with a sensitivity of 72.2-100.0% in the detection of granulomas (Altin et al., 1997; Ozkaya et al., 2012; Lee and Chung, 2000; Hou et al., 2014; Xue et al., 2011; Qingliang and Jianxin, 2010; Lee et al., 1992; Aggarwal et al., 1999; Hoheisel et al., 1994).

Altin et al. demonstrated a significantly better histological yield of EBB than endobronchial needle aspiration (respectively 84.0% vs 19.0%, respectively) in 42 subjects with EBTB (Altin et al., 1997). On the other side, smear and culture of bioptic tissues shows a wide sensitivity (8.0-100.0%), but few studies are available on their diagnostic performance (Ozkaya et al., 2012; Hou et al., 2014; Aggarwal et al., 1999; Hoheisel et al., 1994). Beside the most frequently used forceps biopsies, cryobioprobes have been described to successfully diagnose TB endobronchial masses (Chou et al., 2013).

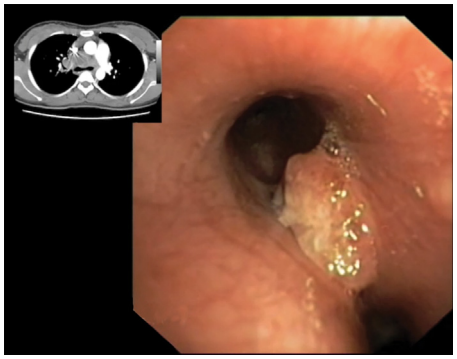

Figure 3. Tumorous lesion at the level of the main carina due to a subcarinal lymph node protrusion into the bronchial tree. Chest computed tomography view at the top.

Real-time PCR can reduce the time to diagnosis, improving patient prognosis (bronchial stenosis), showing a high sensitivity and specificity. Hou et al. reported on a sensitivity of 89.2% in a cohort of 74 patients with EBTB, significantly higher than that of sputum (4.1%) and bronchial brush smear microscopy (39.2%). Furthermore, employing the ABI PRISM 7500HT real-time PCR (Applied Biosystems, Foster City, CA, USA), the Authors showed a higher PCR sensitivity in granular, caseating and ulcerative EBTB than in edematous-hyperemic and fibrostenotic subtypes (Hou et al., 2014).

Studies based on traditional bacteriology on BW and BAL revealed a diagnostic yield of 10.0-37.0% and 12.5%-62.5% for smear microscopy and culture, respectively (Sahin and Yildiz, 2013; Altin et al., 1997; Ozkaya et al., 2012; Aggarwal et al., 1999). Ozkaya et al. demonstrated in a group of 21 patients that the highest smear and culture positivity was found in granular subtype (75%), while both resulted negative in patients with non specific bronchitic and fibrostenotic EBTB (Ozkaya et al., 2012).

Bronchoscopic treatment for patients with endobronchial tuberculosis

TB tracheobronchial stenosis, which is the commonest cause of benign stenosis in high TB incidence countries, represents the worst complication of EBTB. Different degrees of tracheobronchial strictures can occur, from slight luminal narrowing to complete obliteration, thus determining segmental, lobar or whole lung atelectasis despite the administration of effective TB therapy (Um et al., 2008). Left-side bronchi are more frequently involved because they are anatomically compressed by the aortic arch and TB is more often located in the left-sided lymph nodes (Lee et al., 2010; Lim et al., 2011; Verma et al., 2012; Iwamoto et al., 2004). These clinical conditions, which may cause respiratory failure, deserve an immediate endoscopic evaluation and management (Aggarwal et al., 1999; Verma et al., 2012; Iwamoto et al., 2004).

Bronchoscopic procedures (ablation and dilation techniques) represent an alternative and less invasive strategy than conventional surgery in the management of stenosis resulting from endobronchial disease, particularly when surgical treatment is contraindicated or in case of multi-level stenosis (Kashyap and Solanki, 2014; Lim et al., 2011; Verma et al., 2012; Iwamoto et al., 2004) (Table 4).

