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The role of bronchoscopy in diagnosis of chronic cough in adults: a retrospective single-center study

Abstract

Introduction: Cough is one of the most frequent symptoms reported to pulmonologists. The role of bronchoscopy in the diagnostic work-up of chronic cough is not clearly defined. The aim of this study was to evaluate the utility of fiberoptic bronchoscopy (FOB) and additional testing of samples collected during FOB in the differential diagnosis of chronic cough in adults.

Material and methods: This was a single-center retrospective study. Out of 7115 conventional white light FOB examinations, we finally selected 198 with cough as the only indication.

Results: In 40.9% of bronchoscopic examinations, no visible cause of cough was found. Visual signs of chronic bronchitis (CB) were detected in 57.6% of reports. Only in 3 cases (1.5%) bronchoscopy revealed a potential cause of chronic cough other than CB. *Mycobacterium tuberculosis* or other mycobacteria were spotted in none of the samples. In 91.1% of bronchoalveolar lavage (BAL) cytologic examinations, at least one cell count abnormality was detected, but only in case of increased percentage of eosinophils, it might be considered clinically relevant. In 53% of bacteriological culture results, at least one potentially pathogenic bacterium was isolated.

Conclusions: The present study results strengthen the evidence that FOB combined with additional testing of airway specimens obtained during FOB is not a powerful tool in the differential diagnosis of chronic cough, and FOB as a diagnostic tool may be overused. The appropriate timing and decision regarding referral for FOB and additional testing of achieved material requires careful clinical consideration.

Key words: fiberoptic bronchoscopy, cough, differential diagnosis, bacterial cultures, bronchoalvelar lavage

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Introduction

Cough is a protective reflex of the respiratory system that clears the airways from mucus, fluids, particles or other material [1]. An occasional, sporadic cough is normal and healthy. A cough that persists for several weeks or one that brings the blood, bloody or discolored sputum or an excessive amount of airway mucus may indicate a condition that requires medical attention. Cough itself belongs to the most frequent respiratory symptoms for which patients seek help from primary care physicians and/or pulmonologists [2]. Taking into account the symptom duration, it is subdivided into three categories, namely: acute — defined as lasting less than 3 weeks, subacute — 3–8 weeks duration, and chronic cough which persists longer than 8 weeks [3].

Differential diagnosis of chronic cough in the first line should include common causes like upper airway cough syndrome (UACS), asthma, eosinophilic bronchitis, gastroesophageal reflux

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disease (GERD), chronic obstructive pulmonary disease, pulmonary fibrosis, or bronchiectasis. Additionally, drugs (e.g. ACEI, angiotensin-converting enzyme), exposure to cigarette smoke and environmental pollution should be taken into account [1]. Animal studies indicate that cough stress to the airway wall generates a self-perpetuating cough-reflex cycle [4]. It is of note that the causes of cough may overlap. It has been shown in a prospective cohort study of patients with chronic cough that this symptom was due to one condition in 73%, to two conditions in 23%, and to three conditions in 3% of the subjects [5].

According to the most up-to-date ERS guidelines on the diagnosis and treatment of chronic cough [7], the initial evaluation of a patient should include a detailed medical history (most importantly ACEI use, smoking history and irritants exposure), physical examination, chest radiography, lung function tests, and conditionally FeNo and blood eosinophilia. Recommended initial management includes: stopping risk factors, empirical treatment with oral or inhaled steroids or proton pomp inhibitors (PPI) in symptomatic GERD [7]. In a patient with normal chest X-ray and unsuccessful initial management, additional evaluation is suggested, with bronchoscopy at the very end of the list, after esophageal manometry, induced sputum, sputum acid-fast bacilli (AFB), laryngoscopy, methacholine challenge and chest CT [6]. Still, fiberoptic bronchoscopy (FOB) may be a reasonable tool for the anatomical and dynamic assessment of the airways and offers a sampling of distal airways for cytologic and microbiologic studies.

There is a substantial body of evidence suggesting that FOB has a limited role in the diagnosis of patients when chronic cough is the only indication and when no findings in imaging studies are detected [8–10]. However, in selected instances, e.g., the necessity of sampling, presence of risk factors of malignancy, refractory cough, in immunocompromised patients or when "uncommon causes" are considered, the clinical benefit of FOB is noted [8, 10–13].

