



# The spectrum, clinical features and diagnosis of chronic cough due to rare causes

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**Background:** Chronic cough has many diverse causes, including common and uncommon causes. There are few comprehensive reports on rare causes of chronic cough. The purpose of this study is to determine the etiological distribution, clinical features, and diagnostic value of special examinations in patients with rare causes of chronic cough.

**Methods:** A retrospective analysis of patients with chronic cough who underwent medical history taking, full examination, and etiological treatment over a 13-year period was conducted. Causes of chronic cough with a prevalence of less than 3% were defined as rare causes.

**Results:** A total of 1,554 patients were enrolled, and 39 causes of chronic cough were identified. Among them, 1,055 cases were due to common causes, whereas 235 cases were due to rare causes; the causes involved 7 bodily systems. The top five rare causes were protracted bacterial bronchitis, somatic cough syndrome, diffuse panbronchiolitis, obstructive sleep apnea syndrome (OSAS), and interstitial lung disease, accounting for 67.2% of all rare causes. Among 235 patients with rare causes, causes in 90 (38.3%) patients were detected by chest high-resolution computed tomography (HRCT), in 44 (18.7%) patients by bronchoscopy/nasopharyngoscopy, and in 21 (8.9%) patients by pulmonary spirometry and diffusing capacity testing.

**Conclusions:** Among the 31 rare causes of chronic cough in this cohort, the top five were protracted bacterial bronchitis, somatic cough syndrome, diffuse panbronchiolitis, OSAS, and interstitial lung disease. Special examinations, such as chest HRCT and bronchoscopy, should be considered after excluding common causes of chronic cough.

**Keywords:** Chronic cough; rare cause; spectrum; special examination

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## Introduction

Chronic cough is a common complaint of patients in respiratory clinics, and the global prevalence is

approximately 9.6% (1). There are many different conditions related to chronic cough. The most common causes of chronic cough include cough variant asthma (CVA), eosinophilic bronchitis (EB), upper-airway cough

syndrome (UACS), and gastroesophageal reflux cough (GERC), accounting for 51% to 92% of cases of chronic cough (2-7). A few rare conditions, such as obstructive sleep apnea syndrome (OSAS), idiopathic pulmonary fibrosis, and relapsing polychondritis, have also been reported (8-10). Although rare causes account for a low proportion of chronic cough cases, a wide variety of conditions involving systems other than the respiratory system can be involved. Patients with uncommon causes often receive a misdiagnosis and inappropriate treatment for a long time, leading to great impairment in quality of life and a substantial economic burden. There are few systematic reports on the distribution of rare causes of chronic cough. In addition, the diagnosis of rare causes depends on special examinations, such as high-resolution computed tomography (HRCT), nasopharyngoscopy, or bronchoscopy. However, the usefulness of special examinations in diagnosing rare causes of chronic cough has rarely been reported in previous studies (11-13). Hence, we summarize the etiology, clinical features of and diagnostic methods applied to patients with chronic cough due to rare causes who visited our hospital from 2006 to 2018, aiming to highlight rare diagnoses in chronic cough patients.

We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/jtd-20-2671>).

## Method

### *Subjects and diagnostic protocol*

This was a retrospective study. Data were extracted from the medical records of consecutive chronic cough patients who underwent full examinations and treatment who received outpatient care at the First Affiliated Hospital of Guangzhou Medical University from 2006 to 2018. A standard form was used to record demographics, clinical features, laboratory results, primary diagnosis, response to therapy, follow-up, and final diagnosis for chronic cough patients. The inclusion criteria for patients with chronic cough were as follows: (I) chronic cough lasting more than 8 weeks as the sole or predominant symptom; (II) no abnormalities on plain chest film; (III) no acute upper-airway infection in the past 4 weeks; (IV) age older than 16 years old; (V) cause of cough determined by the diagnostic protocol and management of chronic cough as referred to in our previous report (14).

