Guideline of Cough Section

Clinical Practice Guidelines for Diagnosis and Management of Cough—Chinese Thoracic Society (CTS) Asthma Consortium

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Introduction

Cough is the most common symptom in respiratory specialist clinics of tertiary hospitals and outpatient clinics of primary health care facilities. In China, patients with chronic cough account for at least one third of all patients referred to respiratory specialist clinics. Chronic cough without significant abnormal chest radiographic findings is often misdiagnosed as chronic bronchitis or chronic pharyngitis. Misdiagnosis of cough results in unnecessary repetitive testing, such as chest radiographs or computed tomography (CT), and widespread abuse of antibiotics or antitussives with little improvement, and potential adverse effects. Chronic cough impair quality of life badly cause severe economic burden in China (1-5).

To further standardize the diagnosis and treatment of acute and chronic cough, thus providing guidance for clinical practice, the Panel of Chinese Thoracic Society (CTS) Asthma Consortium released the first edition of the Chinese Guidelines for Diagnosis and Treatment of Cough (Draft) in 2005 (6). This document was updated in 2009 (7). The Chinese Cough Guidelines were established based on the evidence of clinical research, expert opinions, and recommendations from the cough guidelines endorsed by the American College of Chest Physicians (ACCP), European Respiratory Society (ERS), Japanese Respiratory Society etc. (8-11). Compared with these guidelines, the Chinese Cough Guidelines vary slightly in structure and content, according to clinical evidence and practice in China. Since the release of the Chinese Cough Guidelines, the management of cough in China has been improved. Recently, there have been significant advances in cough research and increased understanding of the pathogenesis, etiology, diagnosis, and management of cough. To further refine the guidelines and include the latest evidence, in 2014 the CTS Asthma Consortium initiated a task force to revise the 2009 Chinese Guidelines for Diagnosis and Management of Cough. For the first time, evidence-based methodology was adopted according to the requirements for guideline development in China. A comprehensive literature review was undertaken and recommendations were made. This updated revision updated or added the following sections: (I) introduction of evidence-based methodology for guideline development; (II) updated and expanded sections as compared to previous versions; (III) an additional section on the evaluation of cough; (IV) Traditional Chinese Medicine (TCM) for the management

Table 1 Components used in the grading of the quality of evidence and the strength of recommendations

Grade	Description
Quality of evidence	
A	Evidence from high-quality randomized controlled trial (RCT) or systemic reviews/ meta-analyses
B	Evidence from defective RCT, low-quality systemic reviews/meta-analyses, or high-quality observational studies
C	Evidence from non-randomized, case-control, or other observational studies
D	Expert individual opinion
Strength of recommendation	
1	Strong recommendation
2	Weak recommendation
3	No specific recommendation (Insufficient evidence on which to formulate a recommendation)

of cough was added; (V) the etiology and management of chronic cough in children was introduced; (VI) a section on uncommon causes of chronic cough; and (VII) added unexplained cough [refractory cough, cough hypersensitivity syndrome (CHS)].

Introduction of methodology

(I) The target population: patients with cough.

(II) The target users: respiratory specialists from all levels of hospitals, physicians of internal medicine and TCM, general practitioners, pediatricians, and other health-care providers.

(III) Members of the panel: specialists in respiratory medicine, ear-nose-throat, pediatrics, gastroenterology, and TCM; evidence-based medicine professionals, clinical epidemiologists, and medical editors.

(IV) The search database included: (i) English databases: PubMed/Medline, Embase, and Cochrane Library; (ii) Chinese databases: China Biology Medicine disc (CBMdisc), Wanfang Data, China Academic Journals full-text database (CNKI), and Chongqing VIP (CQVIP). The literature search ended with papers published on June 30, 2015. Two independent groups conducted the literature search for each specific clinical issue according to the inclusion and exclusion criteria. An appraisal of the literature using a specifically designed form was performed. Respiratory physicians conducted the preliminary evaluation of the literature. In cases where consensus could not be obtained due to difficulty in literature appraisal, a meeting of the guideline panel was held for critical review and reappraisal. If necessary, the literature search and evaluation would be conducted again.

(V) Quality of evidence and grade of recommendation: The current guideline adopted a grading system for assessing quality of evidence and grading recommendation. The grading system is a combination of the grading system used in the American College of Chest Physicians (ACCP) Guidelines for Diagnosis and Management of Cough [2006] (8,12) and GRADE (grading of recommendations assessment, development, and evaluation) (13) (*Table 1*). The level of evidence was graded in four categories: high, moderate, low, and very low, and presented as A, B, C, and D, respectively. The strength of recommendation was: 1, strong; 2, weak; and 3, no specific recommendation.

The quality assessment of the body of evidence is based on the GRADE approach. Evidence based on randomized controlled trials began with high-quality evidence, but the confidence in the evidence might be decreased for five reasons, including study design limitations, inconsistency of results, indirectness of evidence, imprecision and publication bias. Evidence based on observational studies start with a "low quality" rating, grading upwards may be warranted for three factors (large magnitude effect, dose-response gradient, or plausible confounding which could reduce a demonstrated effect). The quality of evidence across different outcomes as that associated with the critical outcome with the lowest quality evidence. If the evidence was originated from systematic reviews/meta-analyses, the AMSTAR (A MeaSurement Tool to assess Systematic Reviews) instrument was used for assessment. Only Systematic reviews/meta-analyses fulfilling nine or more of the eleven

Table 2 Glossary of terms and list of abbreviations

English abbreviation	English phrase or words
AC	Atopic cough
ACEI	Angiotensin converting enzyme inhibitor
CCIQ	Chronic cough impact questionnaire
CHS	Chronic cough hypersensitivity syndrome
CQLQ	Cough-specific quality of life questionnaire
CST	Cough suppression therapy
CVA	Cough variant asthma
DTT	Dithiothreitol
EB	Eosinophilic bronchitis
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in first second
GERC	Gastroesophageal reflux-related cough
GerdQ	Gastroesophageal reflux disease questionnaire
ICS	Inhaled corticosteroids
LCQ	Leicester cough questionnaire
OSA	Obstructive sleep apnea
PBB	Protracted bacterial bronchitis
PEF	Peak expiratory flow
PIC	Post-infectious cough
PNDS	Postnasal drip syndrome
PPI	Proton pump inhibitor
SAP	Symptom association probability
SPT	Skin prick test
TRP	Transient receptor potential
TRPA1	Transient receptor potential ankyrin 1
TRPV1	Transient receptor potential vanilloid 1
UACS	Upper airway cough syndrome
VAS	Visual analogue scale
VPIC	Viral post-infectious cough

criteria were regarded as high quality systematic reviews/meta-analyses.

The direction and strength of recommendations are determined by all of the evaluation, including the final level for quality of evidence, benefits and harms, patient's values and preferences and use of resource (13). The guideline panel discussed at modified nominal group meetings for each issue or intervention. The decision was made by votes using the modified Delphi method. The voting method included the following rules (14): in areas of continuing disagreement, a recommendation for or against a particular intervention (compared with a specific alternative) required at least 50% of participants who were in favour of, with less than 20% preferring the comparator (the options could be judged equally). Failure to meet this criterion resulted in no recommendation. For a recommendation to be graded as strong rather than weak, at least 70% of participants were required to endorse it as being strong.

(VI) Declaration of conflict of interest: In the process of compiling the guidelines, panel members participating in the seminars signed a written statement declaring any conflicts of interest with pharmaceutical companies.

(VII) Estimation of favorable and unfavorable factors in the implementation of guidelines: (i) favorable factors: (a) with the popularization and in-depth understanding of evidence-based medicine among Chinese physicians specializing in respiratory diseases, there is an increasing demand for high-quality evidence-based clinical practice guidelines; (b) cough is the most common complaint of patients seeking medical attention; however, many patients are misdiagnosed and do not receive proper treatment. Therefore, their quality of life is badly impaired with an increase in economic burden. This evidence-based guideline for the diagnosis and management of cough satisfies the requirement of clinical practice; (c) the application of the previous two versions of Chinese cough guidelines has established a well-recognized foundation for the utilization of this revision. (ii) Unfavorable factors: (a) due to different understanding of the importance of guidelines and recommendations among physicians of different levels, the promotion, propagation, and implementation of the guidelines in community medical facilities may require continuous efforts; (b) because some diagnostic tests, including the bronchial provocation test, induced-sputum test for differential cell count, and 24-h esophageal pH-multi-channel impedance monitoring, are

not available in many hospitals, the potential for application of the guidelines may be limited.

(VIII) Time to update: to be revised every 3–5 years.

(IX) Members of guidelines: panel, secretariat, and review groups: see the list at the end of full text in detail.

(X) This guideline includes an additional Glossary of Terms and List of Abbreviations to facilitate reading (*Table 2*).

Definition, classification, and pathogenesis of cough

Cough is a defensive reflex for clearance of excessive secretions and foreign bodies from airways. However, severe cough frequently affect quality of life badly. Cough is classified into three types based on the duration: acute, subacute, and chronic cough. Acute cough is defined as cough lasting for <3 weeks, subacute cough lasts 3–8 weeks, and chronic cough persists for >8 weeks (6). Cough can also be categorized as dry and wet cough, and a wet cough is defined as sputum volume >10 mL per day. Different types of cough have a spectrum of different underlying causes. Based on chest radiography, chronic cough can be further classified into two subtypes: (I) presence of pulmonary lesions on radiography (for example, pneumonia, tuberculosis, and bronchopulmonary carcinoma), and (II) lack of overt identifiable abnormalities on radiography. This guideline focus on the latter subtype. In China, a majority of patients with chronic cough are 30–40 years old without significant gender preponderance; however, in European and American countries, most patients with chronic cough are 50–60 years old, with a significantly higher incidence in women than in men (15). Chronic cough is related to air pollution (16-19).

The involuntary cough reflex is involved in five sections: the peripheral receptors, vagal afferent nerves, central cough neurons, efferent nerves, and effectors (diaphragm, throat, chest, and abdominal muscles). An effective cough can be induced by stimulation of the irritant receptors of the trachea, bronchopulmonary C fibers, or the mechanically sensitive, acid-sensitive myelinated sensory nerves (Aδfibers). When vagal nerve branches distributed in the upper airway, throat, and esophagus are stimulated, cough can be induced (20). Cough nerve centre is located in the medulla, which is regulated by the cerebral cortex. Cough hypersensitivity is an important pathophysiological mechanism of chronic cough (21-23) related to the activation of transient receptor potentials (TRP), including TRPV1 and TRPA1, and airway inflammation, neural pathways, and nerve center (24-28).

Chronic cough can results in a lot of concomitant disorders, such as incontinence, syncope, insomnia, and anxiety, which involve the cardiovascular, digestive, nervous, urinary, and musculoskeletal systems (2,29).

Medical history and laboratory tests

A thorough medical history and physical examination are important for physicians to develop a differential diagnosis, select laboratory tests, make a tentative diagnosis and empiric therapy (30).

