

Therapeutic-diagnostic Evaluation of Chronic Cough Amongst Adults: Causes, Symptoms and Management at the Primary Care Level, Malaysia

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ABSTRACT

Background: Patients presenting with chronic cough pose a common diagnostic dilemma during routine consultations at public primary care clinics in Malaysia. To date, there has been little attempt at designing a standardized model or algorithm to facilitate an accurate diagnosis of chronic cough. This study proposes a clinical method to detect the causes of chronic cough in a primary care setting in Malaysia. **Materials and Methods:** A total of 117 patients aged above 18 at an urban primary care clinic were tracked over a span of 5 months to diagnose the cause of chronic cough. A therapeutic-diagnostic method was employed to help identify the causes of chronic cough. Subsequently, the demographic details of patients, the prevalence of the different causes of chronic cough and the relationship between history and diagnosis were analyzed statistically. **Results:** Chronic cough had a slightly higher male preponderance (51.3% vs. 48.7%). Patients within the 'above 60' age category had the highest frequency of chronic cough. The most common cause of chronic cough was post-infectious cough ($n = 42$, 35.9%), followed closely by angiotensin-converting enzyme-inhibitor related cough ($n = 14$, 12%). Majority of patients had the symptom of phlegm production ($n = 41$, 54%). 33 patients (29.2%) had recent upper respiratory tract infection (<2 weeks ago) prior to the diagnosis of chronic cough. There were poor association between symptoms and the various entities comprising chronic cough. The exceptions were the following associations: (1) Bronchial asthma and itchiness of throat ($P = 0.021$), (2) gastroesophageal reflux disease and heartburn ($P < 0.001$), (3) upper airway cough syndrome and running nose ($P = 0.016$) and (4) pulmonary tuberculosis and absence of weight loss ($P = 0.004$). **Conclusion:** This study demonstrates that the effectiveness of a therapeutic-diagnostic technique in the diagnosis of chronic cough. Consistent with previous studies, there was poor association between most symptoms and the causes of chronic cough. A study involving a larger primary care population is required to confirm the findings found in this analysis.

Keywords: Angiotensin-converting enzyme-I related cough, chronic cough, post-infectious cough, primary care, therapeutic-diagnostic evaluation

Introduction

In most developing nations, common causes of chronic cough are upper airway cough syndrome (UACS), non-asthmatic eosinophilic bronchitis (NAEB) and gastroesophageal reflux disease (GERD).^[1] Finding the cause for chronic cough in a population remains a diagnostic challenge for most primary care physicians. This requires closer scrutiny as cough still remains as the single most important reason why patients seek medical consultation.^[2]

Cough can be classified into acute, sub-acute and chronic cough based on the duration of symptoms.^[3] A generally

accepted definition of chronic cough is an episode of cough lasting more than 8 weeks.^[4] In Malaysia, physicians are recommended to promptly identify the cause of a cough lasting more than 2 weeks, with pulmonary tuberculosis as a primary concern.^[5]

Studies have shown that despite adherence to an established protocol in the diagnosis and treatment of chronic cough, a large number of patients do not find significant improvement in symptoms or seem to be only partially treated for their illness.^[6] The diagnosis of chronic cough is complex, involving multiple entities that present simultaneously.^[7] It is also known that a detailed history taking process does not significantly assist in distinguishing the various causes of chronic cough.^[7]

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Currently in Malaysia, no studies have been conducted to ascertain the major causes of chronic cough and its relationship to presenting symptoms. Thus, the focus of this study is to determine the prevalence of the various causes of chronic cough, its relationship to common symptoms and the evaluation the significance of a therapeutic-diagnostic method in clinical practice.

Materials and Methods

A prospective cohort study was conducted on patients (aged above 18 years old) who presented to a public primary health care clinic with the chief complaint of cough lasting more than 2 weeks. It was carried out between January and May 2013. A structured questionnaire was used to collect socio-demographic data, history, physical findings, investigations, diagnosis and prescribing data. The questionnaire was used by the researcher to collect information during the assessment of each patient. Patients were monitored for at least 3 months (or until symptom resolution) to gather information about the progress in the treatment and the provisional diagnosis of the cause of the chronic cough.