The diagnostic workflow was established to identify

the causes of chronic cough in 2003 (14) and later slightly modified according to the cough guidelines (15,16). Briefly, detailed medical history, physical examination, chest radiograph, spirometry, assessment of bronchial hyperresponsiveness, and induced sputum test were conducted in all the patients at entry. 24-h esophageal pH-multichannel impedance monitoring were selected in some patients who was suspected for GERC or failed to initial treatment. Diagnosis of CVA was determined if the patient presented bronchial hyperresponsiveness and responded to anti-asthmatic treatment. EB was diagnosed with normal pulmonary function, a lack of airway hyperresponsiveness, sputum eosinophil count  $\geq 2.5\%$  and response to corticosteroids. GERC was confirmed if 24 h esophageal pH value monitoring showed a DeMeester score of  $\geq 12.7$  and symptom association probability of  $\geq 80\%$ , and cough resolved after anti-reflux treatment. UACS was diagnosed based on history, symptoms and signs of rhinitis/sinusitis, and cough improved after specific therapy directed to UACS. To explore uncommon causes, Multidisciplinary consultation and special investigations were conducted, including bronchoscopy, chest HRCT, sinus CT, nasopharyngoscopy, polysomnography, and pulmonary diffusing capacity testing etc. If the above investigations failed to indicate the causes of cough, or if the cough persisted after treatment directed to all potential causes, unexplained cough (UC) was considered. A description of the diagnosis of chronic cough is provided in [Table S1](#).

Causes of chronic cough with rates of less than 3% were defined as rare causes in this study. This retrospective study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (No. 201778) and individual consent for this retrospective analysis was waived.

### *Statistical analysis*

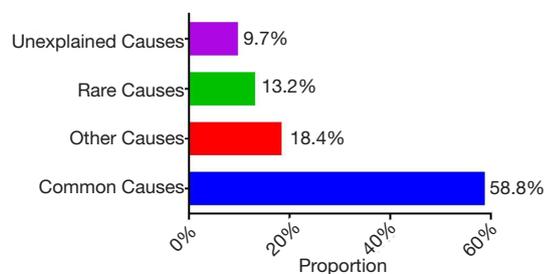
Data are expressed as means  $\pm$  standard deviations (SDs), medians (interquartile ranges, IQRs) or numbers (percentages). Statistical comparisons between groups were performed with one-way analysis of variance (ANOVA) for normally distributed data, Kruskal-Wallis tests for skewed data, and chi-square tests for proportions, with appropriate post hoc tests for multiple comparisons (adjusted with the Bonferroni method). Missing data were not imputed. A P value  $< 0.05$  (two-sided) was considered significant. Statistical analysis was performed using SPSS 25.0.

## Results

### Spectrum of the causes of chronic cough

A total of 1,554 chronic cough patients were enrolled from 2006 to 2018; 807 (51.9%) patients were female. The average age of the patients was  $43.3 \pm 14.1$  years, and the cough duration was 24 (10.0–84.0) months. The spectrum and frequency of chronic cough are shown in *Figure 1*. 1,055 (58.8%) cases were due to common causes, 330 (18.4%) cases were due to other common causes, 235 (13.1%) cases were due to rare causes, and the remaining 173 cases (9.6%) were due to UC. The common causes included EB (18.3%), CVA (16.3%), GERC (13.2%), and UACS (11.1%). Other common causes consisted of chronic bronchitis (6.1%), bronchiectasis (4.5%), atopic cough (4.4%) and postinfectious cough (3.5%).

The rare causes of chronic cough are shown in *Table 1*. According to the anatomic location, we classified the rare



**Figure 1** The spectrum and frequency of chronic cough.

causes into four groups: upper-airway diseases (28 cases, 1.6%), lower-airway diseases (102 cases, 5.7%), lung diseases (27 cases, 1.5%) and other system diseases (78 cases, 4.4%). The other system diseases involved the neuropsychological system, cardiovascular system, endocrine system, hematological system and skeletal musculature system. The top five-rare causes were protracted bacterial bronchitis (44 cases, 2.5%), somatic cough syndrome (previously referred to as psychogenic cough) (37 cases, 2.1%), diffuse panbronchiolitis (31 cases, 1.7%), obstructive sleep apnea syndrome (23 cases, 1.3%), and interstitial lung disease (23 cases, 1.3%), which accounted for 67.2% of all rare causes (*Figure 2*).