Medical history

Information regarding the duration of cough; phase; characteristics; triggers; effect of altering body position; and concomitant symptoms should be identified. Sputum volume, purulence and characteristics; smoking history; occupational or environmental exposure; medication history, including angiotensin converting enzyme inhibitors (ACEI) or other drugs, can indicate the diagnosis (7) (1D). Occupational cough should be considered when patient has an occupational exposure history. Acute cough is often attributable to the common cold and acute tracheobronchitis, while subacute cough is the result of post-infectious cough (PIC). The timing of cough provides additional diagnostic information. Cough variant asthma (CVA) should be considered for patients with predominantly nocturnal cough. (31,32) (2B). A dry cough indicates a non-infectious cough, while a wet cough is more commonly seen in patients with an infectious cough. Respiratory infectious disease should be considered in patients with a large amount of sputum production or purulent sputum (7,32) (2C). Chronic bronchitis is characterized by mucoid sputum and the cough is usually aggravated in the winter and spring. Tuberculosis, bronchiectasis, and lung cancer should be considered with bloody sputum or hemoptysis. Allergic rhinitis and asthma-related cough should be carefully excluded in patients with a personal or family history of allergy. Upper airway cough syndrome (UACS) should be considered in patients with nasal congestion, runny nose, sneezing, postnasal drip, or post-laryngeal reflux (32) (2C). In the presence of acid regurgitation, belching, or retrosternal burning, gastroesophageal reflux-related cough (GERC) should be considered (32,33) (2C).

Physical examination

Physical examination focuses on the somatotype, nose, larynx, throat, trachea, and lungs; lung sounds; and presence/absence of wheezing, moist rales, and crackles. The possibility of obstructive sleep apnea (OSA)- or GER-related chronic cough should be considered in patients with obesity. A majority of patients with chronic cough have normal findings on a physical examination. Expiratory wheezing suggests the possibility of asthma. Sounds of "velcro opening" at the lower lung lobes may indicate interstitial lung diseases. Inspiratory wheezing may suggest central airway tumor or bronchial tuberculosis. Cardiac signs, including enlargement of heart border, premature beats, and murmurs should also be evaluated.

Relevant additional testing

The main tests include chest imaging, induced-sputum cytology, spirometry, the bronchial provocation test, fractional exhaled nitric oxide (FeNO) measurement, and 24-h esophageal pH-multi-channel impedance monitoring. (I) Imaging: chest radiographs are routinely recommended for chronic cough (2D). The flow chart for the diagnosis of chronic cough should be followed (see supplementary file 1). If an obvious abnormality is observed on plain films, additional investigation is selected based on the characteristics of the lesion. Chest CT can be used to detect lesions anterior and posterior to the mediastinum; small pulmonary nodules; thickening and calcification of trachea; stenosis of the trachea; and enlargement of mediastinal lymph nodes. The uncommon conditions can be identified by radiography, including broncholithiasis, relapsing polychondritis, and bronchial foreign body can be identified by CT (1D). High-resolution CT is helpful for the early diagnosis of interstitial pulmonary diseases and atypical bronchiectasis. If sinusitis is suspected, sinus CT is preferred (34) (2D). Repeated radiographs within a short time span should be avoided. (II) Pulmonary function tests: pulmonary function tests include pulmonary ventilation tests and the bronchial provocation test. These tests are valuable for the etiologic diagnosis of chronic cough and should be routinely used (35-37) (1B). Positive findings on the cough provocation test are important in the diagnosis of CVA. Hospitals unable to perform the cough provocation test can monitor the average peak expiratory flow (PEF) variation overtime (38,39) (1B). An average daily PEF variation of >10% suggests CVA. (III) Induced sputum test: induced sputum test is a safe, well-tolerated, non-invasive method for the etiologic diagnosis of chronic cough and airway inflammation (40-43) (1C). Eosinophilia identified by induced sputum is suggestive of eosinophilic bronchitis (EB), and can also be seen in patients with CVA (40) (1C). Induced sputum cytology can be used to monitor response to inhaled corticosteroids (ICS) in patients with chronic cough (41-43) (1C). The use of 3% hypertonic saline via ultrasonic nebulizer is recommended, but repeated induced sputum tests within 48 hours should be avoided (44-46) (1C) (for details please refer to supplementary file 2). (IV) FeNO measurement: this is a novel non-invasive technology for the diagnosis of airway inflammation. An increase in FeNO (>32 ppb) suggests eosinophilic inflammation or corticoid-sensitive cough (47-54). However, the sensitivity is not high when FeNO measurement is used for screening of eosinophilic inflammation. Approximately 40% of patients with increased numbers of eosinophils have normal FeNO (52-56) (2C). (V) Allergy skin prick tests and serum IgE test: these tests can identify patients predisposed to allergen sensitization and identify specific allergens. They may be useful in the diagnosis of atopic diseases (e.g., allergic rhinitis and atopic cough). Approximately 60–70% of CVA patients and 30% of EB patients are predisposed to allergen sensitization (31,57). (VI) The 24-h esophageal pH-multi-channel impedance monitoring: this is the most commonly useful method of diagnosing gastroesophageal reflux. Dynamic monitoring measures changes of esophageal pH, the number of times the esophageal pH is <4, the longest duration of reflux, and the percentage of time for which the esophageal pH is <4. The grade of reflux is represented as the DeMeester scores. Cough should be recorded in a real-time manner during the monitoring, so that the symptom-associated probability (SAP) between reflux and cough can be calculated (see supplementary file 3 for methods). The non-acid reflux, such as weak acid or weak alkaline reflux, can be detected by esophageal impedance monitoring (2C). (VII) Bronchoscopy: bronchoscopy is not routinely recommended for chronic cough except for the diagnosis is not confirmed by routine tests or in patients with a poor response to the treatment for common causes of cough. Bronchoscopy can be used for the diagnosis or exclusion of uncommon airway conditions associated with cough, including lung cancer, foreign body, tuberculosis, and relapsing polychondritis (10,58-61) (2C). (VIII) Other examinations: peripheral eosinophilia is indicative of atopic diseases, but in most patients with CVA and EB,

the peripheral eosinophil counts are within the normal ranges. Severe peripheral eosinophilia (eosinophil count >20%) indicates the possibility of parasitic infections or eosinophilic pneumonia.

Diagnostic principles and algorithm of cough

Refer to section VI and section VII for the diagnostic flow chart of acute and subacute cough.

The etiological diagnosis of chronic cough should follow the principles as described below (5) (1D): (I) Attention should be paid to the medical history, including ear, nose, and throat, and digestive tract diseases, occupational and environmental exposure, smoking and medication history. The diagnosis can be determined if clinical signs are alleviated after being away from occupational or environmental exposure. (II) Selecting investigations, from simple to complex, based on the medical history. The most common causes of chronic cough are EB and CVA. Together they are responsible for approximately 50% of chronic cough cases (62). Spirometry, the bronchial provocation test, and induced-sputum cytology are recommended as the initial tests for chronic cough (7,40,63) (2B). The measurement of FeNO is recommended as to supplement of the induced sputum test (47-53) (2C). The 24-h esophageal pH-multi-channel impedance monitoring is an important method for the diagnosis of GERC, but it is recommended as the second-line test because it is time-consuming and costly (2D). (III) The common causes of cough, including UACS, CVA, EB, GERC, and atopic cough (AC) should be initially considered as the most possible etiology for chronic cough (37,62,64-69). Bronchoscopy is valuable in the diagnosis of uncommon causes of chronic cough. (IV) Diagnosis and management can be implemented simultaneously or sequentially. If certain tests are unavailable, the treatment should be based on the clinical characteristics and the therapeutic response (30). Further evaluation should be considered if patients fail to respond to the treatment (2C). With typical symptoms of rhinitis, sinusitis, or postnasal drip, treatment for UACS should be initially prescribed. If patients present with symptoms related to gastroesophageal reflux cough after eating food, treatment for GERC should be given empirically. (V) Response to the treatment is the prerequisite for confirming etiologic diagnosis. When the cough is partially relieved, the factors affecting the effectiveness of treatment or other causes of chronic cough, such as UACS concurrent with GERC, CVA, or EB, GERC concurrent with EB or CVA should be evaluated (2C). (VI) When the treatment is ineffective, the following factors should be evaluated: diagnosis, therapeutics, and occupational or environmental exposure (2C).

Flow chart for the etiologic diagnosis of chronic cough (see Supplementary file 1)

Assessment of cough

The assessment of cough includes: the visual analogue scale (VAS), cough symptoms score, quality of life questionnaire, cough frequency monitoring, and the cough provocation test. These tests are used to monitor the disease status and treatment efficacy (29,70).

The VAS scoring system

Patients mark a point on a straight line corresponding to their perception of the severity of cough. The score ranges from 0–10 cm (0–100 mm), with 0 representing minimal severity and 10 representing extreme severity. Compared with the cough symptoms score, the intervals between grades with the VAS are smaller, which is helpful for longitudinal comparison before and after treatment (29,70,71).

Coughing score

This is a quantitative scoring system of cough used to assess the severity of cough and efficacy of treatment. Daytime and nighttime scoring is done, however it may be difficult to discriminate between grades (29,70,71) (see *Table 3* for details).

Quality of life questionnaire

The Chronic Cough Impact Questionnaire (CCIQ), Cough-Specific Quality of Life Questionnaire (CQLQ), and Leicester Cough Questionnaire (LCQ) are specific for chronic cough and demonstrate good reliability, validity, and responsiveness. These questionaires are important in the assessment of cough severity and efficacy of treatment (29,71-81). The Chinese version of the LCQ is recommended to assess cough-related quality of life (77) (1A).

Coughing frequency monitoring

The cough symptoms score, VAS, and quality of life questionnaire are subjective assessment tools. Cough

Table 3 Scoring of cough

Score	Daytime cough symptom score	Nighttime cough symptom score
0	No cough	No cough
1	Occasional, transient cough	Transient cough when falling sleep or occasional cough during the night
2	Frequent cough, slightly influencing daytime activities	Cough slightly influencing sleep
3	Frequent cough, significantly influencing daytime activities	Cough significantly influencing sleep

frequency monitoring is used for evaluation of cough severity and treatment efficacy (82-84). There is diversity in tolerance of patients to coughing, and cough frequency does not definitively correlate with cough severity. Since cough frequency monitors are not available in China, their clinical applications are limited.

Cough provocation test

This test is used to assess therapeutic efficacy and study cough mechanisms. It is not a routine test in clinical practice. Patients inhale nebulized aerosol particles, which stimulate the cough receptors. Capsaicin is commonly used for the cough provocation test (see supplementary file 4 for test methods). The cough sensitivity is expressed as the cough threshold C5, defined as the lowest concentration of capsaicin inducing ≥5 coughs (C5).The concentration that induces ≥2 (C2) or ≥5 (C5) coughs is an indicator of cough sensitivity. In China, the reference value for C5 in the capsaicin provocation test in normal subjects is ≥125 mol/L (22). Increased cough sensitivity is an important characteristic of chronic cough, and is frequently observed in AC, GERC, UACS, CVA etc. (23). In addition, significantly increased cough sensitivity is identified in viral post-infectious cough (VPIC) (21,85). The cough provocation test is safe, well tolerated, and repeatable, and is useful in identifying patients with cough hypersensitivity, and to quantitatively evaluate chronic cough. However, the cough provocation test cannot be used to assess cough frequency and severity (21,85-89). In Europe and USA, women have higher cough sensitivity than men (90,91) .

Diagnosis and management of acute cough

A thorough evaluation of medical history, physical examination, and specific diagnostic tests can be used to exclude severe diseases as a cause of acute cough. Acute cough may be an early sign of serious disease, including acute myocardial infarction, left heart failure, pneumonia, pneumothorax, pulmonary embolism, and foreign body aspiration (92-97). The common cold, acute tracheobronchitis are the common causes of acute cough. Exacerbation of asthma, chronic bronchitis, or bronchiectasis may lead to acute cough. An increasing proportion of acute cough is related to occupational or environmental exposures.

