DOES THE ESTABLISHED CAUSE OF CHRONIC COUGH DEPEND ON DIAGNOSTIC APPROACH?

The objective of the present study was to evaluate the prevalence of chronic cough causes and to compare the efficacy of two diagnostic approaches used in ambulatory vs. hospitalized setting. Eighty patients with chronic cough, 40 in each group, were enrolled into the study. The etiology of cough was determined on medical history and on either basic (in out-patients) or detailed (in in-patients) investigations on most common causes of chronic cough. We diagnosed etiology of cough in all subjects. The most frequent causes of cough were gastroesophageal reflux disease (GERD) and upper airway cough syndrome (UACS). Nonasthmatic eosinophilic bronchitis (NAEB) and multiple cough causes were recognized more often in hospitalized patients (P<0.05). We conclude that the main causes of chronic cough were GERD and UACS. An extensive diagnostic approach allows recognizing NEAB more frequently and reveals the complex nature of chronic cough.

Key words: chronic cough, diagnostic approach, gastroesophageal reflux disease, nonasthmatic eosinophilic bronchitis

INTRODUCTION

Chronic cough is a very common complaint. According to questionnaire surveys, its prevalence in the general population, including children, may vary from 9 to 33% (1). Even if only minority of these patients seek medical attention, they still compose a large and challenging group, requiring diagnostic and treatment.

The most common causes of chronic cough in non-smoking, non-treated with ACE-inhibitor adults with normal chest radiogram, include the upper airway
cough syndrome (UACS), gastroesophageal reflux disease (GERD), asthma, and nonasthmatic eosinophilic bronchitis (NAEB). The prevalence of these conditions varies in different reports (2-11). That may depend on racial and lifestyle differences, access to specialists or differences in the definition of some cough reasons (12, 13). However, even if the guidelines on cough diagnosis and management (14-16) are followed in detail, the cause of chronic cough may remain unexplained in up to 33-46% of cases (1, 17). That suggests the necessity of further studies to elucidate cough mechanisms and etiology.

Many diagnostic approaches have been proposed in the literature, including: (i) anatomic, diagnostic protocol focusing on anatomical sites, where afferent limbs of vagal nerve are localized, (ii) complex investigations for the most common cough causes before treatment, and (iii) algorithms, which have been based on the effects of empirical treatment (4, 9, 18). Currently, the implementation of algorithms originating from the anatomic, diagnostic protocol proposed by Irwin and Madison (18) is recommended by a majority of experts. These algorithms have a high success rate in the diagnosis and treatment of cough. The possibility, however, arises that such an approach may hamper research on the mechanisms of cough and on rare or coexisting causes of it.

The aim of the present study was two-fold: (i) to assess the prevalence of different conditions listed as the potential causes of chronic cough in patients who were unsuccessfully treated by general practitioners and (ii) to compare diagnostic efficacy of two different approaches: empiric, ambulatory treatment based on clinical data and basic diagnostic tests, vs. specific therapy based on the results of extensive causes evaluation of cough.

MATERIAL AND METHODS

The study protocol was approved by the Ethics Committee of Warsaw Medical University in Warsaw, Poland. Recruitment for the study was performed among patients with chronic cough unsuccessfully treated by their general practitioners and referred to pulmonologist for further diagnosis and treatment. Specific inclusion criteria were as follows: (i) age ≥18 years, (ii) cough lasting more than 8 weeks, (iii) normal or insignificant chest radiogram, (iv) unsuccessful ambulatory treatment, and (v) wash-out period of previously administered, antitussive drugs of at least 7 days. A total of 80 patients with chronic cough were enrolled, of the mean age of 51.8 yr (range 21-84 yr), 40 in each study group (the out-patient and in-patient groups). There was women predominance (F/M - 67/13), with a similar sex distribution in both groups.