### The clinical characteristics of rare causes

The patient demographics and characteristics of chronic cough due to rare causes, common causes, other common causes, and unexplained causes are shown in *Table S2*. Of cases with rare causes, females accounted for 54.9%, the average age was  $48.2 \pm 15.1$  years, and the average cough duration was 24 (10 to 72) months. Regarding timing, cases with rare causes reported daytime cough, nighttime cough, morning cough, and cough before sleep, accounting for 89.3%, 37.9%, 52.7% and 66.2% respectively. Over one-third of cases with rare causes had laryngeal paresthesia, sneezing, nasal congestion, throat clearing, or chest tightness. The most common previous diagnoses of cases with rare causes were pharyngitis (39.0%) and chronic bronchitis (33.5%). Regarding previous treatment

**Table 1** The spectrum and frequency of rare causes of chronic cough based on anatomy

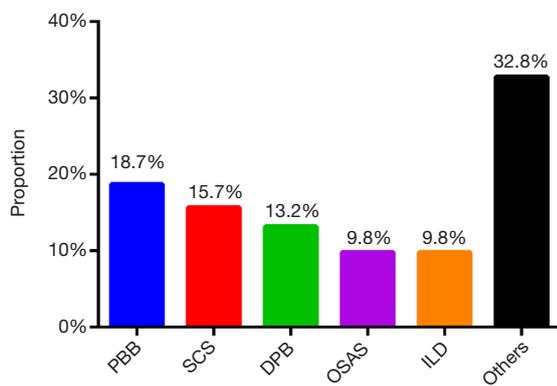
Anatomy	Causes
Upper-airway (28, 1.6%)	OSAS (23, 9.79%), mucous cyst of salivary gland (1, 0.43%), laryngocarcinoma (1, 0.43%), VCD (2, 0.85%), laryngeal amyloidosis (1, 0.43%)
lower-airway (102, 5.7%)	PBB (44, 18.72%), DPB (31, 13.19%), FACC (4, 1.70%), bronchial tuberculosis (5, 2.13%), bronchial foreign body (2, 0.85%), broncholithiasis (1, 0.43%), BACC (1, 0.43%), Kartagener syndrome (1, 0.43%), relapsing polychondritis (8, 3.40%), sarcoidosis (1, 0.43%), postoperative cough (4, 1.70%)
Lung (27, 1.5%)	ILD (23, 9.79%), atypical pneumoconiosis (2, 0.85%), COP (2, 0.85%)
Other systems (78, 4.4%)	Somatic cough syndrome (37, 15.74%), hyperventilation syndrome (15, 6.38%), ACEI-induced cough (8, 3.40%), arrhythmia (5, 2.13%), HIVD (3, 1.28%), goiter (1, 0.43%), occupational cough (2, 0.85%), styloid process syndrome (1, 0.43%), HES (3, 1.28%), catamenial cough (1, 0.43%), LCH (1, 0.43%), cardiogenic cough (1, 0.43%)

Data are presented as (cases, percentage of total cases of chronic cough). OSAS, obstructive sleep apnea syndrome; VCD, vocal cord disfunction; PBB, protracted bacterial bronchitis; DPB, diffuse panbronchiolitis; FACC, fungus-associated cough; BACC, bronchial adenoid cystic carcinoma; ILD, interstitial lung disease; COP, cryptogenic organizing pneumonia; ACEI, angiotensin-converting enzyme inhibitor; HIVD, herniated cervical intervertebral disc; HES, hypereosinophilic syndrome; LCH, Langerhans cell histiocytosis.

in patients with rare causes, antibiotics (80.3%) and antitussives (74.6%) were the most popular therapeutic agents. However, there were no significant difference in clinical characteristics to discriminate between cases with rare causes and cases with other causes of chronic cough.

### Usefulness of special examinations in diagnosing rare causes of chronic cough

Some special examinations were performed to diagnose rare



**Figure 2** The spectrum and frequency of rare causes. PBB, protracted bacterial bronchitis; SCS, somatic cough syndrome; DPB, diffuse pan bronchiolitis; OSAS, obstructive sleep apnea syndrome; ILD, interstitial lung disease.

causes of chronic cough, including chest HRCT, sinus CT, pulmonary diffusing capacity testing, nasopharyngoscopy and bronchoscopy. The special examinations performed to diagnose rare causes of chronic cough are shown in *Table 2*. Among 235 cases with rare causes, the causes of 44 (18.7%) cases were detected by bronchoscopy or nasoscopy. Abnormality in pulmonary diffusing capacity was observed in 21 (8.9%) cases with rare causes, indicating the cause of chronic cough. There were 90 (38.3%) cases with rare causes whose causes were indicated by chest HRCT.

### Discussion

To the best of our knowledge, this was the first study to describe the distribution and clinical features of rare causes of chronic cough in a large sample population. A total of 31 rare causes were identified, and in some cases, special examinations were useful for diagnosing rare causes.

