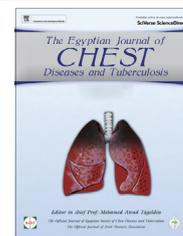




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## ORIGINAL ARTICLE

# Utility of tests used to diagnose asthma, gastroesophageal reflux and upper airway cough syndrome in patients with chronic cough and normal chest radiography

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### KEYWORDS

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**Abstract** *Background:* Despite the clinical significance of cough, research efforts aimed at improving diagnostic capabilities and developing more effective therapeutic agents have been, to date, disappointing in their limited scope and outcomes. Asthma, gastro-oesophageal reflux disease (GERD) and upper airway cough syndrome (UACS) are common causes for chronic cough with a normal chest X-ray (CXR).

*Aim:* To describe the frequency of these three causes in a cohort of outpatients with chronic cough and normal CXR and to identify the diagnostic tests best able to identify the aetiology in the vast majority of cases using the response to specific therapy as a gold standard.

*Methods:* Nonsmoking outpatients of both genders who complained of cough for more than 8 weeks and had normal findings on CXR were studied prospectively. All patients were subjected to spirometry (including postbronchodilator reversibility), sinuses CT scan, rhinoscopy, and 24-h esophageal pH monitoring to get “an initial diagnosis”. The assumed causes were confirmed by treating them sequentially. “The final diagnosis” depended on a successful response to therapy.

*Results:* Hundred patients were studied: the laboratory tests established initial diagnoses of asthma, UACS, GERD, or various combinations of these in 78 patients, of those; 35 patients (44.9%) had a single cause, 39 patients (50%) had two causes, and 4 patients (5.1%) had all three causes. After treatment of those 78 patients, the final diagnoses were established as follow: 47 patients (60.3%) has a single cause, 28 patients (35.9%) had two causes and 3 patients (3.8%) had all three causes. There was a good agreement between the laboratory tests and the definite

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causes (agreement in 65 patients [83%] and discrepancy in 13 patients [17%],  $k > 0.75$ ). Twelve patients had their diagnoses changed for two causes to a single cause and one patients had the diagnosis changed from three causes to two causes.

*Conclusion:* Asthma, UACS, GERD, or some combination of these represent 78% of the causes of chronic cough in our sample. Therefore, these conditions should be considered first during diagnostic evaluation of patients with chronic cough and normal CXR. In spite of some discrepancy between initial and final diagnoses, the study identifies the group of diagnostic methods best able to identify the cause in the vast majority of cases of chronic cough including sinuses CT scan, rhinoscopy, pulmonary function tests, and esophageal pH monitoring.

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## Introduction

Cough is among the most common complaints for which patients worldwide seek medical attention. Thus, the evaluation and treatment of cough result in tremendous financial expenditure and consumption of health care resources [1,2]. Cough can be divided into acute cough (lasting less than 3 weeks), subacute cough (lasting for an 3–8 weeks) or chronic cough (lasting for more than 8 weeks) [3]. Chronic cough can cause multisystem problems including anxiety, fatigue, insomnia, myalgia, and urinary incontinence forcing patients to seek medical help. These effects and the possibility of more serious causes of cough warrant spending time to arrive at an accurate diagnosis and treatment plan [3].

Chronic cough accounts for 10–38% of respiratory outpatient practice in the USA [4]. The prevalence of chronic cough among the nonsmoking adult population ranges from 14–23% [5]. Reviewing the literature reveals that asthma, upper airway cough syndrome (UACS) (previously known as postnasal drip syndrome) or gastroesophageal reflux disease (GERD) are well known as common causes of chronic cough [1–7]. However, the frequency of these three causes varies in different series [8]. Diagnostic challenges facing the clinician in the management of chronic cough include the determination of whether any of these three causes are indeed the underlying cause of cough [1,2,9].

The key to the diagnostic algorithm for chronic cough is first to establish the presumptive causes of cough and then to confirm or exclude them with subsequent specific therapy. Medical history such as character of chronic cough and the concomitant symptoms may point to its etiology [10] and laboratory investigations may add essential evidence to the determination of presumptive causes. Since cough could be due to a single cause or multiple causes, the patients will probably present with one or more abnormalities on laboratory investigation. However, the diagnostic values of these tests cannot be overestimated since false positive or false negative results are frequent, as demonstrated by previous work [4]. Therefore, established presumptive diagnosis cannot predict the favorable response to the specific therapy due to the discrepancy between presumptive and definite causes [11].