The present study aimed to evaluate the utility of FOB and additional testing of samples collected using FOB in the differential diagnosis of chronic cough. We hypothesize that the visualization of the airways itself is not sufficient to determine the underlying cause of chronic cough, but reasonably selected additional tests of airway samples collected during FOB may increase its diagnostic value.

Material and methods

The study is a retrospective, single-center, observational cohort study of patients referred with a diagnosis of chronic cough to the Bronchoscopy Unit of the Department of Pneumology and Allergy and the Department of General and Oncological Pulmonology of Medical University of Lodz FOB examinations were performed between November 2006 and April 2017 by experienced pulmonologists. During this period, 7115 conventional white light FOB examinations were carried out. The results of examinations were routinely collected in a digital database. Due to the retrospective nature of the study, no ethics committee approval was needed.

Study inclusion criteria were the following: diagnosis of chronic (> 8 weeks) unexplained cough as the only indication for FOB and no radiological findings (chest radiography and/or chest computed tomography); aged above 18. Patients with any lung-related disease diagnosed before FOB referral (e.g. neoplasm, asthma, COPD, sarcoidosis) or presenting with other accompanying symptoms (e.g. hemoptysis) were excluded from the study.

All patients' cases which met study eligibility criteria were analyzed. Medical documentation, the outcome of FOB examinations and results of additional testing of samples collected during FOB: tests to exclude tuberculosis infection AFB smears and cultures], non-specific microbiological cultures of bronchial washings and cytologic examinations of bronchoalveolar lavage fluid (BALf) were analyzed.

Drug resistance definitions used in our study are based on the previously published definitions by Magiorakos [14]. Based on the previously used methodology of building worksheets for categorizing bacteria to a particular group of resistance, we created worksheets for bacteria found in our study.

Results

After careful review of the study inclusion and exclusion criteria, we have finally enrolled 198 patients in the study, 121 females (61%) and 77 males (39%), with the median age of 51.5 years (37.75–61). Figure 1 shows the flow chart of patient selection for the study.

Chronic bronchitis signs were visualized in 114 (57.6%) patients. The endoscopic diagnosis of chronic bronchitis was based on the visual assessment when the following features were present: dilated mucus glands' ducts, atrophic mucosa, mucus aggregation, hyperemia, mucosal fragility.