Study design

Data relevant to chronic cough were noted in all patients presented to pulmonologist. They included: cough characteristics, present and past medical history, history of smoking, environmental and occupational exposure, and concomitant medication (particularly ACE inhibitors). All patients also underwent physical examination, chest X-ray, and spirometry with reversibility test, if necessary. Then, the patients were proposed to be diagnosed and treated further in an ambulatory or hospital setting and, in accordance with their choice, the subjects were scheduled as out-patient or in-patient.
In the out-patient group presumptive diagnosis of cough etiology was based on medical history, physical examination, and results of the above mentioned investigations. Then, an empiric treatment with H1 antagonists, inhaled corticosteroids, or proton pump inhibitors was initiated. The effectiveness of that treatment was evaluated after next 6 weeks. If no response was noted or only partial improvement was achieved, additional tests were proposed: skin prick tests with common aeroallergens, methacholine inhalation challenge (MIC), induced sputum analysis, and ENT examination. Simultaneously, the treatment was widened by adding subsequent drugs according to the probability of the cough reason in each subject.

In the subjects included in the in-patient group, extensive diagnostic evaluation of cough etiology was conducted in the hospital setting, prior to initiation of specific therapy. The diagnostic algorithm applied in this group included: sputum induction for eosinophilic count, methacholine challenge test, skin prick tests with common aeroallergens, ENT examination, sinus CT scans, video laryngoscopy, and 24-h esophageal pH monitoring. The patients also underwent fiberoptic rhinoscopy, rhinomanometry, acoustic rhinometry, or nasal cytology, if necessary. Specific treatment was initiated on the basis of the results obtained.

**Definitions and specific evaluation of the main, cough provoking conditions**

**Asthma:** Diagnosis of asthma was based on the well known GINA guidelines (19). In patients with presumptive diagnosis of cough variant asthma, spirometry with reversibility test (Lungtest 1000, MES, Krakow, Poland) and methacholine inhalation challenge were performed. Additionally, total IgE concentration, sputum eosinophilia and skin prick tests with common aeroallergens were evaluated to better characterize the underlying condition.

**Chronic obstructive pulmonary disease (COPD):** Chronic obstructive pulmonary disease was diagnosed in accordance with the GOLD guidelines (20).

**Nonasthmatic eosinophilic bronchitis (NAEB):** In case of a negative MIC, the induced sputum was examined for eosinophilic count for NAEB diagnosis. Sputum induction was performed with inhalation of increasing concentrations of sterile NaCl solution (3.0, 4.0, 4.5, and 5.0%), used to provoke sputum production. Induced sputum was processed as previously described (21). NAEB was diagnosed if the number of eosinophils exceeded 3% of nonsquamous cells.

**Upper airway cough syndrome (UACS):** For evaluation of UACS, including chronic rhinitis or chronic sinusitis, ENT examination, video-laryngoscopy (laryngostroboscope STORZ 8020, telepharyngoscope STORZ 8704 D, and telecamera STORZ SL PAL 20212020) and sinus computed tomography scans (16-slice sCT Light Speed 16 general Electric Medical System, Milwaukee, USA) were performed. Chronic sinusitis was determined as based on clinical signs and CT evaluation according to the Lund and Mackay score. Chronic rhinitis was diagnosed on the basis of clinical symptoms, and if suspected, ENT examination additionally included fiberoptic rhinoscopy, rhinomanometry, acoustic rhinometry, or nasal cytology.

**Gastroesophageal reflux disease (GERD):** Gastroesophageal reflux disease was assessed with 24-h esophageal pH monitoring and video-laryngoscopy. The measurement of esophageal pH was performed with two-antimony-pH-electrode (electrodes were placed at the distal tip of a catheter and 15-18 cm above it) esophageal catheter (Simline MU, Medtronic A/S; Denmark) connected with a Digitrapper pH 400 recorder. The catheter was inserted through the nose and fixed 5 cm above lower esophageal sphincter; the distance being estimated in a stepwise manner on the basis of pH changes. An acid reflux episode was defined as a rapid drop in pH below the value of 4 for at least 12 s. The diagnosis of GERD-associated cough was made if cough episodes, marked by the patients on the recorder and noted down in the diary, appeared in ≤5 min after the preceding reflux. Additionally, the number of reflux episodes measured on proximal electrode and the percentage of total pH <4, pH <4 in the upright and supine positions, on both proximal and distal recorder, were
taken into consideration to diagnose pathological GERD. Videolaryngoscopy was performed to evaluate changes in the laryngeal mucosa in accordance with Belafsky's reflux finding score (23) as a result of the gastropharyngeal reflux.