To date, only one case series has described TB cavity collapse performed by a bronchoscopy (Corbetta et al., 2016). Interestingly, Corbetta et al. described a minimally invasive lung collapse therapy recommended for emphysema-associated hyperinflation,

Table 4
Summary of bronchoscopic treatment options described in literature.

Therapy	Technique	Bronchoscope used	Scientific evidence level	Indications	Adverse events
Dilation	Rigid bronchoscope (Iwamoto et al., 2004; Low et al., 2004; Ryu et al., 2006)	Rigid	RCSs	*Fibrostenotic* EBTB dilation	NR
	Metal bougie (Lim et al., 2011; Ryu et al., 2006)	Rigid	RCSs	*Fibrostenotic* EBTB dilation	NR
	Balloon (Iwamoto et al., 2004; Ryu et al., 2006; Shitrit et al., 2010; Ferretti et al., 1995; Lee et al., 1999; Cho et al., 2015)	Rigid and flexible	RCSs	*Fibrostenotic* EBTB dilation (particularly in presence of annular cicatricial stenosis)	Mild haemoptysis, transient fever
	Stents placement (silicone and metallic) (Lim et al., 2011; Verma et al., 2012; Iwamoto et al., 2004; Low et al., 2004; Ryu et al., 2006; Bolliger et al., 2006; Cavaliere et al., 1988)	Rigid (silicone) Rigid and flexible (metallic)	RCSs	*Fibrostenotic* EBTB dilation (particularly in presence of tracheo-bronchial malacia)	Granulation tissue growth, mucostasis, stent migration
	Mitomycin-C application (Cary et al., 2015; Faisal et al., 2016; Penafiel et al., 2006)	Rigid and flexible	CRs	*Fibrostenotic* EBTB relapse prevention after dilation	None
Ablation	Nd-YAG laser (Lim et al., 2011; Low et al., 2004; Ryu et al., 2006; Bolliger et al., 2006; Cavaliere et al., 1988)	Rigid and flexible	RCSs	*Fibrostenotic* EBTB treatment	NR
	KTP laser (Qiu-Sheng and Cai-Ping, 2013)	Flexible	CRs	*Tumorous* EBTB treatment	None
	Carbon dioxide laser (Cary et al., 2015; Tong and Van Hasselt, 1993)	Rigid	CS	*Fibrostenotic* EBTB treatment	None
	Electrocautery (Shim, 1996; Amat et al., 2012)	Rigid	CS	*Fibrostenotic* (web-like stenosis) and *tumorous* EBTB treatment	None
	APC (Jin et al., 2013)	Flexible	RCS	*Tumorous* EBTB treatment in stenosis prevention	Mild bleeding, laryngeal spasm, cough
	Cryotherapy (Marasso et al., 1993; Mu et al., 2011)	Rigid and flexible	RCSs	*Fibrostenotic* EBTB treatment and *granular* EBTB treatment in stenosis prevention	Mild bleeding

RCS: retrospective cohort study; CS: case series; CR: case report; NR: not reported; EBTB: endobronchial tuberculosis; Nd-YAG: neodymium:yttrium aluminium garnet; KTP: potassium titanyl phosphate; APC: Argon Plasma Coagulation.

characterized by the placement of endobronchial one-way valves (EBVs) in four TB patients (with multi-drug resistant and difficult-to-treat extensive disease) and in one patient with atypical mycobacteriosis (Sciurba et al., 2010). The patients were considered not eligible for surgery owing to a large pulmonary involvement or serious clinical conditions. EBVs and medical therapy resulted in cavity collapse in all patients (partial in one and complete in four), and sputum smear became negative within 3-5 months after EBVs implantation.

No complications occurred and the valves were removed in 3 out of 5 patients after 8 months and no relapses were recorded after 15 months of follow-up (Corbetta et al., 2016).