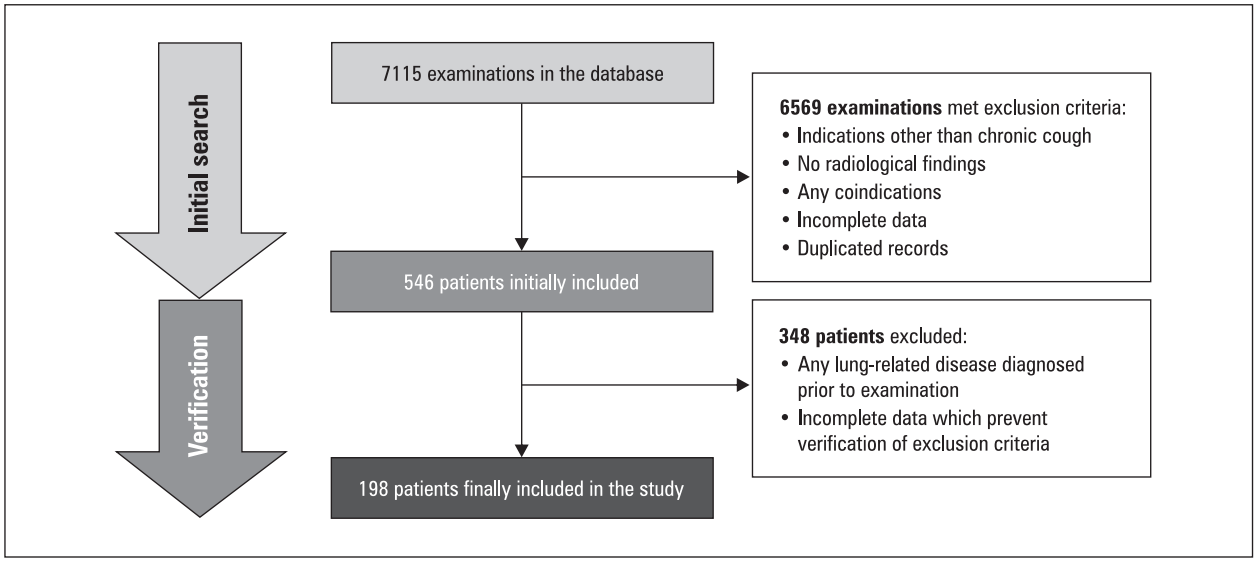

Figure 1. The flow chart showing patient selection to the study

In 81 (40.9%) examinations, no visible lesions of the airways were noted. In three (1.5%) patients, FOB revealed the probable cause of chronic cough: suspicion of a tumor (pathology not determined, sent to another center and lost to follow-up), bronchial polyp, and tracheomalacia (Figure 2).

None of the studied patients had a positive result of tuberculosis testing (AFB smear and/or culture). In 45 (22.7%) patients, bronchoalveolar lavage (BAL) was performed. In 41 cases (91.1%), BALf cytologic examination showed at least one cell count abnormality, in 12 cases (26.7%), at least three abnormalities, see Table 1. In 5 (11.1%) examinations eosinophils count of ≥ 3% was detected.

In 111 (56%) FOB examinations, non-specific bacteriological cultures were performed. One potentially pathogenic bacterium was detected in 51 (46%) samples, and 2 potentially pathogenic bacteria were detected in 8 (7%) samples. There were 2 alert pathogens within cultured bacteria. Remaining 52 (46.8%) cultures were sterile.

Multidrug resistance (MDR) was detected in case of 40 bacterial strains (59.7%), and in 1 case (1.5%), extensive drug resistance (XDR) was identified. In 21 (36%) patients with positive cultures, FOB revealed no visible airway changes. Isolated bacterial strains are shown in Table 2.

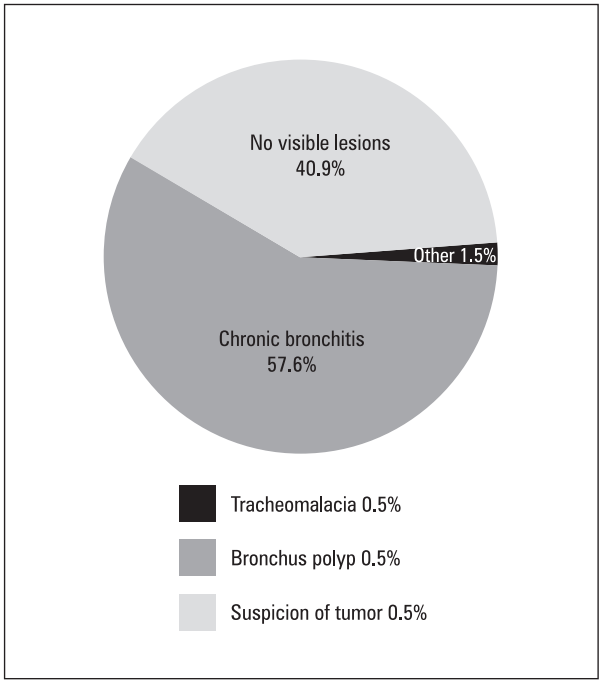

Figure 2. Fiberoptic bronchoscopy outcome

Discussion

This retrospective, observational, cohort study aimed to evaluate the utility of FOB in the differential diagnosis of chronic cough. Our study results showed that only 1.5% of FOB examinations revealed directly probable cause of chronic cough. 57% of the subjects had endoscopic signs of chronic bronchitis. However, we need to keep in mind that this is a subjective operator's assessment and chronic bronchitis is a clinical definition. Therefore, we suggest that such an endoscopic conclusion might be overused, especially when the operator is looking for potential cause of chronic cough and does not identify any other pathology. It is worth mentioning that according to Markovitz *et al.*, respiratory tract inflammation may be induced by the act of cough-