**Treatment**

Specific treatment was provided on the basis of either most suspected cough etiology (ambulatory patients) or detailed examination results (hospitalized patients). There were no differences between specific treatment regimens administered in the subjects from the in-patient and out-patient groups. In case of treatment with an ACE-inhibitor, the drug was withdrawn and replaced by an alternative one. Cough in patients with asthma was treated with inhaled glucocorticosteroids and long acting beta-agonists; being the most commonly prescribed agents. COPD therapy was provided in accordance with GOLD guidelines and, beside smoking cessation, included anticholinergics and β2-agonists. For NAEB, inhaled glucocorticosteroids were prescribed. The treatment of UACS included first generation antihistamines, decongestants and/or intranasal glucocorticosteroids, depending on the allergy suspicion in UACS. GERD-related cough was treated with antireflux diet, lifestyle modification, proton pomp inhibitor, additionally supported by H2-antagonist in case of persistent symptoms. Moreover, all subjects were informed to avoid both active and passive smoking.

**Statistical analysis**

Patient data, cough characteristics, and prevalence of its etiology were presented as mean values ±SD. The age of the subjects between both study groups was compared using a non-parametric Mann-Whitney test. Chi2 test was performed to study specific distribution of cough etiologies in the out-patient and in-patient groups. A P-value <0.05 was regarded statistically significant.

**RESULTS**

The mean cough duration was 4.2 ±3.8 yr. There were no significant differences between the out-patient and in-patient groups in terms of age, gender, or symptom duration. Smoking history was positive in 16 subjects, 9 were ex-smokers, and 7 patients were current (in two cases occasional) tobacco smokers. Comparison of demographic and clinical data in patients from the two study group is presented in Table 1.

The most common condition associated with chronic cough was GERD (59/80 patients, 74%). This was followed by UACS (42/80 patients, 53%), asthma (23/80 patients, 29%), NAEB (20/80 patients, 25%), and ACE inhibition treatment with ACE inhibitors (7/80 patients, 9%). Interestingly, COPD was diagnosed only in 2 patients with chronic cough.

Multiple potential causes of cough were recognized in 56 patients (70% of the whole group), including two coexisting causes in 30 patients (37.5%), three in 24 patients (30%), four in 2 patients (2.5%). A single reason of cough was diagnosed in 24 patients (30% of the whole study group). Single or two causes of cough were diagnosed significantly more often in ambulatory group in comparison with
three or more cough reasons, which were established significantly more frequently in hospitalized subjects. (Table 2)

GERD was the most common cause of chronic cough in both out-patient and in-patient groups and was diagnosed in 27 and 32 patients, respectively; the difference was non-significant (NS). In the first group, the diagnosis of GERD was made on the basis of clinical symptoms or response to proton pomp inhibitors therapy (PPI) and was confirmed additionally by ENT examination (n=7). In the second group, GERD-related cough was diagnosed on the basis of 24-h pH monitoring in 20 subjects from the 34 examined. In 9 patients the result was normal, or cough episodes appeared prior to refluxes. In 5 patients, recordings could not be assessed due to technical problems. The reflux finding score