Dilation techniques for tuberculosis patients with TB-related stenosis

Bronchoscopic airway dilation may be accomplished through rigid or flexible bronchoscopes.

The rigid bronchoscope itself provides dilation with the shear mechanics of the scope (Xue et al., 2011; Shim, 1996; Iwamoto et al., 2004; Watanabe et al., 1988; Low et al., 2004; Ryu et al., 2006). Metal bougie dilators provide the same effect but dilation performed by this technique, described only in a few studies (Lim et al., 2011; Ryu et al., 2006), may damage the mucosa (Xue et al., 2011; Shim, 1996). Balloon dilation is a minimally invasive and safe technique that can be performed with flexible bronchoscopes, by gentle balloon inflation through the stricture. It is particularly appropriate for annular cicatricial stenosis, since the balloon dilates the stenotic bronchus by expanding radially. As suggested by Shitrit et al., fibrotic process with fixed stenosis may be more responsive to a successful balloon dilation than those with active inflammation, calcification, or in whom the surrounding cartilage is destroyed (malacia). This approach is frequently the first treatment for tracheobronchial stenosis, with long term successful results ranging from to 6.3% to 73.0%. The wide effectiveness range depends on different conditions of the treated tracheobronchial walls among studies (Iwamoto et al., 2004; Ryu et al., 2006; Ferretti et al., 1995; Lee et al., 1999; Cho et al., 2015). When balloon dilation fails and more than one dilation is required, stent procedures are needed.

Airway stenting is an important strategy for managing tracheobronchial stenosis. Stenting is usually performed after balloon dilatation when the patient has a bacteriological conversion (Iwamoto et al., 2004). The major indications for the placement of airway stents are: patency of the central airways, racheobronchial malacia, fistulas due to TB erosion. Because stent-related complications are frequently observed in patients with benign stenosis caused by TB, and airway remodelling usually follows brochoscopic interventions, a removable stent should be selected (e.g., silicone stents such as Dumon stents (Dumon et al., 1996)). Furthermore, the dynamic properties of self-expandable metallic stents (such as Ultraflex and Gianturco stents) may lead to their fracture due to metal fatigue with severe repeated coughing (Iwamoto et al., 2004; Madden et al., 2006; Chung et al., 2011; Gottlieb et al., 2009).

Iwamoto et al. reported successful long-term outcomes of six patients treated with Dumon stents (both tubular and Y-shaped) to re-establish the patency of the central airway, without any severe complications in comparison with cases treated with expandable metallic stent (Ultraflex). They described the growth of granulation tissue more frequently in Ultraflex stent patients (between the mesh of uncovered Ultraflex stents and at the edges of the covered ones) than in those treated with silicone stents (Iwamoto et al., 2004). Interestingly, the Authors employed radial EBUS probes to assess the condition of the bronchial wall and to diagnose cartilaginous bronchomalacia.

Low et al. described an immediate and long-term clinical recovery in 7/11 (63.6%) patients treated with Dumon stents (Low et al., 2004); similar successful findings were observed by Ryu et al. for 75 patients with tracheobronchial tuberculous stenosis (Ryu et al., 2006): they placed silicon stents (both Dumon and Natural stents) which provided immediate symptomatic relief and improved lung function in 88% of the cases. After airway stabilization, stents were successfully removed in 49/75 (65%) patients after a median of

14 months. The most common complications were late and included migration (51%), granuloma formation (49%), mucostasis (19%), and restenosis (40%) (Ryu et al., 2006).

Lim et al. described the outcome of 71 patients who were treated with silicone stenting for post-TB tracheobronchial stenosis. The Authors described immediate symptom relief in 100% of cases with a rate of successful stent removal of 56% after 12.5 months. Granulation, mucostasis and stent migration were the most common complications (Lim et al., 2011). Similar findings were described by Verna et al. who safely removed a Natural stent in 31/41 (76%) patients, after a median of 18 months (Verma et al., 2012).