The questionnaire was designed by the researcher after an extensive review of the assessment methods that help diagnose the causes of chronic cough [Table 1].^[8-12] Based on information gathered from the literature review, a general guideline was formulated using therapeutic or investigative measures (therapeutic-diagnostic method) and salient history derived from patients.

Ethical consideration

This project was approved by the Medical Research and Ethics Committee of Malaysia (Research ID: NMRR-13-141-14935). The questionnaire was anonymous and confidentiality was maintained.

Statistical analysis

The sample size estimation of 91 patients was calculated using a confidence interval of 95% and the margin of error of 5%. Based on a similar study conducted in Sweden,^[13] the prevalence level of chronic cough was set at 6.5%. Another study in a more Asian environment revealed a lower prevalence of 2.5%, giving a sample size of only 37.^[14]

SPSS software (IBM® SPSS® Statistics Version 20) was used to interpret the statistical data obtained from the study. An analysis of the demographic details of the study population was performed. The calculation of the frequency and the prevalence of the various disease entities classified under the diagnosis of chronic cough were made. Finally, χ^2 methods were employed to determine the association between symptoms and diagnosis of chronic cough.

Results

Demographics of and prevalence of chronic cough in primary care patients

Out of the 151 patients recruited into the study, 117 patients with chronic cough were given a provisional diagnosis at the

end of their respective consultation over the span of 3 months. The remaining 34 patients were excluded from the study for the following reasons - 11 failed to attend scheduled appointments, 21 had missing details and could not be contacted, 1 was not a suitable candidate (the patient had been diagnosed with a possible cause of chronic cough prior to the commencement of the study) and 1 was a repeat sample.

The demographic details of the study population are summarized in Table 2. There were an equal number of male (51.3%) and female (48.7%) patients with the complaint of chronic cough at the primary care center. The lowest rates of chronic cough cases (5.1%) were seen in the 30-39 age category. On the other hand, the highest levels of chronic cough were seen within the above 60 age group (35.9%).

Most patients seeking treatment at the clinic were of Chinese ethnicity (47%). Many patients had secondary school education (29.1%) and those without any formal education formed a smaller part of the analysis (11.1%).

Pattern of chronic cough in primary care

Prevalence of the causes of chronic cough

The prevalence of the causes of chronic cough is summarized in Table 3. 42 out of 117 patients (35.9%) had post-infectious cough while 14 patients had angiotensin converting enzyme-inhibitor induced cough (ACE-I) (12.0%). 11 patients were diagnosed with UACS or acute bronchitis (9.4%), followed by 8 patients with chronic obstructive airways disease (COAD) (6.8%). There were only 2 (1.7%) cases of possible lung cancer and 3 (2.6%) cases of pneumonia.

Gender comparison

Male patients were frequently diagnosed with post-infectious cough (33.3%), followed by UACS (13.3%), ACE-I related cough (13.3%), chronic obstructive pulmonary disease (COPD) (11.7%) and heart failure (10%). Females were often diagnosed with post-infectious cough (38.6%), followed by acute bronchitis (14.0%), ACE-I related cough (10.5%) and GERD (8.8%) respectively. Males had higher rates of the heart failure (85.7%) and UACS (72.7%). There was a preponderance of bronchial asthma (BA) (80.0%), acute bronchitis (72.7%) and GERD (71.4%) cases amongst the female population. The comparison between gender and the causes of chronic cough did not yield any statistical significant results.

Age and ethnic group comparison

COPD (62.5%), ACE-I cough (50%), post-infectious cough (35.7%) and suspected lung cancer (50%) were more prevalent in the population with the age of above 60 years old. Heart failure was more frequent in the above 60 and 50-59 age category (42.9% respectively). PTB was detected more frequently in the 18-29 age group (57.1%). The 40-49 age group had higher levels of GERD (42.9%) and pneumonia (66.7%).