Common cold

A viral infection is the cause of the common cold (96,98,99). The diagnosis is based on history and physical examination, viral culture, and/or serological testing; chest imaging is not necessary (96,100) (1D). In addition to cough, nasal discharge, sneezing, nasal congestion, postnasal drip, throat irritation and clearing the throat are common symptoms associated with the common cold. Systemic symptoms are not common (94,98-103); this is in contrast to the flu that is associated with fever and myalgia as well as cough (101-104).

Symptomatic treatment is used for the common cold. (I) Antibiotics are infective in decreasing the duration or relieving symptoms. Antibiotics may lead to concurrent adverse effects. Antibiotics are not recommended for patients with the common cold (96,105-109) (1A). (II) Decongestants: decongestants in adults can rapidly relieve nasal congestion with minimal adverse side effects. (III) Antihistamines: the use of first-generation of antihistamines as a single therapeutic agent is not recommended due to insufficient of clinical benefits (110-113) (1A). Combined treatment with decongestants and first-generation antihistamines (brompheniramine maleate and pseudoephedrine) can significantly improve cough, sneezing, and nasal discharge in adult and adolescent patients (114-116) (2A). However, adverse reactions should be monitored. Pseudoephedrine in pediatric patients should be used with caution (110,112,113). (IV) Antipyretics and analgesics: these medicines are prescribed for symptomatic relief of fever, sore throat, and muscular aches in patients

with the common cold (1A). Acetaminophen is the most widely used antipyretic and analgesic agent in clinical practice. Non-steroid anti-inflammation drugs (NSAIDs) are not recommended for patients without fever, headache, or muscular ache (100,117-123) (1A). (V) Antitussive: for patients with severe cough, central or peripheral acting antitussive agents can be used. Central-acting agents (i.e., dextromethorphan, codeine) have limited efficacy to suppress cough in patients with the common cold and should not be used alone (100,111,113,124) (2D). A combination of first-generation antihistamines and an antitussive agent is recommended for cough due to the common cold (100,113,125-130) (1A). (VI) Ipratropium bromide: nasal spray can improve runny nose and sneezing in adult and adolescent patients, however, adverse events including nasal dryness, nasal congestion, and epistaxis may occur (131,132) (2A). Although TCM treatment may be useful in treating the common cold, high-quality clinical evidence are lacking (133,134).

Acute tracheobronchitis

Acute tracheobronchitis is characterized by an inflammation of tracheobronchial mucosa due to biological or non-biological factors. The most common etiology is a viral infection, including rhinovirus and influenza virus; bacterial etiology is less common (99,135-141). Cold air, dust, and irritant gases can cause acute tracheobronchitis. Most cases are self-limited, however, infants and the elderly patients may develop refractory bronchitis.

Clinical manifestations

Symptoms related to upper respiratory tract infection, such as fever, headache, muscle aches and pains, sore throat, rhinorrhoea, sneezing are noted initially. Cough become progressively severe, with or without sputum production. Purulent sputum indicates bacterial infection. Systemic symptoms can resolve in several days, while cough and sputum production may last for 2–3 weeks. No obvious abnormalities or only slight increase of lung markings can be observed in chest radiographs. Coarse breath sounds, with wet or dry rales, can be heard in both lung fields.

Diagnosis and differential diagnosis

The diagnosis is established by clinical manifestations. Viral culture, serology, and sputum tests are not required (136,142-144) (1D). Acute tracheobronchitis should be considered for patients with cough within 3 weeks and with or without sputum production, when the common cold, pneumonia, asthma, and acute exacerbation of chronic obstructive pulmonary disease (COPD) have been excluded (96,142,144-149) (1D). In patients with a tentative diagnosis of acute tracheobronchitis, the likelihood of developing pneumonia is low if the heart rate is ≤100 beats/min, respiratory rate ≤24 times/min, body temperature of ≤38 ℃ and the chest radiograph is normal (96,147,150-152) (3C).

Treatment

Symptom-targeted therapy is the main principle of treatment. Adequate use of antitussive agents should be considered for patients with severe dry cough, and expectorants or mucolytic agents can relive cough in patients with difficulty expectorating sputum (153-158) (1B). Sustained-release guaifenesin can improve symptoms related acute respiratory infection (153,155,156) (2A). Data from lots of studies showed that it is not necessary to use antibiotics regularly due to the unclear efficacy (96,105,107,147,159-167) (1A). For patients with purulent sputum, antibiotics are recommended (1D). For patients with acute bronchitis, if antibiotics are not prescribed, the rationale should be explained since patients may request antibiotic treatment due to their previous experience and expectations (168-174) (1B). When there is evidence of a bacterial infection, such as purulent sputum or increased level of peripheral leukocyte count, antibacterial agents are selected based on the presumed pathogens and the results of antibiotic sensitivity tests. Prior to obtaining the culture and sensitivity results, oral antibiotics such as β-lactams and quinolones can be used (7). Regular use of β_2-agonist is not necessary, however, for adult patients with acute bronchitis and concomitant asthma, β_2-agonist may be beneficial (175) (2A). Currently no high-quality data are available to verify the safety and efficacy of TCM in the treatment of acute bronchitis (176,177).

Diagnosis and management of subacute cough

The most common cause of subacute cough is PIC, followed by CVA, EB, and UACS (178,179) (1B). For management of subacute cough, the first step is to determine if the cough is secondary to a previous respiratory infection and if empirical treatment is required. If the treatment is ineffective, other causes should be considered using the diagnostic process for chronic cough. A diagnosis of PIC is made on the basis of a history of the common cold, upper

respiratory tract infection, and protracted cough (178). The bronchial provocation test and induced sputum test are recommended if available (2C). A few cases of "refractory PIC" may be EB, CVA, and GERC (178).

If the cough persists for 3–8 weeks after the acute symptoms of respiratory infection resolve, and the patient has an irritating dry cough or a cough with a small amount of mucoid sputum, and normal chest radiograph (103,179-181), then PIC should be considered. Viral infection is the most common trigger of PIC. Patients with a history of PIC and cough hypersensitivity are more predisposed to PIC (178,180).

PIC is usually a self-limiting disease. However, a few patients present with refractory cough and may progress to chronic cough. Post-viral infection cough may not require antibacterial treatments. For the patients with severe cough, antitussives, antihistamines, and decongestant are recommended for short-term use (2C). Methoxyphenamine is effective for PIC (182) (2C). Since montelukast is not recommended for PIC (183) (2B). The efficacy of ICS for the treatment of PIC is not certain, therefore not recommended (184,185) (2B). In TCM it is believed that PIC is caused by "the evil wind invading the lung, causing an obstruction of qi," therefore the treatment should follow the principles of "dispelling the wind and opening the inhibited lung-energy," and "antitussive and relieving the sore throat." The Suhuang Zhike capsules, comprised of Chinese ephedra, purple perilla leaf, lumbricus, folium eriobotryae, and perilla fruit is an effective treatment for PIC (186) (2C).

Protracted cough is commonly caused by *Mycoplasma pneumoniae* or *Chlamydia pneumoniae*. *Haemophilus influenzae* and *Streptococcus pneumoniae* are more common pathogens in infants, the elderly, and susceptible patients (187-189). Serological antibody test is the most effective method for diagnosing mycoplasma or chlamydia infection. Serology is helpful for early diagnosis and is routinely used in clinical settings (190,191) (1C). Serum cold agglutinin titers of ≥1:64 or mycoplasma IgM antibody titer with four-fold increase from the acute to the recovery phase indicates a recent infection with *M pneumonia*e (190) (2D). A serum chlamydia antibody titer elevation with four-fold increase from the acute to the recovery phase or the antibody titer of IgM ≥1:16 or IgG ≥1:512 at any single time point are helpful to verify chlamydia infection. Macrolides or quinolones are effective for protracted cough caused by the *M pneumonia*e and *infection pneumonia* (7) (2C). Amoxicillin or cephalosporin can be used for 2–3 weeks to treat protracted cough due to infection with Gram-positive cocci (192,193) (2B).

For adolescent and adult patients, pertussis ("whooping cough") should be considered when the *Bordetella pertussis* antibody titer is increased (194-196) (2C). Typical symptoms of pertussis, such as paroxysmal cough, vomiting after coughing, and inspiratory wheezing, are of limited value in the clinical diagnosis of pertussis (197,198) (2A). Anti-pertussis immunoglobulin G (anti-PT-IgG), polymerase chain reaction (PCR), and bacterial culture are helpful in the diagnosis of pertussis (199-204) (2C).

Once pertussis is diagnosed, early treatment with macrolides should be initiated. With treatment during the catarrhal phase, 1–2 weeks before coughing paroxysms occur, symptoms may be lessened. Although treatment cannot affect the natural progress of pertussis, it can reduce the severity of the disease (11,205) (1B). Antibiotics are not recommended for patients with pertussis in the non-catarrhal phase (protracted phase) (206) (1A). Corticosteroids, β_2-adrenergic receptor agonists, pertussis specific immunoglobulins, and antihistamines are not recommended (207) (1A).

Diagnosis and management of chronic cough due to common etiology

Common causes of chronic cough including CVA, UACS, EB and GERC should be initially considered when diagnosing chronic cough (1A); AC is also a common cause of chronic cough. The common causes account for 70–95% of cases of chronic cough (62,64,66-69). Since a majority of patients with chronic cough are not related to infection (208), antibiotics should be not be used (1C).

Upper airway cough syndrome (UACS)—postnasal drip syndrome (PNDS)

PNDS is characterized by cough, which may result from the direct or indirect stimulation on the cough receptors in the postnasal and pharyngeal areas. Because it is not clear that upper airway-related cough is caused by direct stimulation of postnasal dripping or stimulation on upper airway cough receptors by inflammation, the ACCP Guidelines for Diagnosis and Management of Cough [2006] suggested using the term upper airway cough syndrome (UACS) to replace PNDS (209). However, this change in terminology remains controversial (210). Since PNDS is more intuitive and visual in a certain proportion of patients with typical

postnasal dripping, this guideline continues to use PNDS.

UACS/PNDS is one the most common causes of chronic cough, generally related to rhinitis and sinusitis. The diagnosis of UACS/PNDS are confirmed by the effectiveness of empirical treatment (62,211-213) (1B). In addition to nasal diseases, UACS/PNDS may be related to throat and pharynx diseases, including chronic laryngopharyngitis and chronic tonsillitis (7,211). Chronic cough may also be caused by cough hypersensitivity (214,215).

Clinical manifestation

(I) Symptoms: in addition to cough and sputum production, other symptoms include nasal congestion, excessive nasal secretions, frequent throat clearing, post-laryngeal mucus adherence, and postnasal dripping. Allergic rhinitis can also present with nasal itching, sneezing, and watery nasal mucus production. Rhino-sinusitis usually presents with nasal congestion, purulent nasal mucus, and can be accompanied occasionally with facial ache/swelling, and abnormal sense of smell (216). (II) Signs: the common signs of allergic rhinitis include pale or swollen nasal mucosa, and clear or sticky mucus in the nasal tract and in the bottom of nasal cavity. For non-allergic rhinitis, the nasal mucosa shows hypertrophic or congestive changes, and the oropharyngeal mucosa may have "cobblestone-like changes" or post-pharyngeal mucus adherence. (III) Auxiliary examinations: sinus imaging may reveal signs of chronic sinusitis, including mucosal hypertrophy and fluid within the sinus cavity. Seasonal cough suggests the possibility of contact with specific allergen (such as flower pollen, dust mites) and the allergen skin prick test is helpful for the diagnosis. Chronic sinusitis can be divided into subtypes based on etiology: viral, bacterial, fungal, and allergic sinusitis. Nasal polyps may occur with UACS/PNDS. If sinusitis is suspected, CT imaging should be initially performed, and nasal endoscopy, allergen skin prick tests, and immunological tests should be selected when necessary.