Zhou et al. recently evaluated the long-term effects associated with the temporary placement of metallic stents in patients with benign tracheobronchial stenosis (post-TB strictures in the majority of the cases). Uncovered metallic stents with flexible bronchoscope were placed in 40 patients and, then, easily removed after a median of 18 days. Only mild complications (granulation tissue growth, stent migration, or mal-expansion) occurred. After a median of 27 months following stent removal, 22 patients were symptom-recurrence free. Growth of granulation tissue and tracheobronchial malacia were independent factors of poor prognosis (Zhou et al., 2015).

Other Authors studied prognostic factors associated with successful airway stenting in patients with EBTB-related stenosis (Lee et al., 2010; Lim et al., 2011).

Lim et al. demonstrated in a group of 71 patients treated with silicon stents that successful stent removal was independently associated with atelectasis lasting < 1 month before bronchoscopy intervention and absence of complete lobar atelectasis, which is suggestive of extensive cicatricial healing and dense fibrotic changes (Lim et al., 2011). Similar findings were observed by Lee et al. who found that parenchymal calcification and bronchiectasis in atelectasis distal to bronchial stenosis at CT scans are associated with treatment failure (Lee et al., 2010), supporting the hypothesis that chronic changes of lung parenchyma or bronchi are unfavourable prognostic factors (Lim et al., 2011). On the contrary, TB activity at the time of intervention, mucus plugging, the extent of airway narrowing, and volume loss on CT scans did non affect the final outcome (Lee et al., 2010).

In patients with post-TB stenosis, stents are usually removed when stenosis is reduced (*i.e.*, patency is achieved after 12-18 months) (Verma et al., 2012; Colt and Dumon, 1995; Martinez-Ballarin et al., 1996; Cary et al., 2015). In case of premature removal, emergency reinsertion may be necessary. On the contrary, stents placed for a prolonged period are associated with a higher probability of stent-related complications. The decision of stent removal is usually based on clinical and functional stability (Verma et al., 2012). Verma et al. who carried out a retrospective study enrolling 41 patients with post-TB stenosis who underwent silicone stent placement and removal, showed that the air pockets (tracheobronchial air column length in the space between stent outer surface and the adjacent airway wall) were significantly longer in patients with successful stent removal than in those who failed (Verma et al., 2012).

A novel technique has been recently described to prevent stenosis relapse after dilation.

Mitomycin-C, which is an antineoplastic agent inhibiting fibroblast proliferation and modulating wound healing and scarring, was administered topically with saturated pledgets applied by forceps biopsy (0.4-0.5 mg/ml) in a few cases, as an adjunct therapy to bronchoscopic procedures (e.g., laser treatment and balloon dilation). It can prevent re-stenosis, and then replace airway stenting in tracheobronchial strictures secondary to EBTB (Cary et al., 2015; Faisal et al., 2016; Penafiel et al., 2006).

Ablative techniques in tuberculosis patients with endobronchial disease

Ablative techniques include heat and cold therapies. Ablative heat modalities are represented by laser therapy, electrocautery, and Argon Plasma Coagulation (APC) (Kashyap and Solanki, 2014; Shim, 1996).

Laser resection is based on laser energy delivered via rigid and/or flexible bronchoscopes. Several laser types are available. The neodymium:yttrium aluminium garnet (Nd-YAG) equipment is the most widely used for bronchoscopic interventions having sufficient power to vaporise tissues and to produce an effective coagulation (Bolliger et al., 2006). Laser therapy is recommended for endobronchial malignant lesions but also for EBTB-related stenosis (Shim, 1996). Cavaliere et al. treated six patients with TB tracheobronchial stenosis: normal bronchial patency was not fully achieved, but ventilation significantly improved (Cavaliere et al., 1988). The successful administration of Nd-YAG laser therapy was also described by Low et al. and Ryu et al. who cut fibrous bands in 21 and 13 patients with TB stenosis, respectively, and by Lim et al. who treated 14 web-like stenosis before stent placement (Lim et al., 2011; Low et al., 2004; Ryu et al., 2006).