CVA, EB, UACS and GERC were the four most common causes of chronic cough, accounting for 58.8%, and the proportion of other common causes was 18.4%, similar to previous studies (3,4). The proportion of patients with rare causes in this study was 13.1%. The top 5 rare causes were protracted bacterial bronchitis, somatic cough syndrome, diffuse panbronchiolitis, OSAS and interstitial lung disease, accounting for 67.2% of cases in patients with rare causes. Regarding the anatomical locations of the rare causes, the proportion of lower-airway diseases was

**Table 2** Values of special examinations in diagnosing rare causes in the cohort

Examination	Rare causes (cases)	Total cases, (%)
Bronchoscopy/ nasopharyngoscopy	Relapsing polychondritis (3 cases), Bronchial tuberculosis (5 cases), Bronchial foreign body (2 cases), Mucous cyst of salivary gland (1 case), Broncholithiasis (1 case), TACC (1 case), Pneumoconiosis (1 case), COP (2 cases), Laryngocarcinoma (1 case), VCD (2 cases), Laryngeal amyloidosis (1 case), PBB (6 cases), Sarcoidosis (1 case), DPB (7 cases), ILD (6 cases), HES (2 cases), LCH (1 case), BACC (1 case)	44/235 (18.7%)
HRCT	DPB (31 cases), ILD (23 cases), Relapsing polychondritis (8 cases), COP (2 cases), PPB (9 cases), Bronchial tuberculosis (5 cases), Bronchial foreign body (2 cases), TACC (1 case), Broncholithiasis (1 case), LCH (1 case), Atypical pneumoconiosis (2 cases), Kartagener syndrome (1 case), HES (3 cases), BACC (1 case)	90/235 (38.3%)
Sinus CT	DPB (31 cases), OSAS (1 case)	32/235 (13.6%)
Pulmonary diffusing capacity	ILD (14 cases), DPB (3 cases), TACC (1 case), LCH (1 case), sarcoidosis (1 case), COP (1 case)	21/235 (8.9%)

OSAS, obstructive sleep apnea syndrome; VCD, vocal cord dysfunction; PBB, protracted bacterial bronchitis; DPB, diffuse pan bronchiolitis; FACC, fungus-associated cough; BACC, bronchial adenoid cystic carcinoma; ILD, interstitial lung disease; COP, cryptogenic organizing pneumonia; ACEI, angiotensin-converting enzyme inhibitor; HES, hypereosinophilic syndrome; LCH, Langerhans cell histiocytosis.

the highest, which may be related to the afferent nerves in the airway causing cough (17). Stimulation in the larynx, trachea, and bronchus may present as obvious cough, whereas cough is usually not the main symptom of small airway and alveolar wall damage.

This study found that protracted bacterial bronchitis accounted for the largest proportion of rare lower-airway causes of chronic cough. Protracted bacterial bronchitis is a common cause of chronic cough in children (18), but is rarely reported in adults (19,20). In 2003, Schaefer reported that cough was relieved after intravenous antibiotic treatment in 15 adult subjects with chronic productive cough and normal HRCT scans (19). Martin *et al.* reported adult protracted bacterial bronchitis with productive cough (20,21), suggesting that protracted bacterial bronchitis was also a cause of chronic cough in adults. In this study, protracted bacterial bronchitis produced a chronic productive cough or dry cough, which ruled out bronchiectasis, and patients had a good response after more than 2 weeks of antibiotic treatment. In addition, several rare lower-airway diseases were identified, including bronchial tuberculosis, bronchial foreign body, broncholithiasis, and relapsing polychondritis. Therefore, if common causes are excluded, lower-airway diseases should be considered first.

Cough is mediated by a complete neural reflex pathway, and any condition that affects this reflex pathway may cause cough. The afferent nerves associated with the cough reflex are not only distributed in the airway but also in other systems, e.g., the esophagus, sinuses, external auditory canal, pericardium, and others (17). Therefore, rare causes of chronic cough could involve many systems. This study found that the causes of chronic cough were related to the nervous system, endocrine system, cardiovascular system, skeletal system, etc. as well as psychology. It is generally considered that somatic cough syndrome is a common cause of cough in children aged 6 to 16 years (22,23). There are few reports on somatic cough syndrome in adults (24,25). However, the proportion of cases of somatic cough syndrome was second to protracted bacterial bronchitis in this study, indicating that adult somatic cough syndrome should be considered as a rare cause of chronic cough in adults. Many patients with somatic cough syndrome also have anxiety and depression, which might contribute to increased life pressure and work pressure induced by competitive economic transformation in China. There were a variety of other rare causes, such as hyperventilation syndrome, arrhythmia, goiter, styloid process syndrome,

