



Changing etiological frequency of chronic cough in a tertiary hospital in Shanghai, China

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Background: The frequency distributions of the etiologies of chronic cough have changed over time. This study aimed to investigate the changing etiological frequency of chronic cough in a tertiary hospital in Shanghai, China, and to explore the clinical significance.

Methods: Medical records of 1,311 patients with chronic cough who visit our hospital between January 2009 and December 2016 were retrospectively reviewed. The etiologies of chronic cough were identified according to a standardized step-by-step diagnostic protocol and the changes in the etiological frequency of chronic cough over the years were using the Chi-squared (χ^2) test.

Results: Cough variant asthma (CVA) (449/1,311, 34.2%), gastroesophageal reflux-related chronic cough (GERC) (374/1,311, 28.5%), upper airway cough syndrome/postnasal drip syndrome (UACS/PNDs) (241/1,311, 18.4%), atopic cough (AC) (188/1,311, 14.3%), and non-asthmatic eosinophilic bronchitis (NAEB) (147/1,311, 11.2%) were the common causes of chronic cough in descending order. The post-infectious cough (PIC) (39/1,311, 3.0%) and angiotensin-converting enzyme inhibitor (ACEI)-induced cough (25/1,311, 1.9%) were less common. During the 8-year period, the proportion of CVA ($\chi^2=72.86$, $P<0.0001$) and UACS/PNDs ($\chi^2=68.80$, $P<0.0001$) decreased, while those of NAEB ($\chi^2=51.38$, $P<0.0001$), GERC ($\chi^2=55.95$, $P<0.0001$) and AC ($\chi^2=39.09$, $P<0.0001$) increased.

Conclusions: The etiological frequency of chronic cough varies over time, and it may encourage the adjustment of the current diagnostic and therapeutic strategies for chronic cough.

Keywords: Chronic cough; cough variant asthma (CVA); gastroesophageal reflux-related chronic cough (GERC); upper airway cough syndrome/postnasal drip syndrome; atopic cough (AC); non-asthmatic eosinophilic bronchitis (NAEB)

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Introduction

Chronic cough is defined as cough lasting for ≥ 8 weeks with a normal chest radiograph, and its incidence is about 9.6%,

or even up to 18.1% in certain areas (1). It negatively affects the quality of life of patients and its treatment has been a challenge in clinical practice (2). The common causes of chronic cough are cough variant asthma (CVA), upper

airway cough syndrome/postnasal drip syndrome (UACS/PNDs), non-asthmatic eosinophilic bronchitis (NAEB), gastroesophageal reflux-related chronic cough (GERC) and atopic cough (AC) (3,4). These causes account for 70–95% of chronic cough (5).

The frequency distributions of the etiologies of chronic cough have changed over time due to advancements in medical technology and referral system. Studies suggested that the etiological patterns of chronic cough in America were significantly different from that reported in Irwin's initial study in 1990 (6,7), especially presenting the proportion of GERC increased over time. Besides, the etiological patterns varied among countries, suggesting the proportion of GERC was higher in Occident while CVA and AC were more common in Japan (8). Even in the same research institution, the etiological distribution of chronic cough varied over time (3). Thus, understanding of the etiological distribution can guide the clinical diagnosis and therapies, achieving a better outcome (9).

Eight years ago, we studied the etiologies of chronic cough in Shanghai (10). In order to understand the change in the etiological patterns of chronic cough and to better guide clinical diagnosis and treatment of chronic cough, patients with chronic cough visiting our hospital between 2009 and 2016 were retrospectively reviewed, and the frequency of etiologies of chronic cough was further analyzed.

Methods

Patients

Consecutively patients older than 16 years had cough ≥ 8 weeks and visited the Respiratory Clinic in our hospital from 2009 to 2016 were retrospectively included in the present study. Exclusion criteria were as follows: the presence of adventitious lung sounds on pulmonary auscultation, abnormal radiological findings on chest X-ray or computerized tomography (CT), signs of obstructive lung disease on pulmonary function tests [forced expiratory volume in one second (FEV_1) $< 80\%$ of predicted or ratio of FEV_1 /forced vital capacity (FVC) $< 70\%$] as well as negative airway reversibility, current smokers or ex-smokers who stopped smoking less than 2 years before the first visit to the clinic, and absence of complete medical records. The study was approved by the Ethics Committee of Tongji Hospital (K-2017-014).