The efficacy of potassium titanyl phosphate (KTP) laser was described in two case reports of tumorous EBTB obstructing tracheal and right main bronchial lumen (Qiu-Sheng and Cai-Ping, 2013). Cary et al. (2015) and Tong and Van Hasselt (1993) reported on the carbon dioxide laser resection in five patients with TB tracheobronchial strictures.

Electricity for tissue heating (electrocautery or diathermy) can be used for TB lesions. Electrons flow between the probe and the target tissue (voltage difference), generating heat for tissue coagulation due to the higher resistance of the target tissue. APC, a non-contact treatment mode, is based on ionized argon gas jet flow (*i.e.*, plasma) to conduct electrons. Unlike laser therapy which requires general anaesthesia and is associated with higher costs, diathermy and APC can be used in an outpatient setting with a flexible bronchoscopy and conscious sedation (Bolliger et al., 2006).

Electrocautery was prescribed for patients with TB web-like stenosis and in tumorous type EBTB (Shim, 1996; Amat et al., 2012).

Bronchoscopic APC is a safe therapy administered in cases of tumorous EBTB to prevent luminal stenosis. Jin et al. described the long-term outcome of 41 patients with tumorous EBTB who were exposed to APC and TB drugs in comparison with a control group with similar endoscopic findings who received only antibiotics. The Authors showed that the APC group (mean of 3 treatments before a complete recovery) achieved a cure rate of 100% vs. 84.6% in the control group. Furthermore, APC-treated patients showed a faster recovery (Jin et al., 2013). Cryotherapy, which consists of cold-induced cell death by repeated cycles of cold application followed by thawing, is a safe approach to treat TB stenosis without any risks of airway fire or bronchial wall perforation (Kashyap and Solanki, 2014; Marasso et al., 1993). Marasso et al. described for the first time the successful application of this ablative technique with the rigid bronchoscope in 12 patients with post-TB stenosis (Marasso et al., 1993).

Recently, Mu et al. found that bronchoscopic cryotherapy can improve granular EBTB and prevent progressive stenosis. They evaluated 38 patients treated with cryotherapy through flexible instruments (both bronchoscope and cryoprobes) and TB drugs in comparison with 38 patients who received only anti-TB drugs. Treatment success rate was 100% in the cryotherapy arm exposed to a mean of 4 applications per patient vs. 78.9% in those treated with the only anti-TB drugs. The time to recovery was faster in the cryotherapy arm and no severe adverse events were reported (Mu et al., 2011).

Hilar and mediastinal tuberculous lymphadenitis diagnosis

TB lymphadenitis (TBLA) is the most common extra-pulmonary TB disease (Norbis et al., 2014). The diagnosis of hilar and mediastinal TBLAs can be challenging, occurring as isolated intrathoracic adenopathies without any parenchymal involvement and any specific radiological and clinical features (Navani et al., 2011). A definite diagnosis is essential to rule out sarcoidosis or malignancies (*i.e.* lymphoma and lung cancer) (Navani et al., 2011; Eom et al., 2015).

The endoscopic approach is now considered the preferred means to collect biological samples. This accurate and minimally invasive technique may avoid invasive surgical procedures such as mediastinoscopy and video assisted thoracoscopy (Navani et al., 2011; Eom et al., 2015).

TBLA diagnosis relies on smear microscopy and culture, in association with specific cytological and histological features (Navani et al., 2011; Eom et al., 2015).

Conventional TBNA with both cytology (21-22 gauge) and histology (19 gauge) needles has been the first bronchoscopic technique to diagnose TBLA, showing a sensitivity of 65.0-100.0% and a specificity of 100.0%, with a good safety profile (Cetinkaya et al., 2002; Cetinkaya et al., 2004; De Wet et al., 2015; Bilaceroglu et al., 2004; Baran et al., 1996).