and hypereosinophilic syndrome. When diagnosing chronic refractory cough or “UC”, the above causes should be excluded carefully. Diffuse panbronchiolitis is an idiopathic inflammatory disease that was first reported in Japan in the 1960s, with over 50% of cases occurring in East Asia. It typically presents as chronic cough with copious purulent sputum and exertional dyspnea. More than 80% of patients have chronic paranasal sinusitis, their pulmonary function measurements show significant airflow limitation, and bilateral small nodular shadows are visible predominantly in the lower field of the lung on chest radiographs. In this study, we identified 31 diffuse panbronchiolitis patients who presented with chronic cough as the sole or predominate symptom who had normal respiratory function or mild airflow limitation, normal chest X-ray findings, and mild dilation of the bronchiolar passages and a “tree-in-bud” pattern on chest HRCT. Those patients experienced a significant improvement in cough after the use of long-term therapy with macrolide antibiotics.

Diagnosing rare causes of chronic cough is a challenge for clinicians. This study showed that many rare causes of chronic cough were misdiagnosed as chronic bronchitis or chronic pharyngitis, similar to our previous report in unselected patients with chronic cough. Approximately 80% of patients with chronic cough were diagnosed in our previous survey (26). Chronic bronchitis has a relatively high prevalence in epidemiological surveys of community populations (27,28). However, chronic bronchitis is not a common cause of cough addressed in respiratory specialist clinics, with a prevalence of only 1–7.0% according to previous surveys (2,4,7). The prevalence of chronic bronchitis was 6.1% in this study. There are no objective diagnostic criteria for chronic bronchitis, and the term “bronchitis” is often used as a common descriptor for a nonspecific and self-limited cough, which may explain why so many patients are misdiagnosed with chronic bronchitis (29). Chronic cough is often accompanied by pharyngeal paresthesia, including a scratchy throat, foreign body sensation in the pharynx, and paroxysmal irritation (30). Pharyngitis seems to be a good umbrella term for patients with chronic cough. Additionally, rare causes were frequently diagnosed as UC because there were no abnormal findings after routine examinations, and empirical treatment was unsuccessful. Therefore, the diagnosis of chronic bronchitis, chronic pharyngitis or UC should be made very carefully when common causes of chronic cough are ruled out.

History taking and physical examination are the first steps to establish a differential diagnosis; physicians should then select relevant testing, make a tentative diagnosis, and initiate empiric therapy. Although there were no reliable clinical characteristics, including cough timing, cough triggers and concomitant symptoms, to discriminate between patients with rare causes and patients with other causes of chronic cough, some clinical features were helpful in indicating a single etiology, e.g., ‘inspiratory wheezing’ indicates a central airway tumor or bronchial tuberculosis, ‘Velcro crackles’ indicate interstitial lung disease, and pain and numbness in the neck or arm indicate a herniated cervical intervertebral disc; moreover, arrhythmia might be the cause of cough. In the diagnostic procedure for chronic cough, chest HRCT is generally not the first option (31). Chest HRCT is more sensitive than chest X-ray, helping to identify rare causes in the airway and pulmonary parenchyma (31,32). Our study showed that chest HRCT resulted in high positive rates in the diagnosis of rare causes. Chest HRCT played an important role in diagnosing not only early interstitial lung disease but also established interstitial lung disease, bronchial foreign bodies, bronchial tuberculosis, broncholithiasis, relapsing polychondritis and other causes in this study. Bronchoscopy is recommended as a supplementary examination to diagnose rare causes (31), and its diagnostic value for common causes seems limited in unselected patients (12). Bronchoscopy not only confirmed a few airway-related causes but also contributed to observing indications of rare causes, such as cryptogenic organizing pneumonia, hypereosinophilic syndrome, Langerhans cell histiocytosis, etc., when combined with histopathology and chest HRCT. Therefore, we propose that HRCT and bronchoscopy should be considered if no abnormalities are observed in routine examinations and if patients do not respond to empirical treatment. A few specific examinations should be selected based on the patient's condition, e.g., PSG monitoring for patients with obesity or snoring and PET-CT for patients with suspected relapsing polychondritis.