According to the revised version of the diagnostic

criteria published by the Respiratory Society of the Chinese Medical Association (10-13), the diagnostic standard of common causes of chronic cough was as follows:

CVA was diagnosed when the patients presented a predominately dry cough with airway hyperresponsiveness or airway reversibility, and cough could be significantly improved or diminished after anti-asthma therapy.

UACS was considered when the patients had a history of chronic rhinitis or sinusitis, presenting associated symptoms and/or signs such as sensation of post-nasal drip or throat-clearing, nasal discharge, nasal obstruction or sneezing, erythema and "cobblestone" appearance of the posterior pharyngeal mucosa, or mucoid/purulent nasal discharge dripping into the pharynx. Sinus images showing the presence of mucosal blur or thickening (> 6 mm), or presence of an air-fluid level. The diagnosis can be established when cough improved significantly or diminished after antihistamine therapy (oral cetirizine 10 mg once a day) or the addition of macrolides (oral erythromycin 250 mg twice a day, used as anti-inflammatory agent) in case of chronic sinusitis.

The diagnosis of NAEB was established when the patients presented predominately dry tickly cough with or without little viscous sputum, normal lung function test, negative bronchial provocation test $\geq 2.5\%$ eosinophils in the induced sputum, and relieved cough after glucocorticoids treatment (oral prednisone 25 mg daily for 6 days followed by inhaled budesonide 200 μ g twice a day).

GERC was defined when the mainly daytime cough was present along with DeMeester score ≥ 12.70 and/or symptom association probability (SAP) $\geq 75\%$ on multi-channel intraluminal impedance-pH monitoring (MII-pH); and anti-reflux therapy (omeprazole 20–40 mg twice a day plus domperidone 10 mg three times a day) was effective, or neuromodulators (gabapentin 100–300 mg three times a day or baclofen 10–20 mg three times a day) as an add-on therapy in the case standard anti-reflux therapy failed.

AC was suspected when the patients showing negative airway hyperresponsiveness as well as induced sputum eosinophile presented a predominately dry tickly cough with a history of allergic disease, and/or previous anaphylaxis or allergic reaction; allergen skin prick test showed positive; or serum total IgE increased or allergen-specific IgE was positive. The diagnosis was confirmed when cough relieved or diminished after glucocorticoids or antihistamine treatment.

If the patients had a definite history of upper respiratory infection before cough onset and the cough persisted but

could relieve spontaneously or with symptomatic treatment while other respiratory symptoms disappeared, the patients were diagnosed with post-infectious cough (PIC).

Angiotensin-converting enzyme inhibitor (ACEI)-induced cough was defined when the cough in patients taking ACEI currently could get cough relief after drug withdrawal.

Psychogenic cough was considered when there was psychological stress associated with negative emotional stimulation. The cough symptom was usually accompanied by coexisting anxiety or depression, without signs of other possible physiological causes of cough on clinical auxiliary examination, and it could get relief or significantly improved with psychotherapy.

Obstructive sleep apnea hypopnea syndrome (OSAHS)-related cough was considered when cough significantly improved or diminished by continuous positive airway pressure (CPAP) treatment in patients who were definitely diagnosed as OSAHS after excluding the other causes of chronic cough.

Diagnostic procedure

The diagnosis of the etiology of chronic cough followed a previously described step-by-step protocol (10,11). The protocol was based on the Guidelines for Diagnosis of Chronic Cough in China (12) and was locally adapted to fit the processes at our clinic. A full medical history was obtained, and physical examination was performed in all patients. First-line examinations included pulmonary function tests, bronchial provocation with histamine, and induced sputum cytology. Paranasal sinus imaging and MII-pH as well as other tests were ordered when necessary.