Diagnosis

The etiological causes of UACS/PNDS can involve several conditions of the nose, sinus, pharynx, and throat and multiple nonspecific symptoms and signs. Diagnosis should be made based on the history, physical examination, and tests. Effective treatment to the underlying disease, following by exclusion of lower airway diseases or GERC is recommended. The criteria for diagnosing UACS/PNDS are (6) (2C): (I) paroxysmal or persistent cough, often in the daytime and rare after sleep; (II) history and clinical manifestations of nasal and/or throat conditions; (III) auxiliary tests supporting nasal and/or throat conditions; (IV) cough improve after specific therapy. Treatment should be determined based on potential conditions related to UACS/PNDS.

Treatment

(I) Etiological therapy: (i) for non-allergic rhinitis and the common cold, first-line treatment consists of the first-generation antihistamines and decongestants (1A), which are efficacious in most patients within several days to two weeks; (ii) intranasal ICS, including budesonide, fluticasone propionate and betamethasone acetate, and oral second-generation antihistamines is used for allergic rhinitis (217) (1A). Second-generation antihistamines include loratadine, desloratadine, and desloratadine citrate disodium. If second-generation antihistamines are not available, first-generation antihistamines can be used with the similar clinical response except for the greater drowsiness. Leukotriene receptor antagonists are effective to allergic rhinitis (218,219) (1A). For patients with severe allergic rhinitis that fails to respond to routine treatment, immunological therapy to specific allergens may be effective. However, immunological therapy require a longer time to demonstrate effectiveness (217,220,221) (2B). (iii) Chronic sinusitis: (a) bacterial culture of nasal secretions in patients with chronic sinusitis primarily identify *Staphylococcus aureus*, *Staphylococcus epidermis*, and *Streptococcus pneumonia* that are generally colonized bacteria related to acute onset of disease. Moreover, culturing bacterial colonies can result in the formation of bacterial biofilms (222,223). In general, bacterial sinusitis is caused by a mixed infection, and broad-spectrum antibiotic therapy is necessary. The antibacterial spectrum should cover Gram-positive, Gram-negative, and anaerobic bacteria. For patients with acute onset, the therapeutic duration should be no less than 2 weeks, and for patients with chronic diseases treatment should be longer than 2 weeks. Amoxicillin/clavulanic acid, cephalosporins, or quinolones are the most commonly used antibiotics (5). (b) Evidence to support the efficacy of long-term low-dose macrolides for chronic sinusitis treatment is limited (224,225). Long-term treatment with macrolides are not recommended (3B). (c) Combined regimens with nasal ICS for more than 3 months are recommended. For patients with chronic sinusitis and coexisting nasal polyps, ICS can be used to avoid unnecessary operation (226) (1A). Sequential

treatment with ICS following oral steroids has better efficacy than ICS alone (227) (2A). d. It is uncertain whether surgical or medical treatment has a better response (228). However, when medical treatment is not satisfactory, nasal endoscopic surgery can be considered (229) (2B). (II) Symptom-targeted treatment: (i) local decongestants can relieve the congestion and swelling of the nasal mucosa and help drainage of secretions, and alleviating the nasal congestion. However, long-term use is not recommended because of the potential to develop medicamentous rhinitis. The therapeutic course of nasal decongestant spray is less than 1 week (230-233) (1B). The combination of first-generation oral antihistamines plus decongestants is recommended for 2–3 weeks (234-238) (2D). (ii) Mucolytics (carbocisteine/erdosteine) may be beneficial for chronic sinusitis (239-241) (2B). (iii) Nasal washing with normal saline can provide an effective therapy for chronic nasosinusitis and chronic rhinitis (242-246). Avoidance or reduction of the exposure to allergens is helpful to relieve the symptoms of allergic rhinitis.

CVA

CVA is an atypical form of asthma and one of the most common causes of chronic cough (37,64,66-69). It presents with cough as the predominant or sole symptom. There is no wheezing or dyspnea, expect to bronchial hyperresponsiveness. A multicenter prospective study showed that CVA accounted for 33% of chronic cough in China (62). In some patients, cough may be the sole or predominant symptom despite significant impairment in lung function. Cough may become the predominant symptom after wheezing has improved in classic asthmatics (247).

Clinical manifestation

Patients have severe, irritating dry cough, particularly at night or early morning (32). The patients are sensitive to cold air, dust, odors, and smoke, but these factors alone can trigger other causes of chronic cough (32).

Diagnosis

Diagnosis is based on history, physical examination, the bronchial provocation test, and the response to asthmatic treatment. Responding well to bronchodilators is an important feature of CVA. However, a few CVA patients (approximately 30%) are not responsive to bronchodilators alone (248,249) and the response to bronchodilators is not necessary as a diagnostic criterion of CVA (2B). Average PEF variation can be selected for diagnosis, if the bronchial challenge test is not available. Sputum eosinophilia and elevated FeNO level suggest a diagnosis of CVA (40,47,50,53).

The following diagnostic criteria for CVA are recommended (1A):

(I) Chronic cough, usually with irritating cough occurring during the night;

(II) Positive bronchial challenge test (fall in FEV_1 from baseline of ≥20% with 12.8 micromole of methacholine or with 7.8 micromole of histamine), or average daily diurnal PEF variability ≥10% over 2 weeks, or positive bronchodilator reversibillity test (increase in FEV_1 ≥12% and 200 mL from baseline, 10–15 minutes after 200–400 mcg albuterol or equivalent);

(III) Cough resolved after asthma treatment.

Treatment

The therapeutic principles for CVA are the same as those for typical asthma. (I) Combined treatment with ICS plus bronchodilators can improve the cough more rapidly and effectively than treatment with ICS or a bronchodilator alone (250,251). A combination of ICS and bronchodilator (β_2 receptor agonist), such as budesonide/formoterol and fluticasone/formoterol, is recommended (1B). The treatment should last for more than 8 weeks, and in some patients, long-term treatment may be required (2D). (II) A short-term oral corticosteroid (10–20 mg/d, for 3–5 days) is recommended for patients refractory or less responsive to ICS treatment, or in patients suffering from severe inflammation of the airway (2C). If patients are not responsive to oral corticosteroids, the patient should be evaluated again. A false positive provocation test or the existence of other diseases, such as early-stage eosinophilic granulomatosis with polyangiitis and GERC, should be considered. (III) Leukotriene receptor antagonists are effective in improving cough, airway inflammation, and the quality of life (252-256) (2B). For a minority of patients refractory to treatment with ICS, leukotriene receptor antagonists may be effective. However, the treatment course and effects of inhibition on airway inflammation need to be further studied. (IV) In TCM, CVA is caused by "the evil wind invading the lungs", so the treatment should follow the principles of traditional medicine in "dispelling the wind and opening the inhibited lung-energy" and "antitussive and reliving the sore throat."

The Suhuang Zhike capsule is effective for treating CVA (257) (2B).

Prognosis

About 30–40% patients with CVA will develop typical asthma. A longer duration of disease, higher airway hyperresponsiveness, and higher level of eosinophils in induced sputum are the risk factors for developing classic asthma. Long-term use of ICS may be helpful to prevent development into typical asthma (258-260) (2B).

EB

EB is one of common causes of chronic cough and accounts for 13–22% of chronic cough (37,65,66,69). Characteristics of EB include chronic eosinophilic inflammation of airway, inflammation of the central airway, and with more infiltration of mast cells which is located more in the airway smooth muscle cells. These pathologic features may explain why there is a lack of bronchial responsiveness in EB. The degree of inflammation and level of oxidative stress are lower than in patients with CVA (261-264). Approximately one-third of the patients have concurrent with allergic rhinitis (57,65).

Clinical manifestations

Patients present with dry cough or a little mucoid sputum that is more common during the day. Patients are often sensitive to smoke, dust, odors, and cold air, which induce cough. Patients do not have wheezing or dyspnea. The pulmonary ventilation function and variations of PEF are normal without signs of airway hyperresponsiveness.

Diagnosis

EB shares similar clinical features to CVA. Sputum eosinophilia is the key to diagnosis, with eosinophils being more than 2.5% of cells in sputum (63). The sensitivity of FeNO is not high for diagnosis of EB, but FeNO of >32 ppb suggests eosinophil-related chronic cough (e.g., EB or CVA) (48,50,52,54) (2C). Exposure to ocyanic acid and chloramine in flour can induce EB (265-270) (2C). Occupational factors, the history, eosinophil counts in induced sputum (or bronchoalveolar lavage fluid), airway responsiveness, and the response to steroid treatment should be considered when diagnosing EB, (1B). The following diagnostic criteria are recommended: (I) chronic cough, presenting as irritating dry cough or with bit amounts of sticky sputum; (II) unremarkable chest radiographic findings; (III) normal pulmonary ventilation function, a lack of airway hyperresponsiveness, and normal average weekly PEF variation; (IV) sputum eosinophil count ≥2.5%; (V) exclusion of other diseases with eosinophilia; (VI) cough improves after treatment with corticosteroids.

Treatment

EB patients respond well to corticosteroids. Cough will be resolved or relieved shortly after the treatment. The use of ICS is the first therapeutic option, and treatment course with more than 8 weeks is recommended (2C). Initial treatment is a short course of oral prednisone (10–20 mg/d for 3–5 days) (7) followed by ICS. If the patients show no response to the treatment with low-dose corticosteroids, systemic diseases related to eosinophilia, including hypereosinophilic syndrome and eosinophilic granulomatosis with polyangiitis, should be considered.

Prognosis

Over half of the EB patients will relapse after treatment. Patients with concurrent rhinitis and persistent eosinophilic inflammation are at risk for recurrence (57). Previous reports showed that a small proportion of patients with EB develop chronic airway obstructive diseases (asthma or COPD) (271-273). A recent study with a large sample and long-term follow-up demonstrated that only 5.7% patients with EB would develop asthma, suggesting that EB might be a distinct disease and not an early stage of asthma, COPD (57).

GERC

GERC is a special kind of gastroesophageal reflux disease that presents with chronic cough as the sole or predominant symptom. Studies have showed that GERC is a common cause of chronic cough (35,62,64-67). The prevalence of patients with GERC is lower in China than that in Western countries. The pathogenesis of GERC involves microaspiration, esophageal-bronchial reflux, esophageal motility dysfunction, autonomic nervous system dysfunction, or neurogenic airway inflammation (274-277). Esophageal-bronchial reflux plays an important role in GERC. In addition to gastric acid reflux, cough in some patients may be related to abnormal nonacid reflux that is a weakly acidic or alkaline reflux, such as bile reflux.

Clinical manifestations

Apart from cough, 25–68% of patients with GERC have

classical reflux symptoms, such as regurgitation, heartburn, and belching. However, cough may be the sole symptom in some patients (33,278). Cough generally occurs after meal, daily in an upright position. The cough is usually nonproductive (dry) or accompanied by small amounts of mucoid sputum, and is triggered or aggravated by ingestion of acidic or fatty foods (33,279).

Diagnosis (2C)

(I) Chronic cough primarily during the day. (II) 24-h ambulatory esophageal pH monitoring or multi-channel intraluminal impedance-pH monitoring (MII-pH) shows a DeMeester score of ≥12.70 (280) and symptom association probability (SAP) of ≥80% (281). A symptom index of ≥45% is useful for the diagnosis of GERC (282). (III) Cough resolves or disappears after anti-reflux treatment.