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ambulatory group, n</th>
<th>Hospitalized group, n</th>
<th>P</th>
<th>Both groups, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, n</td>
<td>40</td>
<td>40</td>
<td>NS</td>
<td>80 (100)</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- females</td>
<td>34</td>
<td>33</td>
<td>NS</td>
<td>67 (84%)</td>
</tr>
<tr>
<td>- males</td>
<td>6</td>
<td>7</td>
<td>NS</td>
<td>13 (16%)</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>53.8 ±17.5</td>
<td>49.9 ±17.0</td>
<td>NS</td>
<td>51.8 ±17.3</td>
</tr>
<tr>
<td>Cough duration (yr)</td>
<td>3.6 ±2.2</td>
<td>4.6 ±5.4</td>
<td>NS</td>
<td>4.2 ±3.8</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- current smoker</td>
<td>2</td>
<td>5</td>
<td>NS</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>- ex-smoker</td>
<td>5</td>
<td>4</td>
<td>NS</td>
<td>9 (11%)</td>
</tr>
<tr>
<td>- non-smoker</td>
<td>33</td>
<td>31</td>
<td>NS</td>
<td>64 (80%)</td>
</tr>
<tr>
<td>ACE inhibitor intake</td>
<td>6</td>
<td>2</td>
<td>NS</td>
<td>8 (10)</td>
</tr>
</tbody>
</table>

Values are means ±SD; NS-non significant.

Table 2. Diagnosed causes of chronic cough.

<table>
<thead>
<tr>
<th>Cause of cough</th>
<th>Ambulatory group, n</th>
<th>Hospitalized group, n</th>
<th>P</th>
<th>Both groups, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GERD</td>
<td>27</td>
<td>32</td>
<td>NS</td>
<td>59 (73.8%)</td>
</tr>
<tr>
<td>UACS</td>
<td>19</td>
<td>23</td>
<td>NS</td>
<td>42 (52.5%)</td>
</tr>
<tr>
<td>Asthma</td>
<td>12</td>
<td>11</td>
<td>NS</td>
<td>23 (28.8%)</td>
</tr>
<tr>
<td>NAEB</td>
<td>2</td>
<td>18</td>
<td>&lt;0.05</td>
<td>20 (25.0%)</td>
</tr>
<tr>
<td>ACEI</td>
<td>6</td>
<td>1</td>
<td>NS</td>
<td>7 (8.8%)</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>8</td>
<td>NS</td>
<td>12 (15.0%)</td>
</tr>
</tbody>
</table>

Number of cough causes per subject, n (%)
- one            | 18 (45)             | 6 (15)                | -     | 24 (30.0)          |
- two            | 14 (35)             | 16 (40)               | -     | 30 (37.5)          |
- three          | 8 (20)              | 16 (40)               | -     | 24 (30.0)          |
- four           | 0                   | 2 (5)                 | -     | 2 (2.5)            |
≤ 2 causes       | 32 (80)             | 22 (55)               | <0.05 | 54 (67.5)          |
≥ 3 causes       | 8 (20)              | 18 (45)               | <0.05 | 26 (32.5)          |

Values are means ±SD; NS-non significant.

Table 1. Demographic data of the investigated patients.
assessed during video-laryngoscopy was positive (>7 points) in 29 patients from the 34 examined (the mean score 10.6 ±3.1). This score supported the GERD diagnosis in 12 difficult to diagnose cases.

UACS was recognized in 19 and 23 subjects in ambulatory and hospitalized group, respectively (NS). Chronic rhinitis was diagnosed in 16 and 17 patients, respectively, and sinusitis in 3 and 6 subjects, respectively.

The prevalence of NAEB was significantly higher in the in-patient compared with out-patient group (18 vs. 2 subjects, respectively, P<0.05). Sputum induction was performed in 34 hospitalized patients and 4 subjects in the ambulatory group. Adequate quality of sputum was obtained in 25 and 2 patients, respectively. Increased percentage of eosinophils was noted in 23 hospitalized subjects, (including 5 patients with asthma) and 2 ambulatory patients. The mean percentage of eosinophils in the hospitalized group was 37.1%, compared with 18% in the out-patient group.

There was no difference in asthma prevalence in the ambulatory and hospitalized group. This condition was diagnosed in 12 and 11 patients, respectively (NS). Cough due to ACE inhibitors was found in 7 subjects and was more common in the out-patient group (NS). In a few cases cough of other origin was diagnosed, including arrhythmia-induced cough (n=6), COPD (n=2), chronic heart failure (n=2), and bronchiectases (n=1).

The diagnosis of chronic cough, based mainly on the treatment efficacy in the out-patient and on the results of different diagnostic procedures in the in-patient group, was established in all study subjects.