The patient was given a treatment targeting the suspected etiology based on the findings of clinical auxiliary examinations. Diagnosis was confirmed only when the treatment had resulted in the significantly improved or diminished cough symptoms. If the treatment failed, the additional possible etiologies were further searched according to the diagnostic protocol. If all possible causes of chronic cough were excluded, then a diagnosis of "idiopathic cough" was given.

Laboratory examination

A whole body plethysmograph (MasterScreen Diffusion and Aerosol Provocation System from Jaeger Toennies, Hochberg, Germany) was used for pulmonary function

testing and bronchial provocation test according to the protocol published by the American Thoracic Society (14). The bronchial provocation test was showed positive when $<7.8 \mu\text{mol}$ of histamine (cumulative dose) caused a 20% fall in FEV_1 ($\text{PD}_{20}\text{-FEV}_1$). Induced sputum was performed according to previously described protocol (15). Finally, differential cell count was conducted manually by counting 400 nucleated cells.

MII-pH monitoring was performed following standard protocols developed by the Department of Gastroenterology in our hospital. A combined MII-pH catheter with six impedance-measuring sensors (K6011-E10632, Unisensor, Attikon, Switzerland) and an antimony pH electrode (819100, Medical Measurement System B.V., Enschede, The Netherlands) were used (16). Data from all seven channels were transmitted via a portable data logger (Ohmega, Medical Measurement System B.V.), and processed using Database version 8.7 software (Medical Measurement System B.V., Enschede). The reflux episodes were further classified based on pH, where $\text{pH} <4$ was considered acidic, $\text{pH} 4\text{--}7$ weakly acidic, and $\text{pH} >7$ weakly alkaline (17). A DeMeester score over 12.70 was considered positive for the presence of significant acid reflux (18). Significant non-acid reflux (weakly acidic and weakly alkaline reflux) was considered when SAP was $\geq 75\%$ (19). SAP means the temporal association between the detected reflux and cough recorded by the patients on diary card.

Statistical analysis

All data with the exception of the course of disease were expressed as mean \pm standard deviation (SD). The course of disease was instead expressed as median and quartiles. SPSS software was used for statistical analysis. ANOVA and q-test were used to compare age and lung function. Chi-squared test was used to analyze the constituent ratio of gender and etiologies. Course of disease was analyzed with nonparametric median test. A value of $P < 0.05$ was considered statistically significant.

Results

General information

The medical records of 1,345 patients with chronic cough were reviewed. Thirty-four patients were excluded due to incomplete medical records (34/1,345, 2.5%), and 1,311 cases were finally enrolled to this study, including 486 males

Table 1 Characteristics of patients with chronic cough

Year	Case number	Gender (M/F)	Age (yr) ($\bar{x}\pm s$)	Cause of disease (m), median (P25, P75)	FEV ₁ pre% (%, $\bar{x}\pm s$)	FVC pre% (%, $\bar{x}\pm s$)	FEV ₁ /FVC (%, $\bar{x}\pm s$)
2009	273	95/178	48.4±14.7	5.0 (3.0, 12.0)	98.9±9.9	102.5±12.7	81.8±7.1
2010	158	61/97	47.4±13.8	6.0 (3.0, 19.5)	100.4±11.3	103.6±17.1	81.4±7.3
2011	138	58/80	46.9±15.8	6.0 (3.3, 36.0)	99.1±10.4	102.0±12.9	82.6±7.6
2012	155	63/92	48.2±15.3	7.0 (4.5, 29.0)	98.2±10.5	101.5±14.3	81.9±7.7
2013	152	56/96	49.2±14.9	6.5 (3.5, 23.0)	100.1±11.7	102.2±12.7	82.2±7.5
2014	127	43/84	45.6±15.1	8.0 (4.0, 36.0)	101.7±10.9	102.3±11.5	84.2±7.9
2015	173	58/115	46.9±15.5	7.0 (3.0, 24.0)	102.2±11.8	104.5±14.6	83.0±7.0
2016	135	52/83	47.5±15.8	8.5 (4.0, 36.0)	102.1±12.0	103.0±12.5	83.7±7.0
F	–	2.451*	0.350	0.678*	2.134	0.425	1.576
P	–	0.653	0.844	0.411	0.076	0.791	0.180

* denotes χ^2 value.