It should be noted that negative findings of 24-h ambulatory esophageal pH monitoring do not exclude GERC as cause of cough. In a minority of patients with concurrent or predominant nonacid reflux (e.g., bile reflux) or intermittent reflux, the results of the ambulatory esophageal pH monitoring may be normal. Esophageal pH monitoring combined with intraluminal impedance can identify nonacid reflux (2C). When 24-h ambulatory esophageal pH monitoring or MII-pH is not available, the followings indicate GERC: (I) cough related to eating, such as coughing after or during meal; (II) typical reflux symptoms, including heartburn, regurgitation, or a score of Gastroesophageal Reflux Disease Questionnaire (GerdQ) of ≥8; (III) no evidence of CVA, UACS, or EB, and the cough does not improve with treatment for CVA, EB, or UACS. In patients who meet the above criteria, GERC should be considered as a cause of chronic cough, and diagnostic/empirical therapy for GERC may be initiated (7,32,283) (2B).

Proton pump inhibitor (PPI) is recommended for patients suspected to be due to GERC (284) (2C). A standard or intensive dose of PPI (e.g., omeprazole 20–40 mg, twice daily) should be prescribed for no less than 2 weeks. If cough disappears or is significantly improve after reflux treatment, GERC can be determined. However, GERC cannot be ruled out if patients fail to improve with PPI treatment. When compared with the laboratory investigations (24-h ambulatory esophageal pH monitoring or MII-pH), a trial of PPI is simpler and more cost-effective (284), but has the disadvantage of lower specificity.

Treatment

(I) Lifestyle modification: weight loss is recommended for the overweight patients. Patients should avoid late-night meals, and foods which are acidic, spicy, or fatty, coffee and acidic beverages, smoking and strenuous exercise (2D). (II) Antacids: acid suppression is recommended as the standard treatment for GERC (285-287) (1A). Common choices are either PPI (omeprazole, lansoprazole, rabeprazole and esomeprazole, etc.) or H_2 receptor antagonists (ranitidine or other equivalent drugs). Generally, PPI are superior to H_2 receptor antagonists in acid suppression and symptom relief, and should be administered 30–60 min pre-prandially (288), with a treatment course of at least 8 weeks. (III) Prokinetic agents: most patients with GERC have esophageal motility dysfunction, therefore the addition of prokinetic agents (domperidone and mosapride) is recommended (289) (1D).

If standard antireflux therapy fails to resolve the chronic cough in patients with evidence of reflux, the dosing scheme and treatment course should be reviewed. In addition, refractory GERC due to nonacid reflux should be considered. The persistent cough may not be related to reflux or may be caused by multiple etiologies (290-293). If the treatment fails, it is recommended to perform 24-h ambulatory esophageal pH monitoring or MII-pH again to exclude the possibility of under-treatment or misdiagnosis (2C).

Refractory GERC can be treated with baclofen. Adverse effects of baclofen include drowsiness and fatigue (291,294-296) (2C). When the treatment with the standard dose of PPI is not effective, increasing the dose of PPI may be helpful (297-300) (2A). If treatment with one kind of PPI fails, switching to another PPI may be effective (301) (2C). Combining H_2 receptor antagonist with PPI may ameliorate cough symptoms due to refractory gastroesophageal reflux or nighttime acid reflux (302) (2C). If necessary, a consultation with gastroenterology specialists can determine the optimum therapeutic regime. For a minority of patients with severe reflux resistant to pharmacological treatment, antireflux surgery (primarily laparoscopic fundoplication) or endoscopic therapies may be effective (303-314) (2C). Currently, no data are available that directly compare the efficacy of endoscopic therapy with medical management. Because of postoperative complications and the potential for relapse, surgical indications should be clearly defined. It is recommended that antireflux surgery be considered only when the cough is poorly controlled, severely impacts the patient's quality of life, and despite acid suppression, significant residual reflux identified by 24-h ambulatory esophageal pH monitoring or MII-pH (2D).

AC

AC is a kind of chronic cough that characterized by atopy, and response to corticosteroids or antihistamines, but no sputum eosinophils and airway responsiveness. Patients present with an irritating, paroxysmal dry cough, that occurs during the day and night. Cough can be induced by smoke, dust, cold air, and talking, and is usually accompanied by itching of the throat.

The surveys conducted in China demonstrated that AC was one of the common causes of chronic cough (37,62,66,69). In patients with chronic cough, without airway hyperresponsiveness, and a sputum eosinophilia, AC should be considered as the possible cause of cough (2C). The pathogenesis of AC has not been fully elucidated.

Japanese researchers reported that anti-fungal treatment is effective in fungus-induced cough where fungi have colonized the airway, serving as allergen (315). It is unclear if fungal-related cough occurs in other countries and regions and further studies are needed.

The following diagnostic criteria are recommended (2C)

(I) Chronic cough, primarily dry, irritating cough. (II) Normal pulmonary ventilatory function and bronchial responsiveness. (III) Lack of sputum eosinophilia. (IV) Presence of one of the followings: (i) a history of allergic diseases or exposure to allergens; (ii) positive allergen skin prick test; (iii) increased level of total serum or positive specific IgE. (V) Clinical response to corticosteroids or antihistamine treatment.

Treatment

Corticosteroids, antihistamines, or a combination of both are the treatment options. The treatment course of ICS should last for more than 4 weeks, and oral corticosteroids can be used initially for a short period (3–5 days) for treatment (7,10) (2C).

Diagnosis and management of chronic cough of the other etiologies

Chronic bronchitis

Chronic bronchitis is defined as a productive cough that lasts for 3 or more months per year for at least two consecutive years, after the other causes of chronic cough have been excluded. The cough is aggravated in the winter, with white foamy or mucoid sputum. Nocturnal cough may also occur during acute exacerbations.

Based on the epidemiological investigation, chronic bronchitis is common, but accounts only for a small proportion of the patients with chronic cough referred to specialty clinics. The discrepancy may be related to the lack of objective standard for the diagnosis of chronic bronchitis, therefore patients with chronic cough due to other diseases may be misdiagnosed as chronic bronchitis. Since chronic bronchitis is an early stage or subtype of COPD, the severity of chronic cough and sputum is associated with an increased frequency of acute exacerbation and increased mortality (316,317).

Investigations in Asian regions demonstrated that acute exacerbations of chronic bronchitis are generally caused by *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. Epidemiological studies should be conducted to determine antibiotic resistance in those regions, providing guidance for selection of antibiotics (318-322) (1B). Moxifloxacin and levofloxacin are the commonly used antibiotics for the treatment of acute exacerbation of chronic bronchitis due to their broad anti-bacterial spectrum and few side effects (318,320,321) (2B).

Bronchiectasis

Bronchiectasis is characterized by irreversible bronchial enlargement and distortion due to the chronic inflammation. The primary abnormality is in the subsegments of the bronchi. Typical clinical manifestations include chronic cough, production of mucoid or purulent sputum, and intermittent hemoptysis, which may coexist with chronic rhinosinusitis. Diagnosis for patients with a typical medical history is not challenging, whereas misdiagnosis can easily occur in patients with mild bronchiectasis and unclear medical history. In patients with suspected bronchiectasis, positive findings in the chest radiographs (such as curly hair sign) may suggest the diagnosis, but high-resolution chest CT is the best method to confirm the diagnosis (323-325) (1C).

Regular use of ICS is not recommended for the patients with stable bronchiectasis (325-332). Nonetheless, the combination of ICS with long acting beta agonists (LABA) or long acting antimuscarinics (LAMA) may improve cough in patients with bronchiectasis who have chronic airflow obstruction or airway hyperresponsiveness (323,324,333) (1A). Postural drainage is helpful in eliminating the accumulated sputum (2D). Intravenous

administration of antibiotics is recommended in patients with severe conditions, including highly pathogenic bacteria resistant to oral antibiotics, or failure to respond to oral antibiotics (331,334,335) (2B). Macrolides are helpful to improve symptoms and reduce the risk of acute exacerbation in patients with stable bronchiectasis, bacterial resistance and the adverse effects of long-term antibiotics administration should be considered (336-340) (2B). Regular inhaled mucolytics are not recommended (341) (1A). Statins (342,343) (2B) and mannitol inhalation may also help manage bronchiectasis, but this is not routinely recommended (344-347) (2B).

Bronchial tuberculosis

Bronchial tuberculosis is not rare among patients with chronic cough, in China. Bronchial tuberculosis is generally co-existed with pulmonary tuberculosis, but may exist alone in a considerable proportion of patients. The main symptoms are chronic cough, possibly concomitant with tuberculosis-associated symptoms including low-grade fever, night sweats, and emaciation. For some patients, cough is the only manifestation. Localized inspiratory, dry rales can occasionally be heard. In clinical practice, patients with bronchial tuberculosis and normal chest radiographic findings may be misdiagnosed and under diagnosed (348-352).

If bronchial tuberculosis is suspected, sputum smears hould be conducted first for the detection of acid-fast bacillus. Patients may have a *Mycobacterium tuberculosis*-positive sputum culture. Pulmonary radiographic signs may be minimal, whereas abnormal findings of the trachea and main stem bronchi, including bronchial wall thickening, airway stenosis, and obstruction can be detected. Bronchial lesions especially lesions located in the subsegmental bronchi may be identified by CT. Computed tomography, particularly high-resolution CT, is more sensitive than radiographs. Bronchoscopy is the important approach to confirm bronchial tuberculosis, which has a high positive rate when combined with routine brushing and tissue biopsy (353) (2C).

Cough due to ACEI or other medications

Cough is a common adverse event of ACEI, the incidence is 5–25% in patients taking the drugs, and ACEI-induced cough accounts for 1.7–12% of chronic cough (354-359). The independent risk factors are smoking, previous ACEI-induced cough (360), and nationality (East Asian or Chinese population) (361). Cough is not related to the age or sex of the patient (362) or the dose of ACEI (363).

The diagnosis can be confirmed when cough resolves after ACEI cessation. Usually, cough will disappear or be significantly relieved within 1–4 weeks after discontinuing the drug (364) . For patients with prior administration and the current risk of ACEI-induced cough, angiotensin II receptor antagonists can be used to replace ACEI for the treatment of the underlying disease (2D).

Cough can also be caused by mycophenolate mofetil, macrodantin, propofol, β-receptor blockers, leflunomide, simvastatin, γ-interferon, and omeprazole (29,365-367).

Bronchogenic carcinoma

Cough is an early-stage and common symptom of central bronchogenic carcinoma, with an incidence of 25–86% (368-370). Chest radiographs may be normal in the early stage, therefore misdiagnosis and under diagnosis may occur. In patients with a history of smoking, irritating dry cough, bloody sputum, chest pain, emaciation, and changes in the initial characteristics of cough, lung carcinoma should be suspected. The diagnosis can be confirmed by radiological imaging and bronchoscopy biopsy (2D). Treatment for cough due to lung carcinoma should target at the underlying disease, including radiotherapy, chemotherapy, radiofrequency ablation, and surgical resection (371-373) (1A). Postoperative cough in patients with lung carcinoma is a common issue in clinical practice, and the underlying mechanisms are unclear. The cytokine inhibitor suplatast tosilate resolves cough (369,374) (2C). Protracted and refractory cough may be attenuated with the treatment of central-acting or peripheral-acting antitussives.