DISCUSSION

The present study allowed assessing the prevalence of different conditions responsible for chronic cough and evaluating a potential influence of different diagnostic approaches on establishing the etiology of cough. The vast majority of our patients were women, which is consistent with other studies results (2-11). The predominance of women in cough clinics seems to be explained by increased cough reflex sensitivity to tussogenic agents in women compared with men, which has already been observed in both healthy subjects and patients with chronic cough (22).

We noted that the most frequent causes of chronic cough were GERD, UACS, asthma, and NAEB. This finding is consistent with the results of many other studies (Table 3). However, the prevalence of GERD in our patients was significantly higher than that observed by other authors. The difference may depend on various diagnostic procedures applied in patients with chronic cough to confirm GERD. In our study GERD-related cough was recognized not only on the basis of 24-h esophageal pH monitoring, but also on laryngeal mucosa changes evaluated in video-laryngoscopy (23). Since pH monitoring performed in
Table 3. Prevalence of chronic cough etiology in the study group as compared with other authors.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Author</th>
<th>No. of Patients</th>
<th>UACS (%)</th>
<th>ASTHMA (%)</th>
<th>GERD (%)</th>
<th>NAEB (%)</th>
<th>OTHER (%)</th>
<th>% of diagnosed</th>
<th>% of causes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Poe et al (2)</td>
<td>139</td>
<td>26</td>
<td>34</td>
<td>5</td>
<td>-</td>
<td>Chronic bronchitis -7 Single cases of other etiologies None -12</td>
<td>88%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Irwin et al (3)</td>
<td>102</td>
<td>41</td>
<td>24</td>
<td>21</td>
<td>-</td>
<td>Chronic bronchitis - 5 Idiopathic -1</td>
<td>99%</td>
<td>Single -73 Two - 23 Three - 3</td>
</tr>
<tr>
<td></td>
<td>Pratter et al (4)</td>
<td>45</td>
<td>87</td>
<td>29</td>
<td>11</td>
<td>-</td>
<td>Hodgkin disease - 2 Psychogenic cough -2</td>
<td>100%</td>
<td>Single - 72 Two - 25 Three - 4</td>
</tr>
<tr>
<td></td>
<td>French et al (5)</td>
<td>39</td>
<td>40</td>
<td>15</td>
<td>36</td>
<td>-</td>
<td>Bronchiectases - 3 Pertussis - 3 Other - 3</td>
<td>100%</td>
<td>Single - 7 Two - 53 Three - 36 Five - 4</td>
</tr>
<tr>
<td></td>
<td>Brightling et al (7)</td>
<td>91</td>
<td>24</td>
<td>18</td>
<td>8</td>
<td>13</td>
<td>COPD - 7 Bronchiectases - 5 ACE inh. - 4</td>
<td>93%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Kastelik et al (8)</td>
<td>131</td>
<td>6</td>
<td>24</td>
<td>22</td>
<td>-</td>
<td>Bronchiectases - 8, Postviral cough - 8 Idiopathic -7 ACE inh.-5 COPD - 5</td>
<td>93%</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Palombini et al (9)</td>
<td>78</td>
<td>58</td>
<td>59</td>
<td>41</td>
<td>-</td>
<td>Bronchiectases - 18 Tracheobronchial collapse -14</td>
<td>100%</td>
<td>Single - 38 Two - 36 Three - 17 Four - 9</td>
</tr>
<tr>
<td></td>
<td>Robeiro et al (10)</td>
<td>147</td>
<td>9</td>
<td>29</td>
<td>9</td>
<td>10</td>
<td>COPD - 11 None - 8</td>
<td>92%</td>
<td>Single – 82</td>
</tr>
<tr>
<td></td>
<td>Fujimura et al (11)</td>
<td>176</td>
<td>-</td>
<td>44</td>
<td>2.4</td>
<td>-</td>
<td>Sinobronchial syndrome - 25 Atopic cough - 36</td>
<td>93.7%</td>
<td>Single - 89 Two - 12</td>
</tr>
<tr>
<td></td>
<td>Present study Poland</td>
<td>80</td>
<td>53</td>
<td>29</td>
<td>74</td>
<td>25</td>
<td>ACE inh. - 9 Arrhythmia induced cough -8 COPD - 2.5 Bronchiectases - 1.3</td>
<td>100%</td>
<td>Single - 30 Two - 38 Three - 30 Four - 3</td>
</tr>
<tr>
<td></td>
<td>TOGETHER</td>
<td>1071</td>
<td>6-87</td>
<td>15-59</td>
<td>2.4-74</td>
<td>10-25</td>
<td>-</td>
<td>82-100%</td>
<td>*</td>
</tr>
</tbody>
</table>