(37.1%) and 825 females (62.9%). The average age was 47.3±15.0 years old (range, 16–85 years old). The median duration of cough was 6.0 (3.5, 24.0) months. The patients were divided into eight groups by year according to time of first visit at our department. There were no significant differences in age, gender, cough duration and lung function parameters among the groups (*Table 1*).

Changes in the etiological frequency of chronic cough

The common causes of chronic cough in descending order were CVA (449/1,311, 34.2%), GERC (374/1,311, 28.5%), UACS/PNDs (241/1,311, 18.4%), AC (188/1,311, 14.3%), NAEB (147/1,311, 11.2%), PIC (39/1,311, 3.0%) and ACEI-induced cough (25/1,311, 1.9%), while there was significant difference in the etiological distribution among different year groups ($\chi^2=275.8$, $P<0.0001$). The proportion of CVA ($\chi^2=72.86$, $P<0.0001$) and UACS ($\chi^2=68.80$, $P<0.0001$) decreased significantly, while that of NAEB ($\chi^2=51.38$, $P<0.0001$) increased over year. GERC ($\chi^2=55.95$, $P<0.0001$) showed a rising trend. The proportion of AC ($\chi^2=39.09$, $P<0.0001$) increased significantly since 2010 and remained relatively stable. The proportions of PIC and ACEI use remained unchanged, while the idiopathic cough increased slightly (*Table 2* and *Figure 1*).

Changes in frequency distribution of multi-etiological

The frequency distribution of multi-etiological of chronic

cough varied over year between 2009 and 2016 ($\chi^2=27.34$, $P<0.0001$). The majority of multi-etiological chronic cough had two causes, and AC + GERC were the most common. Chronic cough with three causes was relatively rare, and AC + GERC + UACS was predominant (*Table 3*).

Discussion

This retrospective study reviewed the medical records chronic cough patients who visited our Respiratory Clinic in the last 8 years. The inclusion and exclusion criteria as well as etiological diagnostic criteria were the same. The diagnostic remained unchanged throughout the study, with the exception of the addition of neuromodulators for refractory GERC. This modification influenced the frequency of GERC restrictedly, thus providing an acceptable condition for investigating the changing frequency of etiologies of chronic cough.

The present study showed that CVA was still the most common cause of chronic cough in the past 8 years, which was consistent with previous findings (4,10,20,21). However, its proportion decreased over year. Better education of Chinese cough guideline for physicians and widespread application of bronchial provocation test were likely to be related to the increased diagnosis of CVA in primary and secondary healthcare institutions, because this might decrease referrals to tertiary hospitals. Moreover, bronchodilators and corticosteroids are usually used for empirical therapy of CVA in clinical practice (22,23). Cough

Table 2 Changes in constituent ratio and distribution frequency of etiologies of chronic cough

Year	Case number	CVA, n (%)	NAEB, n (%)	GERC, n (%)	UACS, n (%)	AC, n (%)	PIC, n (%)	ACEI-induced cough, n (%)	Idiopathic cough, n (%)	Others, n (%)
2009	273	145 (53.1)	5 (1.8)	42 (15.4)	93 (34.1)	10 (3.7)	10 (3.7)	9 (3.3)	3 (1.1)	1 (0.3)
2010	158	58 (36.7)	10 (6.3)	33 (20.9)	37 (23.4)	26 (16.5)	4 (2.5)	3 (1.9)	2 (1.3)	4 (2.5)
2011	138	54 (39.1)	12 (8.7)	36 (26.1)	16 (11.6)	26 (18.8)	6 (4.3)	2 (1.4)	0	4 (2.9)
2012	155	47 (30.3)	19 (12.3)	46 (29.7)	23 (14.8)	29 (18.7)	7 (4.5)	3 (1.9)	1 (0.6)	1 (0.6)
2013	152	40 (26.3)	23 (15.1)	58 (38.2)	18 (11.8)	20 (13.2)	2 (1.3)	1 (0.7)	3 (2.0)	1 (0.7)
2014	127	38 (29.9)	22 (17.3)	35 (27.6)	16 (12.6)	18 (14.2)	0	1 (0.8)	9 (7.1)	0
2015	173	39 (22.5)	30 (17.3)	69 (39.9)	25 (14.5)	37 (21.4)	8 (4.6)	2 (1.2)	6 (3.5)	0
2016	135	28 (20.7)	26 (19.3)	55 (40.7)	13 (9.6)	22 (16.3)	2 (1.5)	4 (3.0)	6 (4.4)	2 (1.5)
Total	1,311	449 (34.2)	147 (11.2)	374 (28.5)	241 (18.4)	188 (14.3)	39 (3.0)	25 (1.9)	30 (2.3)	13 (1.0)