Psychogenic cough

Psychogenic cough, also known as habitual cough, is caused by severe psychological conditions. It is more common in children than in adults. Within the classifications of mental disorders, there is no diagnostic terminology for psychogenic cough, and the pathogenesis of psychological cough may involve not only psychological factors, but also disorders of central nervous system control. The term of somatic cough syndrome may be a better descriptor (375). 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, and these factors would be addressed

Table 4 Uncommon or rare causes of chronic cough

Anatomical area	Causes
Upper airway diseases	Subglottic pleomorphic adenoma (383), subglottic mucosa-associated lymphoid tissue lymphoma (384), laryngeal carcinoma (385), epiglottic hypoplasia (386), heterotopic salivary gland (387), enlargement of the tonsils (388,389), elongated uvula (390), obstructive sleep apnea syndrome (391)
Tracheal diseases	Tracheobronchomalacia (392,393), ossifying bronchopathy, relapsing polychondritis (394), tracheobronchomegaly, tracheal stenosis, endobronchial hamartoma (395), tracheal diverticulum (396,397), bronchial foreign body (398-400), tracheal adenoid cystic carcinoma (59), tracheobronchial amyloidosis, broncholithiasis
Pulmonary diseases	Pulmonary alveolar microlithiasis (401,402), pulmonary fibrosis (403-405), pulmonary alveolar proteinosis, lymphangioleiomyomatosis, pulmonary Langerhans cell histiocytosis
Mediastinal diseases	Cardiac paraganglioma (406), pericardial cyst (407), thymoma (408), post-traumatic pseudo-aneurysm (409,410), arrhythmia (411) and left heart failure (412,413), esophageal cyst, esophageal cancer, Hodgkin's lymphoma, mediastinal lipolysis
Others	Cervical spondylosis (414-416), hepatic cavernous hemangioma (417), vagus nerve tumor (418), celiac disease (419), sublingual thyroid ectopy (420), external auditory canal cerumen, pleural endometriosis (421)

in clinical practice (376).

There are no specific diagnostic criteria for psychogenic cough. When the common and rare causes of chronic cough are excluded, psychogenic cough should be considered. For the children with psychogenic cough, psychological intervention including suggestive therapy and psychological counseling may be beneficial (377-382) (2B). The short-term use of antitussives can be used as adjuvant therapy. For the adult patients, antianxiety or antidepressant medications, in combination with psychological interventions, may be helpful. In children, it is important to differentiate psychogenic cough from Tourette syndrome.

Other uncommon or rare causes of chronic cough

The uncommon and rare etiologies account only for a minor proportion of chronic cough, but involve a broad spectrum of conditions. Some uncommon or rare causes of chronic cough reported in the literatures are listed in *Table 4*.

Unexplained chronic cough, chronic cough hypersensitivity syndrome

In most patients with chronic cough, an etiologic diagnosis can be determined and cough can resolve after treatment. However, in some patients with chronic cough an etiologic diagnosis cannot be confirmed after a comprehensive investigation and therapy aimed at known causes. Traditionally, this type of cough is called unexplained cough, chronic refractory cough, or idiopathic cough. The diagnosis of unexplained chronic cough should include the following: all known causes of chronic cough have been excluded through systematic evaluation and patients fail to respond to etiology-targeted treatment. In these patients, many of whom are middle-aged women, triggered by acute infection of upper airways. In addition to chronic dry cough, patients have an itchy throat or an uncomfortable sensation in the throat. Patients are sensitive to smoke, dust, abnormal smells, and cold air, and sometimes talking or nervousness can induce coughing. Because the patients show the characters of cough hypersensitivity, a new diagnostic term, chronic CHS is now used to describe patients with this type of chronic cough (422).

Based on the pathophysiological characteristics of CHS, the treatment should be aimed to reduce the sensitivity of cough. However, therapeutic options for CHS including medicinal and non-medicinal treatment are limited. Clinical studies show that neuromodulators, for example gabapentin, are effective in the treatment of CHS (423) (2B). Other medicines including amitriptyline, baclofen, carbamazepine, and pregabalin may be useful in CHS (424) (2C). Other potential treatments including speech therapy, and cough suppression physical therapy. Cough suppression physical therapy improves the quality of life related to cough, cough hypersensitivity, and cough frequency (11,425-428) (2B).

Etiologic distribution and therapeutic principles for pediatric patients with chronic cough

A cough lasting for more than 4 weeks in children is defined as chronic cough which is different from that in adults. Cough may be the isolated or predominant symptom,

with normal chest radiographic findings. The etiologic distribution of chronic cough in children is not identical to that in adults, and varies with age. For newborns and infants, congenital diseases, including tracheomalacia, supraglottic or glottic abnormalities, vascular malformations, primary ciliary dyskinesia, and bronchiectasis should be considered (429-437). For children younger than 3 years of age, airway infection should be initially considered (2C). The incidence of protracted bacterial bronchitis (PBB) is high in this age group, and half of the patients with PBB have tracheomalacia. *Haemophilus influenzae* is the causative bacteria in PBB (438-443) (2C). Bronchial alveolar lavage fluid (BALF) bacterial culture is useful to confirm the diagnosis. Airway foreign body aspiration is another important cause of chronic cough in children younger than 3 years of age. In children with a long history of cough but lack of response to routine treatment, the foreign body aspiration should be considered, and chest radiographs or bronchoscopy are required (444-448) (2C). Common causes of chronic cough in adults, PNDS and CVA, are not common in this age group. In children aged greater than 3 years, atopic diseases including asthma become common causes of chronic cough. In school-age children, CVA should be initially considered (2C). Upper airway cough syndrome can be caused by allergic rhinitis, rhinosinusitis, and adenoidal hypertrophy, and treatment is effective (438,442) (2C). EB is a common cause of chronic cough in adults; however, there have been no reports in pediatric patients. Causes of chronic cough that are rare in adults but common in pediatric patients include infections with atypical pathogens (mycoplasma and chlamydia), pertussis, foreign body aspiration, psychogenic cough, and congenital diseases. Due to physiological features, gastroesophageal reflux is a common phenomenon in healthy infants with an incidence of 40–65%. However, whether it is a common cause of cough in children remains uncertain.

Treatment principles for chronic cough in pediatric patients are to confirm the etiologic diagnosis and provide targeted treatment (2D). If the cause is unclear or relevant testing is not feasible because of age, empirical or symptomatic treatment can be implemented. If cough is not relieved after treatment, re-assessment should be performed. Antitussive agents should not be used for infants.

Empirical management of chronic cough

Successful treatment of chronic cough depends on etiologic diagnosis. Etiologic diagnosis may require specific equipment and techniques, which are not available in primary care hospitals, and are difficult for patients of low socioeconomic status to afford. Consequently, empirical treatment is an alternative in cases where conditions are limited (213,449-452) (2C). Empirical treatment should follow the principles below.

(I) Treatment schedules targeting the common causes of chronic cough are preferred. Many studies have referred that the common causes of chronic cough are CVA, UACS/PNDS, EB, AC and GERC (62,64,208,453) (1A).

(II) Possible causes of chronic cough should be identified based on the patient's medical history (452,454) (2C). If nonproductive irritating cough is predominant symptom and cough frequently occur at night or early morning, initial treatment for CVA is recommended. If cough is concurrent with overt acid regurgitation, belching, and heartburn, treatment for GERC can be considered. If protracted cough is secondary to the common cold accompanied by runny nose, nasal congestion, nasal itching, frequent clearing of the throat, and postnasal drip, empirical treatment should initially target UACS/PNDS.

(III) According to the patient and treatment response, chronic cough can be classified into steroid-responsive cough (including CVA, EB and AC), UACS and GERS for empirical treatment. This may reduce the blindness of empirical therapy and increase the success rate (30) (2C). Patient-driven therapeutic strategy in a step-by-step and sequential manner (2C) is a diagnostic management regimen, which initially involves the most common causes and simple treatments. The treatment regimens may lead to a longer duration of therapy for patients with chronic cough of uncommon causes. The strategy is targeted at the most common causes first suitable for those patients with unclear characteristics and multiple possible causes of chronic cough (10,452,455-458) (1C). Pseudoephedrine hydrochloride and methoxyphenamine is recommended for the empirical treatment of UACS/PNDS, AC, and PIC (30) (2C). If steroid-responsive cough is suspected, oral administration of low-dose steroids for 1 week is recommended, followed by ICS or combined therapy with β_2-receptor agonists (30) (2C).

(IV) For those with purulent sputum or mucus nasal discharge, antibiotics are recommended (2D). Since most causes of chronic cough are not related to infection (62,208,453), antibiotic abuse should be avoided during empirical treatment.

(V) It is recommended that the course of empirical treatment for UACS, PNDS, CVA, and EB should be 1–2 weeks, and that for GERC should be 2–4 weeks (2D). Oral corticosteroids should be given for no more than 1 week (7). If the patient is responsive to the treatment, the standard therapeutic regimen for the corresponding etiology should be used.

(VI) Empirical treatment may result in the risk of misdiagnosis of severe conditions. Empirical treatment should be used with caution, and serious conditions including bronchial malignant tumors, tuberculosis, and other pulmonary diseases should be ruled out. If empirical therapy is not effective, further investigations should be carried out to identify the etiologic diagnosis (10) (2D).

Cough suppressants and mucolytic agents

Mild cough does not require antitussive treatment. Antitussive agents can temporarily relieve the symptoms, and etiological therapy is the key to cough management. However, if severe dry or frequent cough impacts daily life, antitussive treatment can be prescribed. Mucolytic agents are indicated for patients with productive cough.

Antitussive agents

Antitussive agents can be divided into two types based on the pharmacologic effects: central-acting and peripheral-acting agents. Central-acting agents are those that act on one or several sites of cough center in the medulla oblongata, and peripheral-acting agents act on receptors on afferent or efferent nerves and effectors of the cough reflex arch (3,29,124).

Central-acting antitussive agents

These medications have inhibitory effects on the medulla oblongata. Based on the addiction potential and analgesic effects, they can be further subdivided into narcotic and non-narcotic antitussive agents. The former refers to morphine and its derivatives, which is a powerful cough suppressants. However, because of the possibility of addiction, they should only be used temporarily when other treatments failed. The latter refers to synthetic antitussive agents, such as dextromethorphan and pentoxyverine, which are widely used in clinical settings. (I) Narcotic antitussive agents: (i) Codeine (3): rapidly and directly inhibits the medulla oblongata and suppresses the cough, and has analgesic and sedative effects as usual. This type of medication can be used for patients who have unexplained severe dry cough or refractory irritating cough, in particular a dry cough with chest pain. (ii) Pholcodine: the effect is similar to codeine, but is less addictive. (II) Nonnarcotic antitussive agents: (i) dextromethorphan: it is similar in effect to codeine without analgesic and sedative effects. Therapeutic dosage usually does not have the inhibitory action on the respiratory center, nor side-effect related to medication addition. Dextromethorphan are recommended for chronic cough in adults (459) (2A). (ii) Pentoxyverine: cough suppressant strength is equal to one-third that of codeine with anticonvulsant and antispasmodic effects. It should be used cautiously in patients with glaucoma or heart failure. (iii) Dextrophan: a metabolite of dextromethorphan with better tolerance. It may replace dextromethorphan for clinical treatment in the future.

Peripheral-acting agents

They primarily act on inhibiting at least one element in the cough reflux arch. These drugs include local anesthetics and mucosal protectors. (I) Narcotine: it is a benzylisoquinolines alkaloid antitussive with effectiveness similar to codeine but without analgesic properties. It is suitable for cough induced by various causes. (II) Benproperine: it is a nonnarcotic drug with pharmaceutical effects 2–4 times greater than that of codeine. It inhibits both peripheral afferent nerves and the cough center. (III) Moguisteine: it is a peripheral non-narcotic antitussive drug, with a relatively stronger effect than that of codeine. (IV) Benzonatate: it is a local anesthetic that is a derivative of tetracaine and inhibits the afferent nerves of cough reflux.