There was limitation to the study. Since the prevalence of rare cause of chronic cough is low and its etiological diagnosis based more on special examinations, it is hard to conduct a prospective, multicenter survey on rare causes of chronic cough. This study might be limited by its retrospective nature as well as being derived from a single hospital. Nevertheless, our data provided the clues of the spectrum and usefulness of special examinations in rare cause of chronic cough.

## Conclusions

In conclusion, rare causes of chronic cough accounted for 13.1% of all causes of chronic cough in this cohort. Thirty-one rare causes of chronic cough were identified and involved in many systems, including the respiratory system, nervous system, digestive system, cardiovascular system, endocrine system, hematological system, skeletal musculature system and others. Lower-airway diseases were the most common types of diseases in patients with rare causes. The top 5 rare causes of chronic cough were protracted bacterial bronchitis, somatic cough syndrome, diffuse panbronchiolitis, OSAS, and ILD, accounting for 67.2% of all cases with rare causes. No special clinical features indicating the diagnosis of chronic cough due to rare causes were identified. Special examinations such as HRCT and bronchoscopy play an important role in diagnosing rare causes and should be considered based on the patient's condition after excluding common causes of chronic cough.

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## Footnote

*Reporting Checklist:* The authors have completed the STROBE reporting checklist. Available at <http://dx.doi.org/10.21037/jtd-20-2671>

*Data Sharing Statement:* Available at <http://dx.doi.org/10.21037/jtd-20-2671>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jtd-20-2671>). Dr. KL serves as an editorial

board member of *Journal of Thoracic Disease*. Dr. NZ serves as the Editor-in-Chief of *Journal of Thoracic Disease*. The authors have no other 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 conducted in accordance with the Declaration of Helsinki (as revised in 2013). This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (No. 201778). Since this study was a review of patients for whom we had clinical responsibility, consent to participate was not sought.

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Table S1 Description of diagnostic criteria