Note: N = the number of causes; Others: one case of psychogenic cough in 2009; three cases of OSAHS-related chronic cough, and one case of psychogenic cough in 2010; two cases of left atrial enlargement-induced chronic cough and two cases of psychogenic cough in 2011; one case of ventricular premature beat in 2012; one case of external auditory canal cerumen-induced chronic cough in 2013; and two cases of psychogenic cough in 2016. AC, atopic cough; ACEI, angiotensin converting enzyme inhibitor; CVA, cough variant asthma; GERC, gastroesophageal reflux-related chronic cough; NAEB, non-asthmatic eosinophilic bronchitis; PIC, post infectious cough; UACS, upper airway cough syndrome.

**Figure 1** Variation trends in annual constituent ratio of common etiologies of chronic cough.

symptom was resolved in these patients, therefore they would not visit tertiary hospitals for a definite diagnosis. This might be another reason for the reduced rate of CVA in the special cough center.

The proportion of UACS/PNDs decreased in this study, which was consistent with the previous findings, while NAEB increased over year (10). The diagnosis of UACS/PNDs less depends upon the complex laboratory investigations. Therefore UACS/PND_s is often effectively controlled after antihistamine treatment in primary hospitals, which therefore decreased the referrals tertiary

hospitals. Newer-generation antihistamine cetirizine was used for UACS/PNDs to avoid sedation, which might cause some UACS/PNDs misdiagnosed and accounted for the decreasing proportion of UACS/PNDs to a certain extent. However, the diagnosis of NAEB required the cytological examination of induced sputum, which was a diagnostic modality unavailable in most clinics. Thus, many NAEB patients were transferred to our clinic, leading to an increase in its proportion.

Due to the insufficient recognition of AC in our clinic, some patients achieved cough remission after antihistamine might have been misdiagnosed with silent UACS instead of AC in our previous study (15). Since the implementation of the national cough guidelines, the recognition of AC (13) increased, leading to a significant elevation in the proportion of AC until 2010 and there reached a plateaued after that. In addition, this might be one of the reasons for the decreased proportion of UACS observed in this study.

The proportion of GERC increased significantly in the present study, becoming the second leading cause of chronic cough. Firstly, obesity was a recognized risk factor for gastroesophageal reflux (GER) (24). As the Western lifestyle became increasingly popular in China, the incidence of obesity and GERD also increased (25), as well as the increase in incidence of GERC. In this study, the proportion of GERC was significantly higher than

Table 3 Constituent ratio and distribution of etiologies for multi-etiology of chronic cough

Year	n (%)	AC + GERC	AC + GERC + UACS	CVA + GERC	NAEB + GERC	NAEB + UACS	GERC + UACS	CVA + UACS	Others
2009	45 (16.5)	1	0	10	2	1	9	15	7
2010	16 (10.1)	2	1	3	2	0	3	2	3
2011	10 (7.2)	2	0	2	2	0	0	1	3
2012	23 (15.1)	8	2	5	3	2	1	1	1
2013	15 (9.9)	5	1	4	1	1	2	0	1
2014	11 (8.7)	5	1	1	3	0	0	0	1
2015	40 (23.1)	13	1	10	9	3	1	0	3
2016	24 (17.8)	7	0	4	9	2	1	0	1
Total	184 (14.0)	43	6	39	31	9	17	19	20