Mucolytics

Mucolytics can improve clearance of airway secretions. The mechanisms of mucolytic agents include: increasing the clearance of secretions, decreasing the viscosity of secretions, and improving ciliary activity. There are a variety of mucolytics available, however, their effectiveness would require more evidence-based data. The common mucolytics are listed below.

Guaifenesin

It increases airway secretions and reduces sputum viscosity. It has been shown to cause bronchial dilation. It is used in combination with antihistamine, antitussive agents, and decongestants (460-462).

Myrtol

It is the extract of myrtaceae leaves, a volatile vegetable oil. The major components are eucalyptol, limonene, and alpha pinene. The commonly used preparations are eucalyptus and standard myrtol, which can improve the ciliary movement of the airway and nasal sinus mucosa, and are indicated for acute bronchitis, chronic bronchitis, and rhinosinusitis (463,464).

Ambroxol and bromhexine

These are mucolytic agents. Ambroxol is the metabolite of bromhexine, which can decompose the mucus acidic polysaccharide, decrease the viscosity of the secretion, improve ciliary activity, and increase the concentration of antibiotics in the respiratory tract.

N-acetylcysteine

It breaks down the sulfide bonds of the polypeptide chains of the glycoproteins to reduce the viscosity of sputum.

Carbocisteine

It breaks down the disulfide bonds of mucins to reduce the viscosity of secretion. Erdosteine is the precursor of carbocisteine. Oral administration can generate metabolites containing free sulfhydryl to exert pharmacological effect.

Others

Inhalation of hypertonic saline and mannitol can increase hydration of airway secretions, thus improving the rheology of mucus to enhance clearance. They can improve cough clearance in combined with bronchodilators (344,346).

TCM treatment

In TCM, cough is both a symptom and an independent disease. Chronic cough belongs to the category of "persistent cough" and "refractory cough".

Cough was first mentioned by *Huangdi's Internal Classic* over 2000 years ago, the classic also proposed that the etiology of cough involved all zang-fu organs, rather than just the lung-organ alone (465). Ancient Chinese classified cough by the internal zang-fu organs, which was similar to the anatomical classification of etiology in modern medicine. Cough has a variety of region-tailored types. It was summed up as exogenous and endogenous cough by *Jingyue's Complete Works*in, and this division is still used today (466). Briefly, cough (Ke Sou in TCM) results from lung qi failing in the purification and dispersion, along with lung qi ascending counter low.

With a long history, TCM has abundant experience in treating cough. In clinical practice, TCM treatment does relieve the cough of some patients with unexplained chronic cough. The advantages of TCM are as follows: giving treatment in accordance with seasonal conditions, local conditions and patient's individuality, so as to offer accurate region-tailored treatment; administering multiple-link, multiple-target medications for therapeutic efficacy; following the principles of "symptomatic treatment in acute condition" and "radical treatment in chronic condition," which is a comprehensive management model of "treating both principal and secondary aspect of disease". There are many Chinese medicines, medical formulae, and prepared agents for cough treatment (467-469). A part of the common cough syndromes are listed below (468,470).

[Syndrome of lung Yin deficiency] Dry cough, minor sticky phlegm, or gradual hoarseness, dry mouth and throat, with a slow onset.

Methods of treatment: nourishing Yin and clearing heat; moistening the lung and relieving cough.

Examples of prescription: Decoction of Glehnia Ophiopogon (*Treatise on Differentiation and Treatment of Warm Diseases*), plus/minus: Radix Adenophorae, Radix Ophiopogonis, Radix polygonatum, Radix trichosanthis, white beans, mulberry leaves, Radix Glycyrrhizae.

[Syndrome of lung-kidney yang deficiency] Mild cough, occurring or worsening in cold environment, or accompanied with shortness of breath, soreness of waist and legs.

Methods of treatment: Tonifying lung and kidney; Warming Yang and relieving cough

Examples of prescription: Minor Blue Dragon Decoction (*Treatise on Cold Damage Diseases*) with Pills for Tonifying the Kidney Qi ("Synopsis of the Golden Chamber"), plus/minus: Ephedra, peony, Asarum, Ginger, cassia twig, Schisandra, Pinellia ternata, rehmannia, Chinese yam, Herba Epimedium, Morinda officinal, and licorice.

[Syndrome of stomach qi ascending counterflow] Paroxysmal irritating cough; severe cough causing vomiting of the gastric juice, aggravated when supine or after

satiation; may be associated with belching with fetid odor and acids, noisy or burning, similar to gastroesophageal reflux-associated cough.

Methods of treatment: descending turbidity and resolving phlegm, harmonizing stomach and arresting the cough.

Examples of prescription: decoction of Inula and Hematite (*Treatise on Cold Damage Diseases*) with Pinellia Heart-Purging Decoction (*Treatise on Cold Damage Diseases*) plus/minus: Inula flower, ocher, ginseng, Pinellia, ginger, jujube, berberine, *Scutellaria baicalensis*, honey-fried licorice root.

[Syndrome of liver-fire attacking lung] Paroxysmal cough, with flushing of the face and eyes, and chest pain. Cough aggravation or remission associated with changes of mood; often with a sense of phlegm stagnation in the throat and difficulty in coughing out the phlegm; minor mucoid sputum, dry and bitter mouth.

Methods of treatment: clearing lung fire and purging heat; resolving phlegm and relieving cough.

Examples of prescription: powder of Scutellaria for Dispersing the lung (*Zheng Yin Mai Zhi*), with *Natural Indigo* and Clam Shell Powder (*Chinese pharmacopoeia*), plus/minus: *Scutellaria baicalensis*, cortex lycii radicis, Digupi, indigo naturalis, clam shell, and licorice.

[Syndrome of latent wind-pathogen tightening lung] Paroxysmal cough, accompanied by itchy throat, dry cough with minor sputum production, difficulty in sputum expectoration, often induced by cold air, odor, or laughing; without obvious chills and fever; external infection often induces cough aggravation or recurrence; pink tongue, with thin and white cover.

Methods of treatment: dispelling wind and dispersing lung; relieving cough and reducing phlegm.

Examples of prescription: Ephedra, folia perillae acutae, earthworm, folium eriobotryae, fructus perillae, periostracum cicada, Common hog fenneI root, burdock, Schisandra chinensis or Decoction of Three Crude Herbs (*Bureau of Peaceful Benevolent Dispensary*) with Cough-Stopping Powder (*Understanding of Medicine*), plus/minus broiled ephedra, almond, platycodon grandiflorum, herba schizonepetae, broiled asters, broiled radix stemonae, *Cynanchum glaucescens*, radix scutellariae, and radix glycyrrhizae.

[Syndrome of wind-cold invading lung] Severe cough, with itchy throat and shortness of breath; non-purulent sputum, nasal congestion, runny nose, headache, tongue with thin-white coating, pulse floating and tight.

Methods of treatment: expelling wind and cold; dispersing the lung and ceasing cough.

Prescription example: Cough-Stopping Powder (*Understanding of Medicine*) and Jade-Screen Powder (*Jiu yuan Fang*).

[Syndrome of wind-heat invading lung] Cough being frequent, with sore and painful throat; minor sputum expectoration, which is usually purulent; runny nose with purulent discharge, thirsty, headache, reddish tongue, the tongue with thin yellowish coating, pulse floating or frivolous.

Methods of treatment: dispelling wind and reducing heat; dispersing the lung and ceasing cough.

Examples of prescription: Powder of Honeysuckle and Forsythia (*A Treatise on Differentiation and Treatment of Warm Diseases*).

Concerning TCM, current treatment mainly based on some Chinese classical prescriptions, therapeutic methods, or the experience of senior experts. Due to the lack of definite evidence-based data, medical researches of TCM have a low evidence level (471). In China, there are a variety of prepared Chinese medicine compounds, but most of the treatments are staying at symptom management. The effective components, therapeutic indications, and adverse reactions are uncertain, and all of these need to be further investigated. Because of ambiguity of the differences between the "disease" and "syndrome", the effective use of Chinese medicines is limited. Many Chinese patent medicine are indicated for syndromes, rather than for the specific etiology. In addition, it's always not indicated whether this is antitussive or expectorant agent. Future medical research required TCM concepts combine with modern medical methods, to explore more Chinese Medicinal combination recipes and medicinal monomer with stronger efficacy and clearer indications.

Future developments

As a common problem in clinical practice, comprehensive studies on the etiologic diagnosis, treatment, and pathogenic mechanisms of chronic cough have been conducted for more than 30 years in Western countries and for almost 15 years in China. These efforts have resulted in a series of achievements. Experts from Europe, America, the United Kingdom, Japan, and Australia have developed guidelines for the management of cough. With in-depth studies of chronic cough and the application of guidelines, understanding the causes of chronic cough and

the diagnosis and treatment level of Chinese health care providers has greatly improved. Some hospitals in China have specifically established cough labs for the induced sputum test, FeNO test and 24-h esophageal pH-multi-channel impedance monitoring. Furthermore, subspecialty and specialist outpatient clinics for chronic cough have been established in a lot of hospitals. Although there have been significant advances in the management of cough, clinicians are confronting challenges. First, as a common symptom in clinical practice, chronic cough has attracted more and more attention from clinicians. Nevertheless, a few institutes are currently involved in studying chronic cough in China. Therefore, we hope that more clinicians participate in the studies on chronic cough. Second, more clinicians have appreciated the diagnostic value and usefulness of the induced-sputum test for the assessment of responses to treatment. Although induced sputum tests have been increasingly applied in some hospitals in China, the clinical application is not sufficiently popular. Moreover, the challenges regarding the diagnosis, management, and pathogenesis of chronic cough merit further investigations, including the pathogenesis and treatment of protracted PIC; the mechanisms of UACS/PNDS; the relationship between pharyngeal diseases and UACS; the duration of treatment of EB/CVA and the relationship with classic asthma; the diagnostic criteria and pathogenesis of GERC; the correlation between air pollution and chronic cough; the therapy for unexplained cough or refractory cough; and the pathogenesis of cough hypersensitivity. As we look forward to the future, we realize we still have a long way to go. Only unremitting efforts will keep us moving further.