Table 1. BALf cell count analysis

	Normal value	Number of abnormal BALf cell count results [n, (%)]	Median value (IQR)
All cells	$< 10^6$	31 (68.9%)	1.4×10^6 ($9.8 \times 10^6 – 22.43 \times 10^6$)
Neutrophils	< 3%	5 (11.1%)	4.3% (3.8–4.65%)
Lymphocytes	< 15%	32 (71.1%)	24% (19–29%)
Eosinophils	< 0.5%	15 (33.3%)	2% (1–3%)
Monocytes	< 0.5%	2 (4.4%)	1% (1%)
Basophils	< 0.5%	2 (4.4%)	1.8% (1.2–2.4%)

BALf — bronchoalveolar lavage fluid

Table 2. Bacterial species and number of positive culture results from bronchial washings

Bacterial species	Number of positive results
Moraxella catarrhalis	29
Staphylococcus aureus	12
Streptococcus pneumoniae	9
Serratia mercescens ESBL-	4
Streptococcus agalactiae	3
Acinetobacter baumanii	1
Corynobacterium striatum	1
Escherichia coli	1
Klebsiella oxytoca	1
Klebsiella pneumoniae ESBL+	1
Streptococcus anginosus	1
Streptococcus C	1
Streptococccus constellatus	1
Streptococcus parasanguinis	1
Streptococcus vestibularis	1

ing itself [10]. Additionally, 41% of the studied subjects had no visible airway changes in FOB. Taken together, our results suggest that FOB has a limited role in the diagnosis of chronic cough as the only indication, which is concordant with previously published observations.

The substantial body of evidence suggests that FOB may be overused in the diagnosis of respiratory conditions. Sen *et al.* have suspected that unnecessary FOB is most likely overused in the evaluation of respiratory symptoms (e.g. cough, hemoptysis) [15]. Moreover, Gasparini and Barnes have deduced that FOB provides a little diagnostic information in the context of patients with no radiological findings [8, 9]. It is of note that Irwin *et al.* concluded that FOB has the least relative usefulness of the components (e.g. medical history, physical examination, pulmonary function testing, upper gastrointestinal studies, esophageal pH monitoring, sinus or chest X-rays) of the diagnostic protocol of chronic cough [5].

However, many authors, including those mentioned above, have agreed that FOB is a very useful tool in a properly selected subgroup of patients. According to Irwin *et al.,* in case of suspicion of malignancy (e.g. smoking or hemoptysis history), even if chest radiography is normal, FOB is indicated [11]. Moreover, when sampling is needed (e.g. BALf, transbronchial biopsy, microbiologic culture or cytology) FOB is a desired technique [2, 5, 8, 15].

Markovitz and Irwin have proposed a simple recipe to maximize the yield of FOB and not to overuse that examination. They have advised performing early FOB only when the radiological image is abnormal or when a patient is immunocompromised, even if radiological findings are absent. Otherwise, delaying FOB until the most common causes are excluded, and other diagnostic procedures are exhausted, is recommended [10].

Collecting samples from the respiratory tract to carry out additional testing to expand the diagnostic yield of FOB is a common practice. There is a knowledge gap in the literature how such sampling and additional testing impact on the efficacy of FOB in the differential diagnosis of chronic cough. Moreover, clear indications when additional testing should be applied are lacking. In this retrospective analysis, in 45 (22.7%) cases of all 198 FOB examinations, BAL was performed. Five results (2.5% of all 198 patients and 11% of patients subjected to BAL) of BALf cell counts showed an increased number of eosinophils ≥ 3%. This quantity, but in sputum, is a criterion used for the diagnosis of nonasthmatic eosinophilic bronchitis (NAEB) — one of the probable causes of chronic cough. Nevertheless, cytologic examination of BALf can equally be used for diagnosis of NAEB [16]. Although in our study, BALf analysis results were abnormal in almost

all patients, the observed abnormalities are not characteristic of any specific diagnosis. The most commonly observed abnormalities were an increased total number of BALf cells and an elevated percentage of BALf lymphocytes — the finding that is suggestive of many interstitial lung diseases [17]. However, according to some authors, an increased percentage of lymphocytes is a non-specific finding, probably related to the cough itself [18]. Both an increased number of cells and an elevated percentage of lymphocytes may be related to low-grade bronchial inflammation induced by mechanical insult triggered by unrestrained bursts of cough.