Therefore, the aim of this study was: a – to describe the frequency of three common causes of chronic cough (i.e. asthma, GERD and UACS) in a local group of nonsmoking adult outpatients and normal CXR and b – to identify the diagnostic tests best able to identify the aetiology in the vast majority of cases of chronic cough using the response to specific therapy as a gold standard.

## Subjects and methods

### Subjects

A prospective study of consecutive subjects referred to the respiratory outpatient clinic for the evaluation of chronic cough. Patients were eligible for inclusion if they had a cough for more than 8 weeks, if they were 18 years old or more, and if they had normal findings on CXR. Patients with history of smoking, upper respiratory infection within the last 2 months, comorbidity (such as diabetes mellitus, hypertension, organ failure, malignancy, ...) or intake of angiotensin-converting enzyme inhibitors were excluded.

### Laboratory investigations

Because the study aimed at the quantification of the accuracy of several tests, all tests were used in each patient.

- 1- Spirometry was performed using a computed System (Jaeger, Germany). FEV<sub>1</sub> was measured both at baseline and 15 min after inhalation of 200 µg of salbutamol.
- 2- The 24-h ambulatory esophageal pH monitoring was performed as previously described [7]. Reflux episodes were characterized by acidic pH < 4.
- 3- Rhinoscopy.
- 4- Sinuses CT scan.

### Diagnostic criteria for UACS, GERD and asthma

Diagnostic criteria were established according to previously published guidelines for the management of chronic cough and literature on the subject [7–9,12,13] and were divided into those for initial and final diagnosis.

Upper airway cough syndrome was considered when the patients had: (1) a history of chronic rhinitis or sinusitis, (2) one or more of the following symptoms, the sensation of secretions dripping down into the throat, throat-clearing sign, nasal discharge, nasal obstruction or sneezing, (3) one or more of the following signs, erythema and cobblestone appearance to the posterior pharyngeal mucosa, or mucoid/purulent secretions dripping into the pharynx on rhinoscopy and (4) the presence of mucosal blur or thickening > 6 mm, or an air-fluid level on sinus CT. The patients met with both of (2 and 3) in addition to the either one or both of (1 and 4) were presumed to have UACS. The final diagnosis was established when cough re-

sponded to 2 weeks therapy (antihistamines and topical nasal steroids  $\pm$  macrolides in the case of chronic sinusitis).

Asthma was presumed when the patients presented with episodic wheezing, dyspnea or cough and a reversible airway obstruction  $> 12\%$  postbronchodilator. The diagnosis was confirmed when cough responded to 2 weeks treatment (mainly inhaled corticosteroids  $\pm$  inhaled bronchodilators).

The diagnosis of GERD was based on symptoms such as dyspepsia, heartburn and hoarse voice and 24-h ambulatory esophageal pH monitoring showing abnormal acid reflux. The diagnosis was confirmed when cough improved with at least 4 weeks of anti-reflux therapy (omeprazole 20 mg twice a day plus domperidone 10 mg three times a day) with adjustment of diet.

#### Protocol

Subjects proved to have asthma, GERD, UACS or various combination of these were allowed to continue the second phase of the study (treatment phase). Those with negative test results were excluded from phase 2 and subjected for further investigations to elucidate the cause of cough. For a single cause, the diagnosis was confirmed on observing a response to the subsequent specific therapy. For multiple causes, the specific therapies were instituted in the sequence of UACS-asthma-GERD. When cough resolved completely with the therapy specific to an assumed cause, the diagnosis was definite and the other causes were excluded. Once the initial treatment failed, the therapy for the next cause was commenced. If the cough improved without complete resolution, the previous treatment was overlapped with the subsequent therapy specific to another cause until the cough disappeared and the multiple causes were confirmed.

#### Statistical analysis

Data were expressed as mean  $\pm$  standard deviation (SD). The difference between initial and final diagnoses was analyzed by chi-square test. The agreement between the laboratory findings and the definite causes was expressed by kappa value ( $k$ ) with  $> 0.75$  as good,  $0.40\text{--}0.75$  as fair and  $< 0.40$  as poor. Software SPSS (SPSS Inc., Chicago, IL, USA) was used for statistical calculation. A  $P$  value  $< 0.05$  was accepted as statistically significant.

#### Results

One hundred patients (52 males and 48 females) completed the study, their mean age was  $37.53 \pm 14.6$  years and the mean duration of cough was  $24.02 \pm 13.41$  weeks.

#### Initial diagnoses

A diagnosis of UACS, asthma, GERD, or various combinations of these was made in 78 patients with UACS the most frequent diagnosis encountered (Table 1). Half of those patients (50%) had two causes, 44.9% had a single cause and 5.1% had all three causes (Table 1, Fig. 1).

