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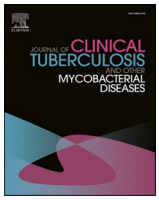

Is there a role for lung or bronchial biopsies for the diagnosis of mycobacterial pulmonary disease in patients with bronchiectasis?

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ABSTRACT

Background: Workup of bronchiectasis patients mandates microbiological characterization often being sought via Bronchoscopy. However, whether to perform bronchial or lung biopsies, is unknown, especially for the diagnosis of NTM pulmonary disease. We aimed to assess the current practice and yield of the different bronchoscopic procedures in this setting.

Methods: Data from an adult cohort with bronchiectasis referred for bronchoscopy for microbiologic sampling was reviewed, including demographics, etiology, imaging and results of the different bronchoscopic procedures performed.

Results: 127 subjects were analyzed (mean age 61, 56% female). BAL culture was positive in 44%. Frequent pathogens were Hemophilus Influenza (20%), pseudomonas aeruginosa (8%) and Staphylococcus aureus (7%). NTM and tuberculosis were found in 6% and 1.5% respectively. BAL cytology was sent in 125 procedures, EBB was performed in 51 patients (40%) and TBLB in 38 patients (30%). BAL cytology and both EBB and TBB (including tissue cultures) had no benefit over BAL with respect to microbiological diagnosis, including identification of mycobacterial disease.

Conclusions: In adult subjects with Non-CF bronchiectasis requiring bronchoscopy for microbiological characterization, BAL cytology and lung tissue biopsies were frequently performed but were of minimal additional benefit over BAL culture (including for mycobacterial pulmonary disease), and are most likely futile.

1. Introduction

Bronchiectasis is a relatively common and increasingly recognized disease characterized radiologically by permanent dilatation of the airways and clinically by chronic sputum expectoration, and recurrent chest infections [1]. Permanent airway dilatation causes chronic colonization by pathogenic organisms, resulting in the characteristic clinical syndrome of chronic inflammation, chronic chough and sputum production, with episodes of exacerbations thus resulting in further destruction of the airways and further inflammation (the so-called "viscous cycle" mechanism) [2]. Although not infrequently idiopathic, various etiologies could cause bronchiectasis, including congenital or acquired immune deficiencies, genetic disorders such as cystic fibrosis or primary ciliary dyskinesia, systemic inflammatory diseases, previous or chronic infections (including infection with non-tuberculous mycobacteria, NTM) and local airway obstruction [3]. Current guidelines recommend that patients diagnosed with bronchiectasis should undergo a thorough investigation for a possible underlying disease that should include a full history and physical examination, immune status, autoimmune serology, testing for genetic alterations and sometimes bronchoscopy [5].

The role of bronchoscopy in patients with non-CF bronchiectasis is generally limited. It is usually recommended in patients, in whom bronchiectasis is limited to one lobe, thereby raising the possibility of focal obstruction [5]. In addition, an important issue in these patients is identifying the type of pathogen infecting or colonizing the diseased airways, as this effects the severity of disease, the prognosis of the patient, and has implications on the correct management plan for the patient [4]. For example, isolation of Pseudomonas Aeruginosa frequently portends a poorer prognosis, with more frequent exacerbations and worse quality of life [6]. This pathogen also warrants consideration of a guideline based eradication strategy, and may affect the choice of long-term treatment given (e.g. inhaled versus chronic oral antimicrobials) [4]. Another example is diagnosis of Non-tuberculous Mycobacteria infection in the airways, frequently requiring specific and prolonged antimicrobial treatment while chronic macrolide monotherapy is

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contraindicated [7]. Sputum samples should be sent for culture (including specific mycobacterial cultures) in all patients with bronchiectasis, and bronchoscopy should be performed for patients who cannot expectorate sputum or when sputum cultures are sterile [2,4]. According to current guidelines, the diagnosis of NTM infection is by a combination of clinical, radiological and microbiological criteria [8]. The microbiological criteria include positive sputum, bronchoalveolar lavage (BAL) or tissue cultures, or identification of acid-fast bacilli or granulomas in tissue biopsies, although negative histology may not exclude this diagnosis [9,10]. However, whether tissue biopsies and cultures should be obtained routinely in patients suspected of having NTM infection and undergoing bronchoscopy is not clear and not stated in the guidelines for NTM or bronchiectasis [1,2,11].