*Chronic cough defined as longer than 3 weeks;
*Number of cough causes: Single - 7-88.5%, Two - 11.5 - 53%, Three - 3-30%, Four - 2.5 - 9%, Five - 4%

The hospital setting could potentially affect some factors present in normal environment and, therefore, decrease GERD intensity, we changed our usual diagnostic approach to GERD. We abandoned using the symptom index (SI), symptom sensitivity index (SSI), or symptom association probability (SAP), proposed by others to confirm GERD-related cough (24, 25). Instead, we decided to use additional diagnostic procedures. We assumed that changes in laryngeal mucosa, assessed in video-laryngoscopy in accordance with the reflux finding
score proposed by Belafsky et al (23), might prove the existence of proximal reflux, even if abnormalities in 24-h pH oesophageal monitoring were not relevant. Refluxes, which reach the pharynx, are believed to cause aspiration to trachea or, at least, irritation of the larynx, which may result in activation of the cough reflex (26). Moreover, changes in laryngeal mucosa might be related not only to acid, but also to non-acid reflux, which is not detected in the esophageal pH monitoring. The multichannel impedance for the assessment of both acid and not acid refluxes was not available in our study. We noted that none of the patients with normal video-laryngoscopy result (FRS <7) had an abnormal result of pH monitoring. Abnormal RFS was helpful in the diagnosis of GERD in the subjects whose quality of pH recordings (n=5) was inadequate, or those, who had normal (n=4) or no pH study results (n=3), but suggestive clinical symptoms. Interestingly, GERD prevalence was also high in ambulatory subjects, although no detailed investigations were performed in that group. That could suggest a higher frequency of GERD in the Polish population, or a high awareness of GERD as a potential cause of cough while determining its etiology.

UACS was the second leading cause of chronic cough in our study group. The prevalence of this disease was similar to that reported by Palombini (9). In many other studies, however, the prevalence of UACS in patients with chronic cough was lower and ranged from 6 to 41% (2, 3, 5-8, 10).

Similarly to UACS, the prevalence of NAEB in our patients was also higher than earlier reported. In the whole study group, it reached 25%. Here, significant differences were found between the out-patient and in-patient groups; 45% vs. 5%, respectively. This difference seems to result from various diagnostic approaches. Cytological sputum evaluation, along with the results of additional studies which could help exclude asthma, is necessary to confirm the NAEB diagnosis. Sputum induction was performed in 34 patients in the hospitalized group, but only in 4 subjects in the out-patients group. Treatment with inhaled glucocorticosteroids, which was undertaken empirically in the ambulatory group, could improve symptoms not only in the asthma patients, but also in the NAEB ones. Therefore, we can not exclude that some subjects with NAEB could have been misdiagnosed as asthma. Increased frequency of NAEB has already been noticed in our earlier studies and eosinophilic count showed some correlation with the total time of pH <4 in pH monitoring (unpublished data). A possible relationship between types of sputum cell was widely discussed in the literature. However, only McGarvey et al (27) have suggested the presence of an association between eosinophilia in bronchoalveolar lavage in patients with GERD and cough. Those observations require further studies.