#### Final diagnoses

The diagnosis of UACS, asthma, GERD, or various combinations of these was confirmed in the 78 patients, again UACS was the most frequent diagnosis (Table 1). In contrast to the initial diagnosis, single causes were the most frequent in the final diagnosis although the differences were not statistically significant (Table 1, Fig. 1). Forty seven patients (60.3%) have a single cause, 28 patients (35.9%) had 2 causes and 3 patients (3.8%) had all 3 causes. The initial and final diagnosis were consistent in 65 patients and discrepant in 13 patients. In the latter, 12 patients had their diagnoses changed from the initial 2 causes to a final single cause and one patient had his diagnosis changed from initial three causes to final two causes (Table 2).

#### Usefulness of the diagnostic tests

The "gold standard" adopted was a specific therapeutic response during the follow-up period, once the pretreatment diagnostic criteria had been fulfilled. The sensitivity, specificity, positive and negative predictive values for the tests were evaluated (Table 3). Good agreement between the laboratory findings and the definite causes was expressed by kappa value ( $> 0.75$ ).

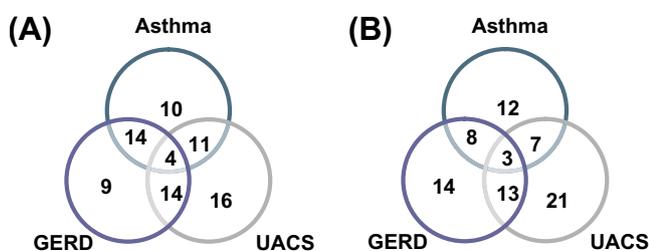
#### Discussion

We studied 100 patients who complained of chronic cough and had normal findings on CXR. An "initial diagnosis" of asthma, UACS, GERD or various combinations of these was made based on the results of laboratory tests. A specific therapeutic response was used as a gold standard to confirm the initial diagnosis "final diagnosis". Asthma, UACS, GERD or various combinations of these were responsible for 78% of cases of chronic cough in our study with UACS the most frequent. There was an agreement between the initial and final diagnoses in 83% of cases. A single cause was more frequent in the final diagnosis than in the initial diagnosis although the differences were not statistically significant.

**Table 1** Comparison of distribution frequency between initial and final causes.

Diagnosis	Initial $n$ (%)	Final $n$ (%)	$\chi^2$	$P$
Asthma	10 (12.8)	12 (15.4%)	0.212	0.645
GERD	9 (11.5)	14 (17.9)	1.275	0.259
UACS	16 (20.5)	21 (26.9)	0.886	0.347
Asthma + UACS	11 (14.1)	7 (9)	1.005	0.316
Asthma + GERD	14 (17.9)	8 (10.3)	1.905	0.168
GERD + UACS	14 (17.9)	13 (16.7)	0.045	0.832
Asthma + GERD + UACS	4 (5.1)	3 (3.8)	0.150	0.699

UACS: upper airway cough syndrome, GERD: gastroesophageal reflux disease.



**Figure 1** Causes of chronic cough in 78 patients as established by the laboratory tests (A) and therapeutic response (B). UACS: upper airway cough syndrome, GERD: gastroesophageal reflux disease.

**Table 2** Discrepancy between initial and final diagnosis in 13 patients.

Initial diagnosis	Numbers	Final diagnosis
Asthma + UACS	4	UACS
Asthma + GERD	2	Asthma
	4	GERD
GERD + UACS	1	UACS
	1	GERD
Asthma + GERD + UACS	1	GERD + UACS

UACS: upper airway cough syndrome, GERD: gastroesophageal reflux disease.

**Table 3** Utility of tests used to diagnose causes of chronic cough.

Test	Sensitivity (%)	Specificity (%)	PPV (%)	NPP (%)	<i>k</i> value
Spirometry	100	81.3	77	100	0.769
Oesophageal pH	100	92.5	92.7	100	0.923
Sinuses CT/rhinotomy	100	97.1	97.8	100	0.974

PPV: positive predictive value, NPV: negative predictive value. *k*: Kappa value.