Table 1: Evidence-based evaluation of patients with chronic cough

Causes of chronic cough	Recommendations (signs/symptoms/investigation/Rx)
UACS-induced cough	Includes differentials such as allergic rhinitis and perennial non-allergic rhinitis Responding to treatment with combination of 1 st generation antihistamines and decongestants ³ Chlorpheniramine 4 mg tds/qid Refer to ENT for chronic sinusitis (sinus imaging) ³ Cough could be >8 weeks (other causes of post infectious cough) ³
GERD	H ₂ blockers x 1/12 and if fail, proton pump inhibitors 2-3 months ³ Add prokinetics (Metoclopramide) if PPI alone does not work ³
ACE-I induced	Resolves within 1 week to 1 month after discontinuation of medication ³
Occupational/environmental	Particulate, stimulant gases, second hand tobacco smoking, mixed pollutants and mould ⁸
Unexplained cough	Due to multiple aetiology rather than one ⁴ True unexplained cough usually seen in perimenopausal women with prolonged dry cough and demonstrable cough reflex sensitivity ⁹
Bronchial asthma	Standard treatment of bronchodilators and steroids ³ Salient history in the diagnosis of BA/COAD ¹⁰ Wheeze (self reported by patient) Dyspnoea (self reported by patient) Allergen induced symptoms Prolonged expiration Smoking dependence in pack years
COAD/chronic bronchitis	Criteria includes ³ 3 months for consecutive 3 years Exposure to cigarette, pipe smoke, passive smoking, hazardous environment exposure No role for prophylactic antibiotics β-agonist to relieve shortness of breath and bronchospasm Ipratropium to improve cough Can combine inhaled corticosteroids and ipratropium to control chronic cough
Acute bronchitis	Criteria includes ³ Cough no longer than 3/52 No role for antibiotics or inhaled bronchodilators Cough with or without phlegm Confirm the diagnosis of pneumonia by ordering a chest X-ray
Post infectious cough	Criteria includes ³ Symptoms of acute respiratory infection at least 3 weeks and not more than 8 weeks Sub-acute post infectious cough lasts for at least 8 weeks to months or years (also consider other causes such as UACS) Treatment of antibiotics has no role Order a chest x-ray to rule out other causes (to especially pneumonia)
Pulmonary tuberculosis	Criteria includes ¹¹ Smear positive for acid fast bacilli Radiographic evidence of tuberculosis (chest X-ray)
Pneumonia	Fever >38°C Radiological features indicative of pneumonia Leukocytosis on full blood count
Heart failure	Chest X-ray with cardiothoracic ratio >50% ECG with left axis deviation and left ventricular hypertrophy changes Responds well to T.Frusemide 40 mg od
Suspected lung cancer	Haemoptysis, fatigue, cough, clubbing of fingers, weight loss and shortness of breath ¹² History of smoking Chest X-ray, sputum cytology and bronchoscopy for identification ³

UACS: Upper airway cough syndrome; ENT: Ear, nose and throat department; GERD: Gastroesophageal reflux disease; PPI: Proton pump inhibitor; ACE-I: Angiotensin-converting enzyme-inhibitor; COAD: Chronic obstructive airways disease; ECG: Electrocardiogram

Acute bronchitis and heart failure rates were more common amongst Indians (54.5% and 71.4%). COPD and UACS were prevalent in the ethnic Chinese community (50% and 54.5%).

Clinical symptoms, pertinent history and its relationship to the diagnosis of chronic cough

Chief complaint and past medical history

The four most common symptoms found in patients were phlegm production (54.0%), night cough (51.3%), itchiness

of the throat (38.7%) and running nose (35.7%). Vomiting (2.7%), hoarseness of voice (2.7%), weight loss (7.1%) and hemoptysis (9.8%) were rare symptoms. No patients had either whooping cough or maxillary toothache [Tables 4 and 5].

The four most common positive findings in the past medical history were recent upper respiratory tract infection (29.2%), ACE-I intake (14.3%), previous history of atopy (11.6%) and

history of diabetes mellitus (11.6%). Least common were previous history of tuberculosis infection (1.8%), passive smoking (1.8%) and a previous episode of sinusitis (1.8%). None of the patients had a previous history of heart failure or COAD.

