Diagnosis and Treatment of Chronic Cough

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ISBN 978-981-33-4028-2 ISBN 978-981-33-4029-9 (eBook)
https://doi.org/10.1007/978-981-33-4029-9

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Preface

Three things cannot be hidden: coughing, poverty, and love (Yiddish proverb).

Cough is one of the most frequent symptoms for which patients seek medical attention. Chronic cough, usually defined by the duration of cough (≥8 weeks in adults and ≥4 weeks in children), is a major clinical challenge for both patients and clinicians. Patients with chronic cough experience a wide range of issues in life, including health concerns, fatigue, depression, urinary incontinence, and even social isolation. Due to the recent COVID-19 pandemic, chronic cough has been perceived as more problematic, causing increased feelings of anxiety and isolation in the patients.

The first breakthrough in clinical management of cough was the development of an anatomical diagnostic protocol based on the neuroanatomy of the vagus nerve pathways regulating the cough reflex. This approach led to improvement in many patients with chronic cough over the last few decades. However, it has also become apparent that the systematic approach is not always successful. Cough remains unexplained or refractory to diagnostic and therapeutic efforts in a considerable proportion of patients visiting cough clinics. Meanwhile, cough is frequently self-remitting, but also waxes and wanes, making it difficult to differentiate true clinical responses from spontaneous remission, or to determine the etiology. In addition, randomized clinical trials revealed that placebo effects are likely substantial even in chronic refractory cough. Together, these factors contribute to the complexity of chronic cough in clinical practice and sometimes lead to overutilization of different diagnostic tests and therapeutic agents. This situation, along with recent advances in cough pathophysiology, has prompted a change in perspective regarding the pathophysiology of chronic cough, which is now termed cough hypersensitivity syndrome (CHS).

Chronic cough research is rapidly evolving, and the concept of CHS is increasingly being incorporated into clinical practice. Recent clinical trials using P2X3 receptor antagonists confirmed that aberrant neurophysiology is a major pathophysiological factor in unexplained and chronic refractory cough, and more novel drugs are expected to become available within the next few years. With the introduction of the concept of treatable traits, the European Respiratory Society Taskforce proposed a revised clinical approach for chronic cough, by viewing it as a distinct clinical entity characterized by vagal hypersensitivity, rather than being a consequence of other diseases; the goal is to identify treatable traits in chronic cough. However, there are also

different views and ongoing discussion on how to best approach the patients, or even how to define chronic cough. This book acknowledges such differences in perspective, and author's own view is presented in each chapter.

This book introduces recent perspectives on various clinical topics associated with chronic cough and provides practical guidance for clinicians. Given the complex nature of chronic cough, clinical guidance should be ideally based on robust scientific evidence such as stringent placebo-controlled trials. However, there are still not many randomized controlled trials in chronic cough, which we think is partly related to conventional views that cough is a consequence of other chronic diseases. In this regard, we tried to combine scientific evidence with clinical experience in each chapter.

Finally, we are proud that all of the chapters were authored by leading experts in cough research and practice and are grateful to them for sharing their clinical experience and scientific knowledge. This book would not have been possible without their participation.

Woo-Jung Song
Sang Heon Cho

Contents

Chronic Cough

1

Sang Heon Cho and Kyung-Min Ahn

Introduction

Cough is a natural protective reflex, which is an intrinsic defensive mechanism for protecting the lower respiratory tract from aspiration, infection, and irritation. However, it can become problematic when this defense mechanism fails to keep its original function in balance, and both hyposensitivity and hypersensitivity can prevent a person from having an appropriate reaction to irritants (Fig. 1.1) [1]. When it becomes persistent and severe, cough becomes troublesome and may have an adverse influence on daily life, and this reflex may become pathological when dysregulated [2]. Patients affected by chronic cough usually complain of unexpected coughing attacks after being exposed to incidental stimuli, such as perfume, or when talking.

Careful history taking with detailed questions regarding the characteristics of cough is crucial for accurate diagnosis, and the clinical approach to cough in adults begins with classification based on duration: acute (<3 weeks), subacute (3–8 weeks), or chronic (>8 weeks) [4]. In children and adolescents, cough is classified as either acute (<4 weeks) or chronic. This classification of cough was first introduced in the cough guidelines of the American College of Chest Physicians (ACCP) CHEST Expert Cough Panel published in 1998 [5, 6]. The panel suggested that cough should be distinguished according to its duration to help narrow the list of possible diagnoses that may be the underlying cause [7].

Chronic cough has an incidence of about 10–12% in the general population worldwide [8]. Although the absolute prevalence in a local population may differ depending on the regional environment and genetic factors, it is clear that cough is a prevalent medical condition cough is a prevalent medical condition in the community. Compared to developed countries, developing countries tend to show higher prevalence rates of chronic cough. This regional discrepancy may be due to differences in underlying comorbidities, such as gastroesophageal reflux disease (GERD) and asthma, as well as environmental triggers.