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Footnote

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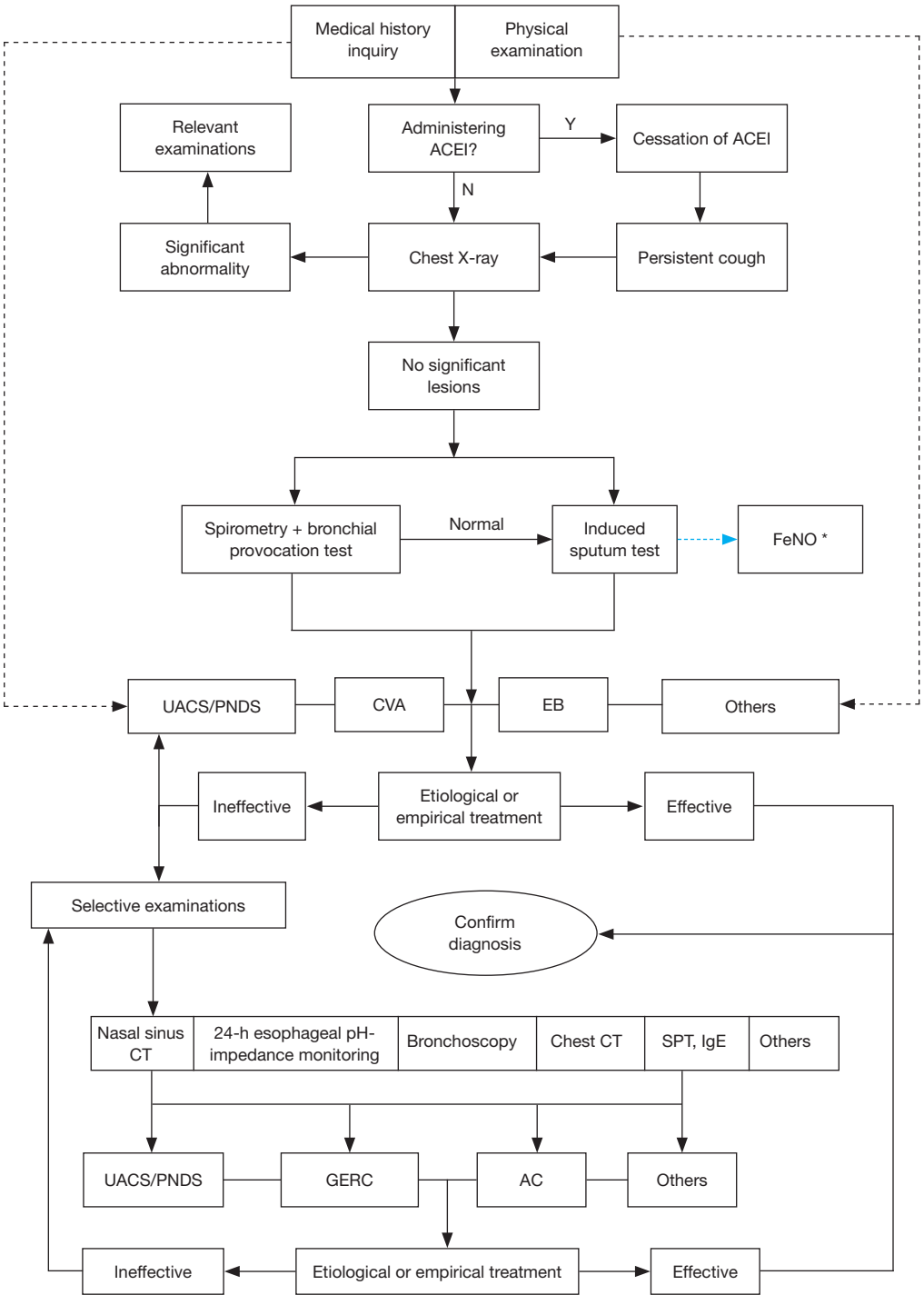
Supplementary

Supplementary file 1 Algorithm for the etiological diagnosis of chronic cough



Note: *, cannot be used as criteria for diagnosis, but can be used as an indicator for eosinophilic inflammation-related cough. (I) For patients with low economic status or for those in primary health care centers, empirical treatment can be adopted based on the medical history and cough-related symptoms. If the empirical treatment fails, to avoid the delay in proper diagnosis and therapy, patients should be referred to hospitals where the tests are available. (II) ACEI, angiotensin converting enzyme inhibitor; FeNO, Fractional exhaled nitric oxide; UACS, upper airway cough syndrome; PNDS: postnasal drip syndrome; CVA, cough variant asthma; EB, eosinophilic bronchitis; CT, computed tomography; Bronchoscopy, fiberoptic bronchoscopy; SPT, skin prick test; IgE, immunoglobulin E; GERC, gastroesophageal reflux-related cough; AC, atopic cough.

Supplementary file 2 Hypertonic saline nebulization-induced sputum test

Sputum induction is performed using nebulization of hypertonic saline. The total and differential inflammatory cell counts may suggest the type and severity of bronchial inflammation, providing clues for the diagnosis and management of cough and prediction of the prognosis.

A single-concentration (concentration of NaCl: 3% or 4.5%) or a step-up concentration method (concentration of NaCl: 3%, 4%, and 5%) is used for hypertonic saline nebulization. In order to avoid adverse events, adults and children with severe asthma should receive normal saline nebulization when performing induced sputum test.

Reagents: hypertonic saline, 0.1% dithiothreitol (DTT), and hematoxylin-eosin or Swiss stains.

Instruments: ultrasonic or compressed nebulizer, water bath, whirlpool or horizontal oscillator, optical microscope.

Procedures:

(I) Hypertonic saline nebulization:

- Single-concentration method: (i) patients receive inhaled salbutamol (400 μg) 10 min before sputum induction; (ii) patients are asked to rinse their mouth with sterile water and blow their nose; (iii) after inhalation of hypertonic saline for 10 min, patients are asked to rinse mouth and blow the nose again, and cough up sputum into a sterile container; (iv) if the patient cannot cough up sputum or the amount of sputum is insufficient, step 3 will be repeated. The induction is terminated when a sufficient amount of sputum is obtained, or the total duration of nebulization reaches to 30 min. Step-up concentration method: (i) patients receive inhaled salbutamol (400 μg) 10 min before sputum induction; (ii) patients are asked to rinse their mouth with sterile water and blow their nose; (iii) after inhalation of aerosolized 3% hypertonic saline for 15 min, patients are asked to rinse mouth and blow their nose again, and cough up sputum into a sterile container; (iv) if the patient cannot cough up sputum or the amount of sputum is not sufficient, 4% hypertonic saline is used for nebulization for 8 min; (v) if patient still cannot cough up sputum or the amount of sputum is not sufficient, 5% hypertonic saline is used for nebulization for 7 min; (vi) if a sufficient amount of eligible sputum is obtained or the total duration of nebulization reaches to 30 min, sputum induction should be terminated.
- Sputum examination: Sputum sample should be processed shortly after expectoration, or preserved at 4 ℃ for less than 3 hrs. Sputum plugs should be picked up with forceps. The selected portion was fully mixed with 2 to 4 volumes of 0.1% DTT. After 10–15 min, the mixture should be filtrated with 48 μm filter or 300-mesh nylon gauze, and then centrifuged at 790 ×g under room temperature for 10 min. The dissolving effects of DTT can be potentiated in a 37 ℃ water bath and horizontal vortex. The supernatant will be removed whereas the cell pellets will be resuspended with normal saline. The total cell count is obtained with a Neubauer hemocytometer. A cell smear is prepared, and stained with hematoxylin-eosin or Swiss stain. Differential cell count is obtained by counting 400 non-squamous cells.

Precautions: (I) for patients with severe asthma or asthma exacerbation, the degree of airflow limitation determined by spirometry and clinical symptoms should be reviewed prior to determining if the patient is a suitable candidate for undergoing the induced sputum test. When the forced expiratory volume in one second (FEV1) is <60% of predicted value or in cases with obvious asthmatic symptoms, spontaneous cough-induced sputum or normal saline for nebulization is recommended. (II) The laboratory should be equipped with rescue protocols, instruments, and medications for adverse events such as acute exacerbation of asthma. During the induction period, the overall conditions of the patient and lung function should be closely monitored. (III) Steroids, antihistamines, and theophylline, which may affect the results, should be withheld for at least 3 days prior to the test. However, patients are allowed to continue anti-asthma medications if the test aims to assess the response to treatment and is conducted during the follow-up period.

Supplementary file 3 Multi-channel intraluminal impedance-pH monitoring (MII-pH)

Equipment: esophageal multi-channel impedance-pH monitoring device.

Procedures: (I) Prior to the procedure, calibrate the pH electrode in the buffer solutions at pH 4.0 and 7.0 (as specified by the manufacturer) to ensure the accuracy and stability of the instrument. (II) Select one nasal cavity for ease of passage of the catheter. After anesthetizing the nares with topical spray of 2% lidocaine, an esophageal manometry catheter is transnasally inserted into the

esophagus. The location of lower esophageal sphincter is determined by the stationary pull-through technique. A combined catheter with six-impedance channel sensors and a pH electrode is used. The central positions of the impedance channel sensors are located at 3, 5, 7, 9, 15, and 17 cm above the lower esophageal sphincter. The pH electrode is positioned 5 cm above the manometrically located proximal border of the lower esophageal sphincter, with the external reference electrode fixed at a point in the middle-lower segment of sternum. The catheter is connected to a portable monitoring device that records and stores data from all seven channels (six impedance and one pH) with a frequency of 50 Hz.

Monitoring duration: over 18 hours.

Analysis of results: analysis includes the identification, enumeration, and classification of acid and non-acid reflux events, as well as the measurement and calculation of the parameters, including food bolus clearance, food bolus exposure, and esophageal acid clearance. A global measure of esophageal acid exposure is expressed by the DeMeester score, which is calculated by from the following six parameters: (I) total percentage of time with pH <4.0; (II) percentage of time with pH <4.0 when seated upright; (III) percentage of time with pH <4.0 when recumbent; (IV) the total number of reflux episodes; (V) the total number of reflux episodes lasting >5 min; and (VI) the duration of the longest reflux episode. Meanwhile, symptom-associated probability (SAP) is calculated to establish the temporal association between cough and the reflux detected.

Precautions: (I) fast for 10 hours before the test; (II) avoid acidic food in the meal prior to the examination; (III) stop antacids for 7 days, prokinetics for 3 days, and all these medications for 24 hours before examination. Maintain the treatment with these medications during the follow-up period observing the therapeutic efficacy; (IV) strictly and accurately record a diary of events; (V) during the monitoring period, maintain the usual daily lifestyle and do not limit the activities, but avoid acidic or spicy foods and beverages, as well as antacid medications.

Supplementary file 4 Cough provocation test

Cough is triggered by inhaling aerosolized capsaicin particles. A nebulizer is used to aerosolize capsaicin. Cough sensitivity is expressed as the cough threshold (C5), defined as the lowest concentration of capsaicin required for the induction of ≥5 coughs.

Reagent preparations: capsaicin (30.5 mg) is dissolved in 1 mL Tween 80 and 1 mL absolute ethanol, and mixed with 8 ml normal saline to yield a 0.01 mol/L stock solution. Prior to the test, the stock solution is serially diluted with normal saline into the following concentrations: 1.95, 3.9, 7.8, 15.6, 31.2, 62.5, 125, 250, 500, and 1,000 μmol/L.

Equipment: An inspiratory flow-driven dosimeter-controlled nebulizer is preferred. The flow velocity of compressed air is 0.11 L/s with a total output of 160 mg/min (normal saline as the control) and single inhalation time of 0.5 s. The subjects are instructed to gradually inhale from residual volume to total lung capacity. During the first half of inspiration, an aerosolized capsaicin solution is inhaled.

Procedures: (I) Normal saline is first inhaled as a negative control; (II) capsaicin solution is inhaled from the lowest concentration (1.95 μmol/L) for 30 s and the number of coughs that occur is recorded. If of the number of induced coughs do not meet C5, the next concentration of capsaicin is inhaled; (III) the test is terminated when ≥5 coughs are induced. The concentration of capsaicin represents the cough threshold C5. If after inhalation of the highest concentration (1,000 μmol/L) of capsaicin ≥5 coughs do not occur, the test should be discontinued, with the recorded cough threshold C5 of >1,000 μmol/L. If the subjects feel discomfort including severe heartburn, tachypnea, and dyspnea during the procedure, the test must be stopped immediately.

Precautions: (I) the solution used in the test should be prepared freshly; (II) contraindications: pregnancy, acute exacerbation of asthma, pneumothorax, recent hemoptysis, and severe heart diseases; (III) keep the subjects calm during the test. With the inhalation of capsaicin, avoid activities, such as speaking, which may influence the cough count.