Relationship of diagnosis and symptoms

Most symptoms elicited from the study population had no significant association to a particular cause of chronic cough [Table 6]. However, there was a significant association between BA and itchiness of the throat ($P = 0.021$, Fisher’s exact test). Patients diagnosed with GORD had a significant association with heartburn ($P < 0.001$, Fisher’s exact test). UACS was related to the symptom of running nose ($P = 0.016$, Fisher’s exact test) and the diagnosis of PTB was not associated with weight loss ($P = 0.004$, Fisher’s exact test).

Table 2: Demographics of patients presenting to the primary care clinic with chronic cough

Variable	n	Percentage
Gender		
Male	60	51.3
Female	57	48.7
Age		
18-29	22	18.8
30-39	6	5.1
40-49	22	18.8
50-59	25	21.4
>60	42	35.9
Ethnic group		
Malay	27	23.1
Chinese	47	40.2
Indian	41	35.0
Others	2	1.7
Education		
None	12	11.1
Primary	25	21.4
Secondary	34	29.1
College/tertiary	24	20.5
Not specified	21	17.9

Table 3: Prevalence of the various causes of chronic cough

Diagnosis	n	Percentage
ACE-I	14	12.0
Acute bronchitis	11	9.4
BA	5	4.3
COPD	8	6.8
GERD	7	6.0
Lung cancer	2	1.7
Heart failure	7	6.0
Post infectious	42	35.9
UACS	11	9.4
PTB	7	6.0
Pneumonia	3	2.6

ACE-I: Angiotensin-converting enzyme-inhibitor; BA: Bronchial asthma; COPD: Chronic obstructive pulmonary disease; GERD: Gastroesophageal reflux disease; UACS: Upper airway cough syndrome; PTB: Pulmonary tuberculosis

The efficacy of the therapeutic-diagnostic method in diagnosing the causes of chronic cough

The diagnostic method employed in the study helped to establish the provisional diagnosis for all 117 patients by the end of the 5 month follow-up. The diagnosis was considered valid when (1) The patient has experienced resolution of symptoms and/or (2) A positive finding is found through targeted investigations.

Discussion

A mixed approach of ‘test and treat’ and ‘treat to test’ was adopted in this study. This facilitated the formulation of a provisional diagnosis for all 117 patients in the study. This is consistent with the evidence from current literature that seem to indicate that therapeutic-diagnostic method has a success rate of 90% in determining the causes of unexplained chronic cough.^[15]

Consistent with a previous finding,^[15] post-infectious cough was identified as the most common cause of chronic cough in this study. Although UACS, cough variant asthma and esophageal disease were seen as the major contributors to chronic cough, much of these studies were carried out at a specialist center.^[17]

Table 4: Common symptoms in study population

Common symptoms	Frequency (n)	Percentage
Phlegm production	61	54.0
Night cough	58	51.8
Itchiness of throat	43	38.7
Running nose	40	35.7
Throat clearing	36	32.7
Sore throat	21	18.8
Heartburn	14	12.6
Fever	11	9.9
Hemoptysis	10	9.8
Perceived weight loss	8	7.1
Hoarseness of voice	3	2.7
Vomiting	3	2.7
Whooping cough	0	0
Maxillary toothache	0	0

Table 5: Past medical history in study population

Past medical history	Frequency (n)	Percentage
Recent history of upper respiratory tract infection	33	29.2
ACE inhibitor intake	16	14.3
Previous history of atopy	13	11.6
History of diabetes mellitus	13	11.6
History of TB contact	5	4.7
History of previous TB infection	2	1.8
Passive smoking	2	1.8
Previous sinusitis	2	1.8
History of chronic rhinitis	0	0
History of heart failure	0	0
History of COAD	0	0

ACE: Angiotensin-converting enzyme; TB: Tuberculosis; COAD: Chronic obstructive airways disease