In cases of bronchiectasis in whom bronchoscopy is indicated, following inspection of the main airways, BAL is almost uniformly performed, with fluid obtained sent for routine bacterial, mycobacterial and fungal cultures, acid fast and fungal stains and for cytological examination. In our experience, many pulmonologists also perform additional routine endobronchial and/or transbronchial biopsies (EBB and TBLB), for acquisition of tissue pathology and tissue cultures, which may increase the yield for diagnosis of NTM pulmonary disease (NTM-PD) or fungal infection. However these may prolong the procedure and increase the risk of bleeding and pneumothorax.

In this study, we assess the diagnostic yield and added benefit of the different bronchoscopic procedures in the work up and management of subjects with bronchiectasis, specifically hoping to find whether obtaining tissue samples in these subjects increase the yield of identifying the relevant microbial pathogen, and thus should indeed be considered routine practice.

2. Materials and Methods

This study was conducted in accordance with the amended Declaration of Helsinki, and was approved by our local institutional review board (approval number HMO-0424–18). Given the retrospective and non-interventional design of the study, obtaining subject's informed consent was waivered.

We conducted a retrospective analysis of all subjects with bronchiectasis who underwent bronchoscopy in our center during the years 2009–2017, for the purpose of obtaining microbiologic sampling. Following approval of our local ethical research board, charts were obtained for all subjects, and data was extracted using our electronic chart system.

Exclusion criteria included patients with a known history of cystic fibrosis, and subjects under 16 years of age. Otherwise all patients who underwent bronchoscopy for this indication were included.

The following data was obtained for all subjects: demographics, etiology of bronchiectasis (when known), imaging findings, spirometry and results of sputum cultures prior to bronchoscopy. We reviewed the bronchoscopy reports for data regarding the exact modality used (BAL alone, or combined with EBB/TBB/EBUS), and complications during or after the procedures. Finally, we obtained microbiological and pathology reports for the specimens sent during the procedure. Clinically significant results were considered in cases in which abnormal findings resulted in change of management, when non-invasive measures failed to do so.

All patients underwent CT scan prior to performing bronchoscopy and sputum cultures including specific cultures for mycobacterial and fungal infections. All bronchoscopies were performed in stable patients, and none were performed during an exacerbation, hospitalization or evidence or respiratory failure. When performing bronchoscopy, thorough inspection of all accessible airways is done along with aspiration of visible secretions in the airways. BAL is subsequently performed in the most infected lobe. Both bronchial secretions and BAL fluid are routinely sent for cytological analysis as well as bacterial, fungal and mycobacterial cultures. Viral cultures or PCR are not routinely sent in patients with chronic Bronchiectasis. Endobronchial biopsies were carried out at the discretion of the operator, usually in cases in which gross airway pathology is observed. Transbronchial biopsies were attempted when there was a high suspicion of NTM-PD and the desire to complement BAL with direct tissue cultures and histology.

3. Results

One hundred and twenty seven subjects with bronchiectasis underwent bronchoscopy for respiratory microbiologic sampling during the study period. Fifty-six (44 %) were male, mean age 60.8 (range 17–89). Eighteen subjects (14 %) underwent the procedure also due to recent hemoptysis.

Sixteen subjects (12 %) had a known etiology for bronchiectasis prior to the procedure including primary ciliary dyskinesia, inflammatory bowel disease, collagen vascular disease, granulomatosis with polyangiitis, lymphoma, chronic lymphocytic leukemia, hypogammaglobulinemia following bone marrow transplant, previous tuberculosis and foreign body aspiration.

Twenty-seven subjects (21 %) had disease localized to only one lobe, while the rest had multilobar disease.

Spirometry results were available for 25 subjects (20 %), with an average FVC of 84 % predicted, FEV1 of 76 % predicted and FEV1/FVC of 0.73.

Sputum cultures were available for 14 subjects (11 %) prior to bronchoscopy and were positive in four subjects, with isolation of NTM in two subjects, Aspergillus and Pseudomonas Aeruginosa. Bronchoscopies were performed in these cases in order to verify infection with these pathogens or to assess for co-infection.