Note: n (%): n means the number of cases, % means proportion of cases with multi-etiology of chronic cough in total cases of every year; Others: one case of CVA + GERC + UACS, two cases of AC+UACS, one case of CVA + OSAHS + UACS, one case of GERC + OSAHS, one case of GERC + OSAHS + UACS, one case of ACEI-induced cough + CVA in 2009; one case of GERC + OSAHS, one case of ACEI-induced cough + AC + GERC, one case of CVA + GERC + OSAHS in 2010; one case of ACEI-induced cough + PIC, one case of psychogenic cough + GERC, one case of GERC + OSAHS in 2011; one case of GERC + OSAHS + UACS in 2012; one case of GERC + NAEB + psychogenic cough in 2013; one case of ACEI-induced cough + CVA in 2014; one case of CVA + GERC + UACS, one case of NAEB + GERC + UACS, one case of ACEI-induced cough + CVA in 2015; and one case of ACEI-induced cough + CVA in 2016. AC, atopic cough; ACEI, angiotensin converting enzyme inhibitor; CVA, cough variant asthma; GERC, gastroesophageal reflux-related chronic cough; NAEB, non-asthmatic eosinophilic bronchitis; PIC, post infectious cough; UACS, upper airway cough syndrome.

that from a multi-center study in China, where GERC accounted only for 4.6% of chronic cough (13). Since Shanghai is an economically developed city in China, an increasing number of the residents could afford a fat-rich diet and thus they were susceptible to suffer from GERC. In addition, some studies reported that static pressure of lower esophageal sphincter and esophageal motility decreased when anxiety and depression were exacerbated (26). Modern lifestyle is associated with higher level of mental stress, which might increase the prevalence of GERD as well as GERC. Secondly, MII-pH was used to replace ambulatory 24 h esophageal pH monitoring in the diagnosis of chronic cough in our department since 2009, which significantly improved the diagnostic accuracy of GERC, especially in patients with cough due to non-acid reflux (27). In addition, neuromodulators such as baclofen and gabapentin were prescribed to treat GERC resistant to standard anti-reflux therapy, leading to the improved diagnostic accuracy of refractory GERC, which previously considered as idiopathic cough. Thirdly, the increased referrals from other hospitals may also explain the increased proportion of GERC in the large cohort of patients with chronic cough because of the unavailability of MII-pH and the difficulty in the management of chronic cough.

The proportion of idiopathic cough varied from 1% to 7% in the present study, which was lower than that reported in our previous study and a multi-center study (10,13). As mentioned above, MII-pH and neuromodulators were used for the diagnosis and treatment of GERC in our department recently, which decreased the proportion of idiopathic cough correspondingly. In addition, OSAHS tended to develop cough hypersensitivity and was recognized as a cause of chronic cough (28,29). There were three patients diagnosed with OSAHS-related cough in the present study. This may lead to the decreased proportion of idiopathic cough to some extent.

In this study, the median duration of cough increased from 5.0 (3.0, 12.0) months in 2009 to 8.0 (4.0, 36.0) months in 2016, indicating an increasing trend over years, although there was no significant difference among 8 years. This might be caused by a large data variation. Firstly, due to the difficulty in the diagnosis and management, some patients with chronic cough such as GERC (including refractory GERC) were transferred among hospitals without a definite diagnosis, lengthening the duration of cough. However greater awareness among community physicians may shorten the duration of cough.

There are some limitations in this study. It was a

single-center study and the results may be biased by the socioeconomic and lifestyle characteristics in distinct districts. Thus, it lacks enough representativeness as compared with multi-center studies. Besides, it was a retrospective study, but unified inclusion and exclusion criteria were employed, the sample size was large. And 8-year was long enough to clarify the changing frequency of etiologies of chronic cough.

In conclusion, the frequency of etiology distribution of chronic cough changed over time. These changes seem to be related to the level of referred hospital, the popularization of cough guidelines, as well as the recognition of chronic cough among physicians. According to our study, GERC has become a more common cause of chronic cough, while the proportion of CVA decreased slightly. These findings may be helpful to improve the diagnostic procedure and empirical therapy protocol for chronic cough in the future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Ethics Committee of Tongji Hospital (K-2017-014).

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