Table 6: Relationship between causes of chronic cough and symptoms

Diagnosis/ symptoms	Patients with symptoms, n/percentage	Patients without symptoms, n/percentage	Fisher's exact test (P)	Power analysis
Acute bronchitis				
Night cough	7 (70.0)	3 (30.0)	0.373	0.001
Running nose	6 (60.0)	4 (40.0)	0.163	0.046
Bronchial asthma				
Itchiness of the throat	4 (100)	0 (0)	0.021	-
Night cough	3 (75.0)	1 (25.0)	0.619	0.105
Throat clearing	3 (75.0)	1 (25.0)	0.102	0.105
GERD				
Heartburn	5 (71.4)	2 (28.6)	<0.001	0.095
Itchy throat	4 (57.2)	3 (42.8)	0.427	0.020
Possible lung cancer				
Hemoptysis	1 (50.0)	1 (50.0)	0.171	-
Heart failure				
Phlegm	4 (66.7)	2 (33.3)	0.685	0.088
Post-infectious cough				
Night cough	22 (55.0)	18 (45.0)	0.694	0.092
Phlegm	25 (61.0)	16 (39.0)	0.327	0.275
UACS				
Running nose	8 (72.7)	3 (27.3)	0.010	0.120
Itchy throat	6 (54.5)	5 (45.5)	0.332	0.026
Phlegm	7 (63.6)	4 (36.4)	0.543	0.098
Pulmonary tuberculosis				
Weight loss	3 (50)	3 (50)	0.004	0.016

GERD=Gastroesophageal reflux disease; UACS: Upper airway cough syndrome

Hence, the results of this study exclusively reflects the trend seen amongst patients with chronic cough at a primary care setting.

In a study designed to systematically diagnose patients with chronic cough, ACE-I related cough was found to be the least common cause of chronic cough.^[18] However, results of this study indicate that ACE-I related cough was the second most common cause of chronic cough at a primary care setting. We believe that this could be attributed to an increase in availability of specialty services to patients with chronic diseases (non-communicable disease programs) at the public primary care level in Malaysia.^[19]

There was a poor association between symptoms, past medical history and the various causes of chronic cough. Clinical history to aid only marginally in diagnosing the causes of chronic cough in these patients. Parallel to these findings, studies and guidelines have linked effective diagnosis of chronic cough to a combination of investigative or treatment specific protocol instead of detailed evaluation through history.^[4,20,21]

At present, no formal studies have been undertaken to assess the efficacy of a standardized clinical model to diagnose the numerous causes of chronic cough in Malaysia, especially at a primary care setting. Using a summary of evidence-based criteria derived from international guidelines, the results of

this study suggest that a validated diagnostic and treatment protocol^[4] could help identify the causes chronic cough at a primary care level. In a recent research exploring the evaluation of cases with chronic cough,^[22] a large number of patients were successfully managed using a similar therapeutic-diagnostic algorithm employed in this study.

Study limitations

There are several limitations of this study. The study population was selected from a single regional primary care clinic. Hence, the result obtained might not be representative of all primary care clinics in Malaysia.

The term 'chronic cough' used in this study was inclusive of the criteria that met the requirements of subacute and chronic cough as suggested by Pratter *et al.*^[4] During the study, patients with cough episodes between 3 to 8 weeks were still considered 'chronic' but were given a diagnosis of acute bronchitis which is a common cause of subacute cough.^[3]

Although NAEB is a commonly under-diagnosed cause for chronic cough,^[23] no attempt was made to diagnose NAEB in the study population. This was due to the lack of access to sputum eosinophil count at the institution where this study was conducted. Due to the small sample size, the study design was not able to establish an accurate or clear causal link between symptoms and diagnosis of chronic cough. A larger prospective cohort study involving many regional primary care clinics might help confirm the findings seen in this study.

Conclusion and Recommendations

The findings in the study seem to indicate that a therapeutic-diagnostic strategy could serve as an effective method in the diagnosis of the causes of chronic cough in a primary care population in Malaysia. The therapeutic-diagnostic model could enable clinicians to perform a targeted screening of the numerous causes of chronic cough through salient history and confirm the diagnosis by monitoring the response to treatment. This could lead to greater accuracy in the clinical assessment of chronic cough which, in turn, could step up the process of treatment of these patients.

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