Flexible bronchoscopy in the diagnosis of chronic cough causes in non-smoking adults

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To the Editor:

A chronic cough (CC) is reported in 4–10% of the adult population and negatively affects quality of life [1–5]. Diagnosing and managing CC is challenging [3–5]. Initial evaluation typically includes chest radiography, spirometry, blood cell count (to detect blood eosinophils) and exhaled nitric oxide fraction, if available [4, 5]. Further diagnostic tests are warranted if clinical symptoms and basic tests cannot identify the cause of CC. Secondary diagnostic tests include oesophageal manometry or pH/impedance monitoring, induced sputum for eosinophils, laryngoscopy, bronchial provocation challenge, chest computed tomography (CT) and bronchoscopy [3–5]. Flexible bronchoscopy (FB) provides an opportunity to identify some treatable traits (*e.g.* excessive sputum production, signs of bronchiectasis or chronic bronchitis, signs of eosinophilic airway inflammation, airway collapse), which are crucial to guiding the successful management of CC [5]. According to the American College of Chest Physicians and European Respiratory Society guidelines, FB is considered a second-step diagnostic tool for non-smoking adults with CC [3, 4]. It is typically performed after excluding the most common causes of CC, although its diagnostic value remains debated [6–13].

We retrospectively analysed the results of FB in non-active smokers with CC and no relevant abnormalities on chest radiography who were referred to our department between 2017 and 2020. The study protocol was approved by the institutional review board of the Medical University of Warsaw (KB/101/2009) as part of a larger study assessing the efficacy of CC treatments.

The primary outcome of our analysis was the proportion of patients in whom the FB results changed further therapy for CC. FB was offered as a second-step diagnostic investigation for patients who showed no reduction in CC despite initial diagnostic evaluations and therapeutic trials, and who met at least one of the following criteria: 1) chest CT revealed relevant abnormalities warranting further investigation with FB; 2) chronic bronchial/pulmonary infection; or 3) tracheal or central bronchial abnormalities were suspected.

The main inclusion criteria were as follows: 1) cough lasting >8 weeks; 2) age >18 years; 3) non-active smoking; 4) lack of alarm symptoms; and 5) no relevant abnormalities in the chest radiograph suggesting a lung tumour, advanced chronic pulmonary infection (such as tuberculosis), moderate-to-severe bronchiectasis, or moderate or advanced interstitial lung abnormalities.

In total, 240 patients diagnosed with CC at a cough clinic were included. Among them 30 patients (12.5%) underwent FB according to the above-mentioned criteria: 24 women and 6 men with a median age of 57.5 years (interquartile range (IQR) 51.7–63 years), median cough duration of 48 months (IQR 25.5–100 months), and median cough severity measured by the visual analogue scale (VAS) of 63 mm (IQR 22–72 mm). 22 patients were never smokers, and eight were former smokers. A dry or minimally productive cough was reported by 19 subjects, whereas 11 had a productive cough. The initial diagnosis of upper airway cough syndrome, gastro-oesophageal reflux and asthma were established in 19, 17 and 15 patients, respectively.

FB was performed under local anaesthesia and conscious sedation using a combination of midazolam and fentanyl with video bronchoscope BS-1TH190 (Olympus, Tokyo, Japan). Procedures during bronchoscopy were tailored to the suspected diagnosis, including bronchial washing (three out of 30), bronchoalveolar lavage (BAL) for cell count or microbiology (24 out of 30) and endobronchial forceps biopsy (seven out of 30).

Shareable abstract (@ERSpublications)
Flexible bronchoscopy is a useful tool for diagnosing rare causes of chronic cough in adults, but it should be performed as a second-step investigation, after chest CT and in selected cases, when we expect that it will impact further treatment https://bit.ly/47yAXLH

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Among the macroscopic abnormalities revealed during FB, the most common finding was bronchoscopic signs of tracheobronchitis (13 patients, 43%). However, positive microbiological cultures were found in only three of them (*Haemophilus influenzae*: 10^3 CFU·mL^{-1}; *Serratia marcescens*: 10^3 CFU·mL^{-1}; and *Mycobacterium intracellulare*). In two of these patients, no change in CC therapy was initiated owing to the absence of clinical symptoms of infection and the low threshold for a bacterial culture of BAL fluid. In contrast, a positive culture of *M. intracellulare* was found as relevant for CC. Structural abnormalities were revealed in three patients, including distortion of the intermedius bronchus, a widened anterior part of the main carina with dilated blood vessels (diagnosed as adenoid cystic carcinoma) and vocal cord paresis. In the latter two patients, the detected structural abnormalities were assessed as relevant to CC.

In five out of 30 (17%) patients who underwent FB and in five out of 240 (2.1%) of all patients with CC, the procedure led to changes in diagnosis or therapy. New diagnoses included: adenoid cystic carcinoma, non-tuberculous mycobacterial pulmonary disease (*M. intracellulare*), vocal fold paresis and eosinophilic granulomatosis with polyangiitis. Additionally, in one patient with uncontrolled cough variant asthma tracheobronchitis was identified. Pathological examination of bronchial biopsy samples from this patient revealed eosinophilic inflammation and remodelling which warranted the addition of mepolizumab to intensive inhaled anti-asthmatic therapy. In all five patients, FB findings led to therapeutic adjustment resulting in reduced CC severity (median VAS 55 mm (IQR 40–55 mm) *versus* 10 mm (IQR 7–10 mm); p=0.0625) and improvement in quality of life (median Leicester Cough Questionnaire score 9.7 (IQR 8.8–9.7) points *versus* 17.8 (15.2–17.8) points; p=0.0625) (table 1). However, these improvements were not statistically significant, probably due to the small sample size. In a group of patients referred for FB, the only feature which distinguished patients who had benefitted from FB was shorter CC duration (24 months (IQR 24–36 months) *versus* 72 months (IQR 43–120 months); p=0.036).