Cause of chronic cough	Description of diagnostic criteria in our study
Eosinophilic bronchitis	Normal pulmonary ventilation function, a lack of airway hyperresponsiveness, and normal average weekly peak expiratory flow variation Sputum eosinophil count $\geq 25\%$ Cough improved after treatment with corticosteroids
Cough variant asthma	Evidence of variable airflow limitation [positive bronchial challenge test (fall in FEV1 from baseline of $\geq 20\%$ with 12.8 $\mu\text{mol}$ of methacholine or with 7.8 $\mu\text{mol}$ of histamine), or positive bronchodilator reversibility test (increase in FEV1 $\geq 12\%$ and 200 mL from baseline)] Cough resolved after anti-asthma treatment
Gastroesophageal reflux cough	24-h ambulatory esophageal pH monitoring or multi-channel intraluminal impedance-pH monitoring shows a DeMeester score of $\geq 12.7$ and symptom association probability of $\geq 80\%$ Cough resolved or disappears after anti-reflux treatment
Upper-airway cough syndrome	History and clinical manifestations of nasal and/or throat conditions Auxiliary tests support nasal and/or throat conditions Cough improved after specific therapy targeted to upper-airway cough syndrome
Chronic bronchitis	Chronic cough and sputum production for at least 3 months per year for two consecutive years Other causes of chronic cough have been excluded Cough improved with using of mucolytic therapy and judicious using of antibiotic therapy
Bronchiectasis	Chest HRCT showed bronchial enlargement and distortion Cough improved with treatment directed at bronchiectasis
Atopic cough	Normal pulmonary ventilatory function and bronchial responsiveness Lack of sputum eosinophilia Evidence of atopy Response to corticosteroids or antihistamine treatment
Postinfectious cough	Chronic cough after common cold or acute upper respiratory tract infection Cough gradually resolved with symptomatic treatment
Obstructive sleep apnea syndrome	History of snoring, sleep disturbance at night, and excessive daytime sleepiness Positive polysomnography Cough improved with the treatment with nasal continuous positive airway pressure during sleeping
Mucous cyst of salivary gland	Chronic cough and white frothy sputum Neoplasm in root of tongue on nasopharyngoscopy Pathology revealed mucous cyst of salivary gland Cough improved with resection of the neoplasm
Laryngocarcinoma	Neoplasm in laryngopharynx with bronchoscopy/nasopharyngoscopy Pathology revealed Laryngocarcinoma Cough improved after laryngocarcinoma operation
Vocal cord dysfunction	Vocal fold narrowing (adduction) on laryngoscopy during a symptomatic episode Cough improved with speech pathology techniques designed to relieve glottal constriction during inspiration and to recognize and alter the response to precipitants
Laryngeal amyloidosis	Nasopharyngoscopy revealed the presence of a mass, arising from the right false vocal cord Pathology revealed amyloidosis Cough improved after laryngeal amyloidosis resection
Protracted bacterial bronchitis	Chronic productive cough or dry cough Normal chest HRCT Routine sputum culture for bacteria could be positive Cough improved with more than 2 weeks of antibiotic treatment
Diffuse panbronchiolitis	Symptoms, signs related with nasosinusitis Mild dilation of the bronchiolar passages and a "tree-in-bud" pattern on chest HRCT Improvement in cough after long-term therapy with macrolide antibiotics
Fungus-associated cough	Environmental fungi were positive in the cultured sputum Cough improved with antifungal drugs
Bronchial tuberculosis	Swollen mucosa, mucosal granularity, ulceration, or bronchial scarring on bronchoscopically visible lesions of trachea, main bronchi and/or upper bronchi Bronchial washings are smear-positive for acid-fast bacilli Cough improved with anti-tuberculosis treatment
Bronchial foreign body	Foreign body was found in bronchus according to bronchoscopy Cough improved after foreign body removed
Broncholithiasis	Chest HRCT showed bronchus intermedius calcified nodes Visible stones on Bronchoscopy Cough improved after endoscopic removal
Bronchial adenoid cystic carcinoma	Chest HRCT revealed thickening of right main bronchus and middle bronchial wall Neoplasm in right main bronchus was observed with bronchoscopy Biopsy pathology revealed adenoid cystic carcinoma Cough improved with operative treatment
Kartagener syndrome	History of chronic sinusitis, Bronchiectasis and situs inversus on chest CT Dextrocardia
Relapsing polychondritis	CT or PET-CT showed thickening, calcification or metabolic enhancement of cartilages in nose, ear, rib, etc. Auricular cartilage biopsies showed cartilage inflammation Cough improved after treatment with oral steroids
Sarcoidosis	Normal pulmonary ventilation function; diffusion capacity was decreased mildly Pathologic confirmation from the lymph nodes sampled via endobronchial ultrasound with transbronchial needle aspiration Cough improved after treatment with oral steroids
Postoperative cough	Chronic cough after thoracic surgery Cough could not be explained by other cause of chronic cough
Interstitial lung disease (early)	Cough without dyspnea, local Velcro rales might exist HRCT showed a little ground glass shadow Diffusion capacity was decreased mildly or normal Cough improved with oral corticosteroids
Atypical pneumoconiosis	Long term exposure to sand weather in Northwest China Chest CT scan showed bilateral diffuse nodules Pathological change of sand nodules was identified by transbronchial lung biopsy Other cause of chronic cough was excluded
Cryptogenic organizing pneumonia	HRCT showed pulmonary nodules and ground glass lesions Pathological examination confirms the diagnosis Cough resolved with corticosteroids therapy
Somatic cough syndrome	Cough occurs only during the daytime, and disappears when focusing and when asleep Multiple psychogenic factors such as sensation, belief, mood, learning, and habit can stimulate the cough Excessive thoughts, feelings, or behaviors related to cough Cough improved with suggestion therapy, hypnosis or psychologist psychotropic drugs
Hyperventilation syndrome	Patients presented with cough as well as symptoms related with typical hyperventilation syndrome symptoms The total score of the Nijmegen Symptomatic Questionnaire was $\geq 23$ points Cough resolved after treatment with breathing exercise or psychotherapy
ACEI-induced cough	Cough relieved after withdrawal of ACEI
Arrhythmia related cough	Cough with post sternal thump and premature beats as shown by auscultation and 24 h-electrocardiogram examination Cough relieved with the treatment of arrhythmia drugs
Herniated cervical intervertebral disc	Chronic cough accompanied by pain in neck, shoulder, or upper back, and numbness or tingling in the arm Herniated cervical intervertebral disc was confirmed with magnetic resonance imaging Cough relieved after treatment of herniated cervical intervertebral disc
Goiter related cough	The diagnosis of goiter is exclusive diagnosis Cough relieved after goiter was treated
Occupational cough	The cough symptoms appear in the workplace and improve after withdrawal from the workplace
Styloid process syndrome	X ray confirmed long styloid process Cough resolved after surgery
Hypereosinophilic syndrome	The chest CT showed scattered nodules in both lungs, cardiac enlargement The eosinophil percentage in the peripheral blood and sputum was markedly increased PDGFRA fusion gene could be positive Cough improved with corticosteroids and response to Imatinib
Catamenial cough	Cough occurred or was worse during menstrual period Other causes were excluded Cough improved after endocrine regulation therapy
Langerhans cell histiocytosis	Chest HRCT showed nodular cystic reticulation, mediastinal lymph node enlargement Diffusion capacity was impaired Bronchoscopic biopsy specimen confirmed the diagnosis
Cardiogenic cough	Cough accompanied with signs related with heart failure, which were indicated by electrocardiography, cardiac ultrasonography Cough relief after treatment directed to heart failure