Bronchoscopy data (see Table 1 for full details)

Abnormal findings (other than increased sputum production) were observed upon visual inspection of the bronchial tree in 39 subjects (30 %). Of those, the most common findings were mucosal hyperemia and edema (24 subjects) with bronchial stenosis or narrowing in the affected lobe observed in 12 cases. In one subject, a foreign body was found and removed at the time of bronchoscopy. None of the other findings observed resulted in change of management.

Clinically significant BAL cultures were positive in 56 subjects (44 %). PA was isolated in seven subjects (6 %) and NTM in six (5 %). Mycobacterium Tuberculosis was found in two subjects. Other frequently isolated bacteria were Haemophilus Influenza (20 %) and Staphylococcus Aureus (7 %). All microbiological isolations were new, with the exception of one subject with PA, which was previously also identified in sputum (bronchoscopy in this case was performed in order to rule out NTM co-infection).

Fungal cultures were positive in twenty five patients (19 %), however only two of the patients were considered to have had a true fungal infection (one with Cryptococcus Neoformans and another with Rhyzopus Oryzea). All other isolates were considered to be commensals, and these included mostly Aspergillus species such as A. Niger (13 cases), A. Flavus, A. Nidulans, A. Candidus, A. Terreus and A. Glaucus. Other less frequent fungal species isolated were Cladosporium, Bjerkandera, Rasamsonia, and Geotrichum Candidum.

Cytological analysis was performed on BAL fluid in all but two subjects (125 samples in total), all of which resulted in no clinically significant findings.

Tissue biopsies were performed in 76 subjects (60 %). Endobronchial biopsies were performed in 51 subjects (40 %) and transbronchial biopsies in 38 subjects (30 %). 13 subjects (10 %) underwent both EBB and TBLB. Three subjects also underwent ultrasound guided transbronchial needle aspiration of enlarged mediastinal lymph nodes. EBB yielded no clinically significant findings in any of the subjects in whom it was performed, and TBLB yielded a significant finding in only a single subject (an unexpected breast cancer metastasis causing post-obstructive bronchiectasis).

Tissue was sent for culture in 34 subjects (27 %), with positive

Table 1
Data obtained during bronchoscopy.

Inspection (n = 127)		
	Positive findings no (%)	39 (30.7)
	Findings (no)	Mucosal edema/thickening/ polyps (24) Airway stenosis (12) Major airway dilatation (1) Foreign Body (1) Gastric content/aspiration (1) Tracheobronchomalacia (1) Vocal cord polyp (1) Cobblestoning (1)
BAL Fluid Cultures (n = 127)		
	Total positive no (%)	56 (44)
	Pathogens (no)	Haemophilus Influenza (20) Pseudomonas Aeroginosa (8) Staph. Aureus (7) NTM (6): M. Abscessus (2), M. Marinum, M. Fortuitum, M. Simiae, M. Avium. Strep. Group A (2) Strep. Pneumonia (2) Moraxella Catarhalis (2) M. Tuberculosis (2) Rhyzopus sp. (1) Burkholderia sp. (1) Cryptococcus Neoformans (1) Achromobacter sp. (1)
Tissue Cultures (n = 34)		
	Total positive no (%)	15 (44)
	Pathogens not obtained by BAL fluid culture	1 Staph. Aureus
Endobronchial (n = 51) Transbronchial (n = 38) and EBUS-TBNA (n = 3) Biopsies		
	Total positive no (%)	12 (13 %)
	Findings	Organizing Pneumonia (3) Caseating Granulomas (2) Non-Caseating Granulomas (2) Charcot Leyden Crystals (1) Corpora amylacea (1) Metastatic Breast Cancer (1) 'Heart Failure' cells (1) Foreign body with granulation tissue (1)

cultures seen in fifteen of these (44 %). Tissue cultures added no further information over and above BAL cultures with the exception of one case in which Staph. Aureus was cultured in tissue and not in BAL fluid. Of note, among patients with Mycobacteria pulmonary disease, none had positive tissue pathology or culture with negative BAL culture.