In the case of 111 of all 198 FOB examinations (56%), bronchial washings for cultures were collected, 59 (53.1%) of them were positive, which potentially could uncover the cause of undetermined chronic cough. Due to a retrospective character of the study, it was impossible to follow the patients with positive culture results. Specifically, we do not have any knowledge whether the culture-based antibiotic treatment was introduced, and if so, whether was it effective.

Our study results support the use of additional testing to increase the diagnostic efficacy of FOB. The diagnostic yield of FOB increased from 1.5% (direct visualization of the tracheobronchial tree) to 33.8% by combining BALf cytologic examinations and bronchial washings cultures. Similar conclusions were presented by Heching *et al.*, who increased the diagnostic yield of FOB from 26% to 68% after the addition of microbiologic cultures and histopathologic analysis of specimens [19].

On the other hand, in one study on the utility of FOB in the differential diagnosis of chronic cough, 27 out of 48 FOB procedures included bronchial washings for cultures, and only 3 of them were positive. Furthermore, these three patients were treated with the appropriate course of antimicrobials, which has not improved their cough. According to the authors, this indicates that cultured bacteria have signified contamination, colonization, or were not responsible for cough [9].

In the case of our analysis, all 59 positive cultures identified a total of 67 bacteria. Among them, 40 (59.7%) presented MDR, and 1 (1.5%) was XDR. We are unable to determine which and how many of these bacteria were causes of chronic cough in the studied cohort, nevertheless, so widespread drug resistance might pose a problem in bacterial eradication if such a clinical decision is undertaken. The simple explanation for so frequent detection of MDR bacterial strains would possibly be the common use of antibiotics in everyday clinical ambulatory practice in patients with cough, however, we do not have any data to proof that in our cohort of patients this was true.

Another additional test that is routinely performed in patients with chronic cough undergoing FOB is AFB smears and BALf or bronchial washings cultures for *Mycobacterium tuberculosis* (MTB). Our results demonstrating none of positive results for MTB detection clearly show that in subjects with normal chest X-ray, and when the only symptom was chronic cough, these tests were simply useless.

Interestingly, in 21 (36%) of patients with positive cultures, FOB revealed no visible airway changes. This result may lead to many different hypothetical conclusions. Barnes *et al.* suggest that these bacteria can be a contamination, colonization, or do not explain cough [9]. On the other hand, if found pathogens are the cause of cough, it is a significant argument for collecting samples for microbiological cultures during every single FOB in such a clinical indication.

Taken together, we and others suggest the appropriate balance between the risk and benefits of using FOB in the diagnostic process of chronic cough. Moreover, when a decision of performing FOB is undertaken, additional testing, such as microbiological cultures or BALf analysis should be considered on the case by case basis. The recently published study by Heching *et al.* showed a marked increase of the diagnostic yield by adding microbiological cultures and pathology analysis to the visual assessment [20]. The current update of "ERS guidelines on the diagnosis and treatment of chronic cough in adults and children" discuss a non-invasive alternative in the diagnosis management. The use of fractional exhaled nitric oxide (FeNO) in breath or blood eosinophilia have been proposed to assess airway eosinophilia, but the evidence is still very low [6].

Limitations

There are several limitations of our study which need to be considered. First of all, as a retrospective, single-institution study, it is saddled with all limitations associated with this type of data collection, including lack of data or other potential confounding factors. Furthermore, cultures were not performed in all studied subjects referred for FOB. Moreover, we do not know if positive cultures had any impact on how patients were treated, what was the outcome of treatment, and finally, if cultured microbes were the intrinsic

and sole cause of chronic cough. Furthermore, agents included in worksheets for categorizing bacteria found in our study differ from agents used by Magiorakos [14].

Conclusions

The present study results strengthen the evidence that FOB combined with additional testing of airway specimens obtained during FOB is not a powerful tool in the differential diagnosis of chronic cough and may be overused. The appropriate timing and decision regarding referral for FOB requires careful clinical consideration.

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Author contributions

Conception PS, JMD, AJB, WJP, design PS, JMD, WJP; drafting of the manuscript PS, JS, SM and WJP; acquisition of data PS, JS, ZK, KS analysis and interpretation of data PS, JS, SM, JMD, AJB, WJP, drafting the manuscript for important intellectual content all authors; all authors critically revised the manuscript and gave approval of the version to be published.

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Conflict of interest

Authors declare no conflicts of interests related to this research.

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