Asthma was responsible for chronic cough in 29% of the patients in the present study (30% and 28% in the ambulatory and hospitalized groups, respectively). This is consistent with the results of other studies (3, 4, 6, 8, 10), although both higher (2, 9, 11) and lower (5, 7) prevalence of asthma has also been reported.
Less frequent conditions responsible for chronic cough in the present study’s population included: arrhythmia-induced cough (n=6), COPD (n=2), heart failure (n=2), and bronchiectases (n=1). Cough associated with arrhythmia was related to premature ventricular complexes. The relatively high prevalence of that specific cause of chronic cough may be associated with our special interest in arrhythmia-induced cough. Interestingly, low prevalence of COPD, observed also in other studies, may result from the fact that tobacco smokers associate cough with smoking and often do not treat it as troublesome complaint and do not seek for medical help.

A single cause of chronic cough was diagnosed in 30% of patients, which is consistent with the data presented by Palombini et al (9). However, it is discordant with the data reported by a majority of other authors (3, 4, 6, 10, 11), who, independent of a diagnostic approach, established single causes of cough in 62-89% of patients. Multiple causes of cough were diagnosed in 70% of our subjects, while in others its prevalence varied from 12 to 29% of patients. Only Palombini et al (9) have reported a similar prevalence of multiple causes of cough to that of the present study, whereas other studies showed even a higher frequency (5).

Another goal of our study was to examine whether the prevalence of diagnosed cough-provoking diseases might depend on the diagnostic algorithm applied to establish the etiology of cough. Many diagnostic algorithms of chronic cough have been proposed in the literature. The anatomic, diagnostic protocol proposed by Irwin and Madison (18), often used in many aspects by other authors, allows determining the etiology of cough in up to 82-100% of cases, with a treatment success up to 84-98%.

We compared two different diagnostic approaches, which have been used in daily, clinical practice. The algorithm used in the ambulatory group was an empiric integrative approach similar to the one presented in the Chest guidelines (28); whereas an extensive diagnostic protocol to establish cough etiology, before initiation of specific treatment, was applied in the hospital setting. The causes of cough were recognized in all subjects in both study groups. We found that the use of the extensive diagnostic protocol was associated with a higher prevalence of the NAEB diagnosis. This observation highlights the necessity of sputum evaluation in patients with chronic cough. It suggests that extensive investigations allow finding out diseases that could not be determined in the empiric approach. That was also observed by Palombini et al (9), who reported that an additional use of high-resolution computed tomography (HRCT) of chest and bronchoscopy in cough diagnosis resulted in recognition of some cases of bronchiectases that were not visible on normal chest radiogram and of rare cases of tracheobronchial collapse.

We showed that the extensive diagnostic protocol of causative cough evaluation did not result in significantly higher recognition of other potential cough provoking conditions, such as GìERD, asthma, and UACS. However, the
use of the extensive diagnostic approach allowed a more frequent diagnosis of multiple causes of cough (three or more). Furthermore, various uncommon cough provoking diseases were found in that group more often (8 vs. 4), although this difference failed to reach significance.

Our study has several limitations. First of all, the subjects were included into the out-patient or in-patient group in accordance with their agreement on hospitalization. Lack of randomization could result in selection bias, which caused that patients with more severe cough chose hospitalization. To avoid the bias, we plan to use cough intensity scale in further studies to evaluate cough intensity between both groups. In hospitalized subjects, a few patients refused some investigations, which potentially could decrease the number of established causes of cough. Moreover, the diagnosis of cough was established mainly on examination results. Such a procedure has already been used in single studies, however, the diagnosis should be confirmed by successful, specific treatment. The follow-up period is still not completed to finally confirm cough resolution after specific treatment. That could lead to overdiagnosis of etiology of cough, by recognition the comorbidities that coexisted with cough, but were not its cause. That hypothesis can not be confirmed without a long-term follow-up of specific treatment.

We conclude that GERD, asthma, NEAB, and UACS are the four main causes of chronic cough. GERD is the most common sole condition associated with chronic cough. In a majority of patients with chronic cough, two or more potential causes might be diagnosed. Empiric therapy based on a diagnostic approach to patients with chronic cough may lead to underestimation of NAEB prevalence. Extensive diagnostic approach might be more efficient in the identification of multiple coexisting conditions responsible for chronic cough.

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