All subjects presented chronic cough as the sole or predominant symptom.

**Table S2** Spectrum and characteristic of chronic cough in different causes

Variables	Common causes, n=1,055	UC, n=173	OCC, n=330	Rare causes, n=235	P value
Female	51.7	48.0	47.9	54.9	0.317
Age (years)	42.1±13.8*	41.1±12.8*	45.1±14.4 <sup>#</sup>	48.2±15.1 <sup>#</sup>	<0.001
Duration (months)	24 (8 to 84)*	36 (12 to 96)* <sup>#</sup>	36 (12 to 120) <sup>#&amp;</sup>	24 (10 to 72)*	0.001
Non-productive cough	55.1*	72.8 <sup>#</sup>	46.8*	50.0*	<0.001
Timing of cough					
Daily cough	85.0*	91.7*	89.2*	89.3*	0.031
Nocturnal cough	43.5*	35.9*	39.4*	37.9*	0.138
Morning cough	40.3*	46.5* <sup>#</sup>	45.5* <sup>#</sup>	52.7 <sup>#</sup>	0.007
Cough before sleep	54.8*	56.0* <sup>#</sup>	58.2* <sup>#</sup>	66.2 <sup>#</sup>	0.028
Concomitant symptoms					
Laryngeal paresthesia	28.1*	41.1 <sup>#</sup>	32.8* <sup>#</sup>	41.5 <sup>#</sup>	<0.001
Sneezes	40.2*	27.1 <sup>#</sup>	31.1 <sup>#</sup>	34.6* <sup>#</sup>	0.001
Nasal congestion	35.7*	37.6*	31.0*	36.5*	0.356
Postnasal dripping	26.4*	18.8*	21.9*	29.3*	0.044
Runny nose	30.7*	18.9 <sup>#</sup>	27.1* <sup>#</sup>	27.9* <sup>#</sup>	0.017
Throat clearing	35.5*	31.8*	30.7*	34.8*	0.405
Chest tightness	25.9* <sup>#</sup>	25.3* <sup>#</sup>	21.5 <sup>#</sup>	34.1*	0.015
Shortness of breath	26.5*	17.2*	24.3*	28.5*	0.047
Previous diagnosis					
Pharyngitis	44.5*	45.5*	41.6*	39.0*	0.503
Rhinitis	27.6*	18.5*	22.1*	18.8*	0.016
Acute bronchitis	26*	23.7*	25.7*	20.3*	0.453
Chronic bronchitis	32*	32.6*	31.4*	33.5*	0.973
Pneumonia	8.5*	6.1*	10.8*	13.1*	0.129
Previous treatment					
Antibiotic	78.1	78.4	84.8	80.3	0.104
Oral corticosteroids	18.4	26.7	17.0	20.0	0.108
Inhaled corticosteroid	29.2	39.4	29.7	34.8	0.703
Antitussive	73	78.8	74.5	74.6	0.561
Traditional Chinese medicine	67.1*	69.9* <sup>#</sup>	66.7* <sup>#</sup>	56.8 <sup>#</sup>	0.037
Anti-allergic agents	47.4*	52.6*	37.5 <sup>#</sup>	39.7* <sup>#</sup>	0.040

Data were presented as percentage, mean ± SD, or median (IQR). \*, a subset of different causes of chronic cough categories whose column data do not differ significantly from each other at the 0.05 level.; <sup>#</sup>, a subset of different causes of chronic cough categories whose column data do not differ significantly from each other at the 0.05 level; <sup>&</sup>, a subset of different causes of chronic cough categories whose column data do not differ significantly from each other at the 0.05 level. P values for post-hoc test was adjusted with Bonferroni method. OCC, other common causes; UC, unexplained cough.