We did not observe a difference in outcomes between patients complaining of hemoptysis prior to bronchoscopy and patients without hemoptysis.

Complications of bronchoscopy were reported in nine cases (7 %). There were three cases of pneumothorax (7.8 % of all TBLB) and two cases of significant bleeding, both managed locally. Three subjects developed fever following bronchoscopy and required antimicrobial therapy (only one of whom underwent biopsies). One subject had prolonged hypoxemia. The study flowchart and main results are presented in Fig. 1.

4. Discussion

Bronchoscopy is frequently used as a diagnostic tool in patients with bronchiectasis in whom adequate or informative sputum cultures cannot be obtained [4,12]. However, there is little data regarding the role or diagnostic value of bronchial or lung biopsies in these patients.

In this study, we evaluate the common practice regarding bronchoscopy in subjects with bronchiectasis in our institute. We also assess whether the practice of performing bronchial or lung biopsies or BAL cytology during bronchoscopy in patients with bronchiectasis is indeed indicated, or adds any clinical information for patient management. We found that performance of BAL cytology was almost universal and that EBB and/or TBB were commonly performed (60 % of procedures). We however found that there is minimal or no added clinical benefit in sending either BAL fluid for cytology examination nor tissue samples (EBB or TBLB) for culture or histology over and above BAL cultures in these patients.

These findings have important implications to clinical practice. Guidelines suggest sending BAL fluid microbiological analysis, including specific mycobacterial and fungal cultures [1,4]. As expected, and in concordance with previous studies [13–15], this practice proved to be most beneficial in our cohort with positive cultures obtained in nearly half the subjects, most of whom with negative previous sputum cultures. All the NTM positive cultures were new compared to previous sputum mycobacterial cultures, reinforcing the role of BAL in diagnosis of NTM-PD.

Despite the importance of lung tissue cultures in aiding diagnosis of pulmonary NTM suggested by some [16], sending additional tissue cultures (performed in 27 % of procedures in our cohort) did not result in any new clinically significant information except in one subject, making this practice seem not worthwhile.

Endo-bronchial biopsies were performed in our cohort in 40 % of subjects. This was mostly performed in cases in which inspection of the airways revealed significant mucosal edema, bronchial narrowing or obstruction, findings commonly described in such subjects. Pathology reports in these cases were consistently non-specific, and showed mostly mucosal edema, basement membrane thickening, chronic and acute inflammation and goblet cell hyperplasia, findings that should be expected in subjects with chronic airway disease [17,18] but without clinical implications to date. Given these findings, and although this practice may seem warranted, our data shows that performing EBB in these subjects yields no clinically significant results, and does not alter patient management.

NTM-PD is a frequent finding among patients with bronchiectasis with prevalence reported to be up to 37 % in cohorts from the Unites States [19]. Prevalence in Europe varies according to geographical region, with rates reported to be between 2 and 10 % [20,21]. The prevalence of NTM-PD in Israel is similar to the European data with reports of 6–9 % in different areas of the country [22,23]. In addition, we recently published data regarding the prevalence of NTM-PD in the Jerusalem area, finding a rate of 5.2 % of this disease among patients with bronchiectasis, finding no significant clinical differences among these patients, compared to bronchiectasis patients without NTM-PD [24]. M. Tuberculosis infection in Israel is also quite rare with a reported incidence of 2.3 per 100,000 in the general population in 2023, as per the Israeli ministry of health report [25].

The diagnosis of NTM-PD relies on clinical, radiological and microbiological criteria, with one of the microbiological criteria being a positive direct tissue culture or pathology suggesting mycobacterial disease (such as granulomatous inflammation). In our cohort TBLB was performed quite often (30 % of cases), with the aims of obtaining tissue cultures, and pathology specimens for diagnosis of mycobacterial infections (as per the NTM diagnosis guidelines) [8], and perhaps to investigate for an underlying unexpected diagnosis. In a retrospective study by Ikedo, the practice of performing TBLB in subjects with MAC yielded specific histology in 37 %, specifically epithelioid cell granulomas and/or acid-fast bacilli, however this did not add to bronchial washing cultures [26]. In our cohort, adding TBLB to BAL fluid culture did not result in any added benefit concerning diagnosis of NTM or TB,