This study demonstrated that FB, when used as a second-stage diagnostic tool in a selected group of adults with CC, can lead to accurate diagnoses and a reduction of CC severity in 2.1% of all patients with CC and in 17% of those referred for FB. It is noteworthy that the final diagnoses based on FB results were not anticipated, even after chest CT scans. Thus, our results support the role of FB performed as the second step diagnostic tool in a selected population of adults with CC, aligning with both previous and current guidelines [3–5, 14].

Although most experts agree that FB should not be a routine test for all adults with CC, it still remains unclear which patients with CC may benefit from FB. Bronchoscopy in an unselected population of adults with CC and normal chest radiograph and chest CT adds little to the diagnosis and management of cough and does not typically lead to cough reduction [7, 9, 13, 15]. However, FB may be beneficial in cases where specific abnormalities are detected on chest radiography or chest CT, or in immunocompromised patients [15]. Additionally, bronchoscopy may be considered even in patients with normal chest CT if common causes of CC have been excluded [13]. In this study a shorter cough duration was the only characteristic associated with the higher likelihood of identifying treatable traits for cough during FB. However, due to the small sample size, it is not possible to refine selection criteria for FB or to establish which patients might benefit from the procedure.

TABLE 1 The effect of flexible bronchoscopy (FB)-guided therapy in patients with chronic cough

Diagnosis	Change in therapy	Cough severity (VAS) before FB (mm)	Cough severity (VAS) after therapy guided by FB (mm)	Quality of life (LCQ) before FB	Quality of life (LCQ) after therapy guided by FB
NTM infection (*M. intracellulare*)	Antibiotics	63	10	15.0	18.3
Adenoid cyst carcinoma	Surgery + radiotherapy	40	7	9.7	15.24
Vocal cord paresis	Speech therapy	55	20	8.6	14.6
EGPA	Oral prednisone + ICS/LABA	78	2	8.8	20.5
Severe asthma	Mepolizumab as add-on therapy	40	20	9.9	17.8

VAS: visual analogue scale; LCQ: Leicester Cough Questionnaire; NTM: non-tuberculous mycobacteria; EGPA: eosinophilic granulomatosis with polyangiitis; ICS: inhaled corticosteroids; LABA: long-acting beta-agonist.

According to the guidelines of the American College of Chest Physicians, FB may be beneficial as a second-step investigation to confirm the suspicion of eosinophilic bronchitis (using BAL as an alternative to induced sputum), or to diagnose intratracheal or intrabronchial disorders, which are rare causes of CC [5]. We usually do not perform FB with BAL to assess eosinophilic bronchitis as we find induced sputum to be a less invasive method. However, the analysis of induced sputum is poorly available in some clinics, and in such situations FB with BAL may be considered a substitute investigation.

Diagnosing expiratory collapse of the trachea and main bronchi in patients with CC and its significance as a cause or consequence of coughing is another important point for discussion. Owing to the high and repeated intrathoracic pressure differences during intensive coughing, excessive dynamic airway collapse (EDAC) during FB may be a frequent finding in this population; indeed a recent study reported EDAC in 31% of patients undergoing FB [8]. In contrast, our study did not identify EDAC, possibly due to our underestimation of its relevance for CC or because we did not include forced expiratory manoeuvres during FB. The diagnosis of EDAC can vary among bronchoscopists, because the assessment of tracheal or bronchial wall bulging during FB is subjective [16]. The assessment of the significance of EDAC in refractory CC requires further evaluation.

Flexible bronchoscopy is recommended if mucus plugs are identified on chest CT for clearance, lavage and culture, according to recent European Respiratory Society guidelines [4]. Additionally, the British Thoracic Society guidelines suggest that FB may be useful in patients with a productive cough to exclude infection and assess airway secretions when sputum cultures are unavailable [5]. Interestingly, Digby *et al*. [8] also indicate that FB may be useful in patients with productive refractory CC. In such cases, collecting samples (especially microbiological cultures of BAL fluid and histopathologic biopsies from the respiratory tract) can enhance the diagnostic yield of FB, potentially revealing chronic infection or eosinophilic bronchitis, whether in asthma or non-asthmatic eosinophilic bronchitis [8, 9, 11].

Our study has some limitations. First, it was a single-centre study with a relatively small number of patients who underwent FB. Second, the FB protocols and specimen collections varied between patients due to the retrospective nature of the study. Third, we did not measure the degree of airway collapse during dynamic FB, which might have caused oversight of EDAC. Despite these limitations, we believe the results contribute to the discussion on the role of FB in the management of adults with refractory or unexplained CC.

In conclusion, we believe that FB is a useful tool for diagnosing rare CC causes. However, it should be used as a second-step investigation in selected patients with CC after chest CT imaging, particularly when chronic bronchial infection or any abnormalities of the trachea or central bronchi are suspected. CC of a relatively short duration in particular may support the consideration of FB as a second step diagnostic tool.

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