Two approaches for the diagnosis and treatment of chronic cough were described. One is “test and treat step by step” [7,14] which tests and treats a cause with the highest probability first, with the medical history and physical examination as the initial assessment. The process is continued sequentially until the cough resolves. The second approach is “test all, then treat” [15] where a comprehensive laboratory testing is launched to identify all possible causes, then the diagnosis is confirmed by a specific therapeutic response. Since some patients may lack the clinical data pertinent to a possible cause other than chronic cough [16], this algorithm has the advantage of saving time and minimizing under-diagnosis seen with “test and treat step by step”. In our study, a simplified form of “test all, then treat” was employed to target three common causes of chronic cough (asthma, UACS and GERD). Besides CXR and pulmonary function testing, three additional laboratory tests were used; 24-h esophageal pH, sinus CT scan and rhinoscopy.

Asthma, UACS, GERD or various combinations of these were responsible for 78% of cases of chronic cough in our study. Accumulating data from the literature support these findings, and the presence of at least one of these components varies from 72% to 100% [6,11]. In the vast majority of cases, these three conditions were responsible for chronic cough in nonsmoking patients who were not taking angiotensin-converting enzyme inhibitors and had normal findings on CXR.

The frequent association among the components of this triad of the chronic cough is worthy of special consideration. In 1981, Irwin et al. [17] published a study in which the association between UACS and asthma was detected in 18% of cases. In their second study in 1990 [4] a multicausal pathogenesis was identified in 26% of patients studied. In 1993, Pratter et al. [18] described factors of multiple association in 29% of a series of 45 patients studied. Considering these findings, we reviewed the literature for several possible mechanisms that might explain these interactions. The diseases of the nose and paranasal sinuses are among the most commonly identified causes of chronic cough [12]. Depending on the population studied and the variations in diagnostic algorithm, the diseases of nose and sinuses are reported to contribute to coughing in 20–40% of patients with chronic cough who have normal chest radiograph [3]. The mechanisms of chronic cough in rhinosinusitis are incompletely understood. Several mechanisms have been proposed, single or in combination: postnasal drip, direct irritation, inflammation in the lower airways and the cough reflex sensitization [19]. Some accounts [20,21] have stated that the act of coughing can make asthma worse, so the cough caused by UACS and GERD could maintain or exacerbate cough due to asthma. Such associations help explain the pathogenesis of either bronchoconstriction or coughing, since the primary causative factors, as well as the receptors and the afferent pathways and their hypothetical function, are mostly the same [22]. With regard to the pathogenesis of chronic cough from GERD, two theories have been presented to explain this possible relationship: (i) microaspiration to the airways (the reflux theory) [23]; and (ii) acid reflux to the distal esophagus (the reflex theory) [24]. It can be speculated that GERD might make UACS worse by a vagal reflex mechanism [25].

The false multiple causes due to the algorithm used in this study should not be ignored. Twelve patients with initial double causes based on laboratory findings were finally verified to have a single cause. It suggested that some conditions defined by laboratory tests might be “an epiphenomenon” and were not causal. Several lines of evidence have demonstrated that 33–74% of patients with allergic rhinitis had bronchial hyper-responsiveness (BHR) not associated with elicitation of chronic cough and asthma [26–28]. GERD may also manifest BHR [29] possibly caused by micro-aspiration, esophageal-tracheobronchial reflex [13] and airway neurogenic inflammation [30] and airway eosinophilia caused by unknown mechanism [31]. Furthermore, cough itself can lead to abnormal GERD due to increased intra-abdominal pressure [32] which may explain concomitant GERD in some patients with asthma. It has been reported that only 60–88% of chronic cough with BHR responded to anti-asthmatic therapy [33]. If the therapies specific for two or more causes of cough are simultaneously administered according to initial diagnosis, over-diagnosis

and treatment will certainly occur. In this case, treating initial causes sequentially may be a better choice that will avoid erroneous diagnosis of multiple causes of chronic cough, as indicated in the present study.

As shown by a cost-effectiveness analysis [15] “test and treat step by step” may be superior to “test all, then treat” for lowering medical expenses and it remains to be determined how to best evaluate cost-effectiveness in managing patients with chronic cough. As stated in the evidence-based Cough Consensus Panel Report of the American College of Chest Physicians [34] “since the committee was not aware of any studies that specifically addressed the role of empiric therapy as a diagnostic aid or any cost analyses that related to different ways of managing cough, no specific sections in this document deal with these issues”.

In conclusion, UACS, asthma, GERD, or some combination of these were the most common causes of chronic cough in our study population. A systematic approach to diagnosis is effective for most cases of chronic cough. In spite of some discrepancy between initial and final diagnoses, the study identifies the group of diagnostic methods best able to identify the cause in the vast majority of cases of chronic cough including sinuses CT scan, rhinoscopy, pulmonary function tests, and esophageal pH monitoring.

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