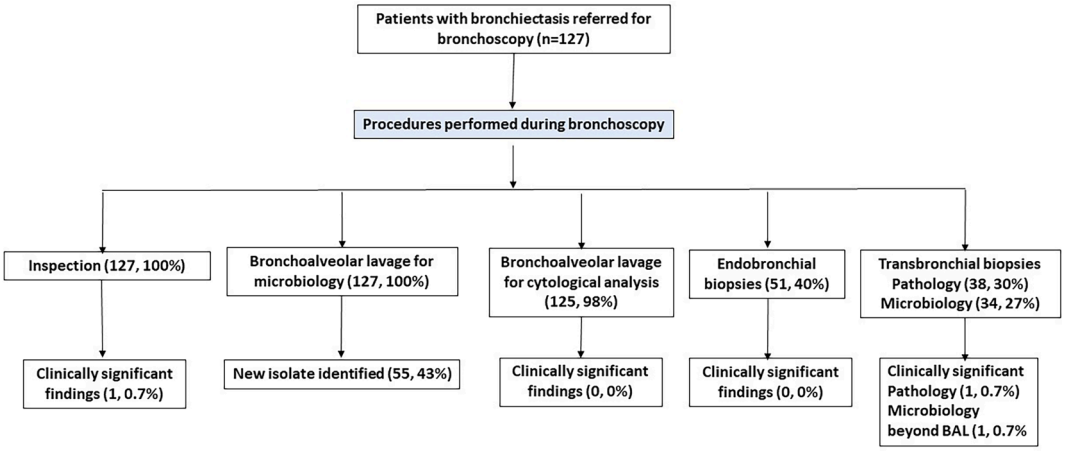

Fig. 1. Study flowchart and main outcomes. This figure shows the different bronchoscopic procedures performed in all patients along with the respective proportions of positive clinically meaningful outcomes of these procedures.

nor unravel any new underlying etiologies for bronchiectasis.

Finally, the practice of performing lung biopsies comes at a price. We found an 8 % risk of pneumothorax in our subjects undergoing TBLB (three cases) and two cases of significant bleeding. Although underpowered, there may be an increased risk of complications following transbronchial biopsies in patients with bronchiectasis compared to other patient groups as frequency of complications for TBLB is usually reported to be as low as 0–4 % of procedures [27].

Limitations of our study include its retrospective design, and the single center data, that may not be applicable to other centers or regions in the world. However, we believe that the findings reported here are important for the decision making process undertaken in patients with bronchiectasis requiring bronchoscopy.

Another limitation to our study may be the relatively low prevalence of mycobacterial disease in Israel [22–24]. Hypothetically, biopsies may be of greatest benefit in patients with suspected tuberculosis or NTM. Thus, biopsies may be of value in regions of the world with higher prevalence of mycobacterial disease and this may warrant analysis of similar data from other geographical regions.

In conclusion, we found that performing TBLB, EBB for histologic examination or tissue cultures, or performing cytology analysis of BAL fluid did not result in any significant additional clinical data when performing bronchoscopies in subjects with non-CF bronchiectasis, nor aid in the microbiological workup in these patients. We recommend these practices be routinely avoided in such procedures, which should include performing bronchial inspection and BAL fluid cultures alone.

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Author contributions

Conception and design RK, NB, ZGF; Administrative support NB, AA; Provision of study materials or patients: N/A; Collection and assembly of data: RK, AA, UL, NB; Data analysis and interpretation: RK, NB; Manuscript writing: All authors; Final approval of manuscript: All authors.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval

This study was conducted in accordance with the amended Declaration of Helsinki, and was approved by the Hadassah medical center local institutional review board (approval number HMO-0424–18). Given the retrospective and non-interventional design of the study, obtaining subject's informed consent was waivered.

CRediT authorship contribution statement

Rottem Kuint: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Avraham Abutbul:** Data curation, Investigation, Writing – original draft, Writing – review & editing. **Zvi G. Fridlender:** Conceptualization, Writing – original draft. **Uri Laxer:** Data curation, Writing – original draft. **Neville Berkman:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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