With the implementation of endobronchial ultrasounds, EBUS-TBNA has become the standard for the diagnosis of a mediastinal lymphadenitis (Navani et al., 2011; Hassan et al., 2011; Ye et al., 2015; Li et al., 2015). In 2011, Hassan et al. and Navani et al. demonstrated for the first time its effectiveness and safety (Qiu-Sheng and Cai-Ping, 2013; Hassan et al., 2011).

In a retrospective cohort study recruiting 19 patients with TBLA, Hassan et al. (2011) found a sensitivity of 95.0% and a specificity of 100.0%. They detected granulomas with necrosis in 16 patients, whereas 12 had positive culture for *Mycobacterium tuberculosis*. The high accuracy was confirmed by Navani et al., who described a sensitivity of 94.0% in 146 patients with TBLA. Furthermore, they showed that necrosis on needle aspiration and sampling more than one lymph node are associated with a higher diagnostic yield (Navani et al., 2011).

Two meta-analyses recently published found a sensitivity and specificity of EBUS-TBNA in the diagnosis of TBLA of 80.0% and 100.0%, respectively (Ye et al., 2015; Li et al., 2015).

Few studies on EBUS-TBNA assessed the utility of PCR (both nested and real-time), showing sensitivity and specificity of 36.8-56.7% and 100.0%, respectively (Eom et al., 2015; Hassan et al., 2011; Senturk et al., 2014; Geake et al., 2015). The diagnostic accuracy of NAAT with EBUS-TBNA can improve when histology and conventional bacteriology are performed (Eom et al., 2015).

To date, few studies have described the performance of Xpert MTB/RIF in the diagnosis of mediastinal TBLA by EBUS-TBNA (Table 1). Dhasmana et al. firstly demonstrated an overall sensitivity and specificity of 72.6% and 96.3%, respectively, in 88 culture positive cases. Furthermore, Xpert correctly detected two rifampin-resistant cases within 24 hours (Dhasmana et al., 2014). More recently, two other studies confirmed the good diagnostic yield of this method (Dhooria et al., 2016a; Lee et al., 2017).

Transesophageal endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) provides access to inferior mediastinum, left paratracheal area and aorto-pulmonary window and is now considered a complementary technique to EBUS-TBNA in diagnosing and staging non small cell lung cancer (Vilmann et al., 2015). Its utility has also been confirmed in diagnosing intrathoracic TBLA (Sharma et al., 2016; Fritscher-Ravens et al., 2011; Puri et al., 2010). In recent years, the transesophageal approach has also been successfully performed with an ultrasound bronchoscope, by a trained pulmonologist (Mondoni et al., 2015). This technique, named endoscopic ultrasound (with bronchoscope) fine needle aspiration or EUS-B-FNA, has successfully been used for TB diagnosis involving mediastinal lymph nodes, when EBUS was technically complicated or in patients unsuitable for a trans-bronchial approach (Mondoni et al., 2015; Oki et al., 2013; Dhooria et al., 2015).

Conclusions

Bronchoscopy can play a key role in the management of difficult-to-treat TB patients. When sputum cannot be collected, it can be a safe and highly reliable method. Moreover, it can be helpful for the evaluation of the lower respiratory airways, the detection of an endobronchial disease, and for sampling hilar and mediastinal lymph nodes. Histology, bacteriology and real-time PCR (*i.e.,* Xpert assay), performed on broncoscopic specimens, may improve the diagnostic yield.

Future studies are needed to better define the role of the newer bronchoscopic technologies (both guidance methods and sampling techniques) in the diagnostic TB pathway to improve early TB diagnosis. Furthermore, future investigations could better assess the role of bronchoscopic therapies, in combination with anti-TB drugs, particularly when more invasive surgical procedures are not recommended.

On the basis of some preliminary results, a widespread implementation of bronchoscopic techniques in reference centres might increase the case detection rate of both drug-susceptible and -resistant TB and the treatment success rate of complicated patients.

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