In children, the prevalence of chronic cough is about 5–15% [9]. There have been relatively few prospective studies in children compared to adult patients, and these studies included nonspecific cough as well as heterogeneous comorbidities and medical environments, which made it difficult to determine causative factors. Nonetheless, it is clear that the common causes of chronic cough in children are very different from those in adult patients. In two studies of chronic cough in children with average ages of 9.2 and 8.4 years, diseases such as upper airway cough syndrome

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S. H. Cho, W.-J. Song (eds.), *Diagnosis and Treatment of Chronic Cough*,
https://doi.org/10.1007/978-981-33-4029-9_1

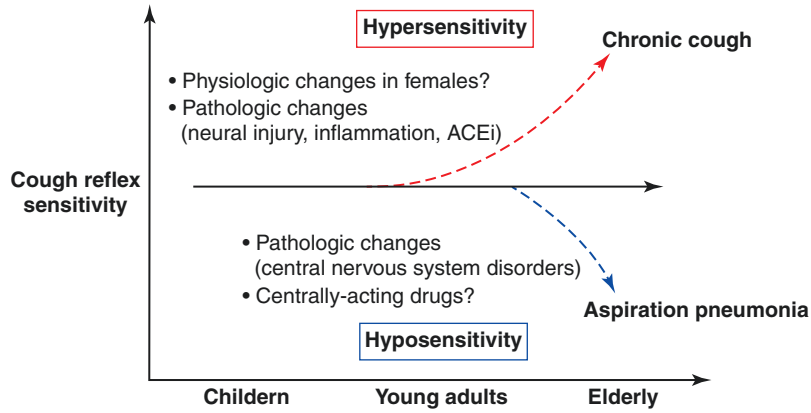

Fig. 1.1 Dual nature of cough problems in the elderly. Reused with permission from [3]

(UACS), asthma, and gastroesophageal reflux disease (GERD) accounted for 83% and 69% of cases, respectively. Nonetheless, in infants with an average age of 2.6 years, only 9% of coughs were due to these causes, with persistent bacterial bronchitis, postinfectious cough, and bronchiectasis accounting for 68% of cases instead. GERD is no longer thought to be the major cause of isolated chronic cough [10].

Impact of Chronic Cough

Chronic cough is one of the most common clinical issues for which patients seek treatment, and it poses a noticeable burden on the quality of life (QoL) of affected patients. Patients usually experience depression, sleep disturbance, and loss of work productivity, as well as social isolation [11, 12]. There are a number of studies regarding the physical and psychosocial complications in patients with chronic cough. In 2008, Morice et al. emphasized the social importance and financial burden of chronic cough [13]. Some patients may experience "cough syncope" in which they tend to have cough attacks followed by syncope [14], which can be fatal when it occurs while the patient is engaged in potentially hazardous activities, such as while driving public transportation or piloting an airplane. Patients may also suffer from social isolation because minor stimuli in daily life can prevent them from engaging in routine activities [8]. For example, eating or talking is a common trigger of cough, which may lead to isolation of patients from social gatherings. This can be a significant obstacle for social life, and a survey of chronic cough patients in New York showed that about 50% of the patients experience depression due to a lack of social interaction [15]. In addition, chronic cough can be associated with financial burden. A number of individuals with chronic cough take early retirement [16], particularly those who are in occupations requiring talking. French et al. attempted to measure the impact of chronic cough on QoL using various factors, i.e., demographic, Adverse Cough Outcome Survey (ACOS) score, and Sickness Impact Profile (SIP) score, which could represent the influence of chronic cough on affected patients [17]. In this study, there were significant correlations between ACOS and psychosocial SIP scores in the patient group, indicating that chronic cough was associated with deterioration of patients' QoL. They also found that the health-related dysfunction caused by chronic cough was actually more closely linked to psychosocial aspects than physical aspects. This study suggested the importance of chronic cough and its adverse effects on patients' QoL as well as physical load [18].

Clinical Approach Based on the Neuroanatomy of Cough Reflex Pathways

An algorithm based on the anatomical distribution of the vagus nerve cough reflex circuit for evaluating chronic cough, the anatomical diagnostic protocol, was first described in 1977 [6]. Although there is still controversy regarding the neural pathways of cough, it is now generally accepted that afferent fibers of the vagus nerve serve as the main mediators of reflexive cough. The various cough receptors include C-fibers, slowly adapting receptors (SARs), rapidly adapting receptors (RARs), and myelinated fibers terminating in the mucosa of the larynx, trachea, and bronchi [19].

Afferent vagal fibers may be triggered by a number of stimuli, such as capsaicin, bradykinin, acid, particulate matter, prostaglandin E2, and nicotine. Stimulation of the C-fibers or mechanically sensitive cough receptors initiates the cough reflex, sending signals to the nucleus of the tractus solitarius of the medulla, the compact fiber bundle, which extends longitudinally through the posterolateral portion of the medulla [20]. This solitary tract, surrounded by the nucleus of the solitary tract, is composed of primary sensory fibers and descending fibers of vagus and glossopharyngeal and facial nerves, which serve as the classical cough core of the regulatory center (Fig. 1.2) [21].

The systematic diagnosis and treatment of the causative diseases of cough, particularly asthma,

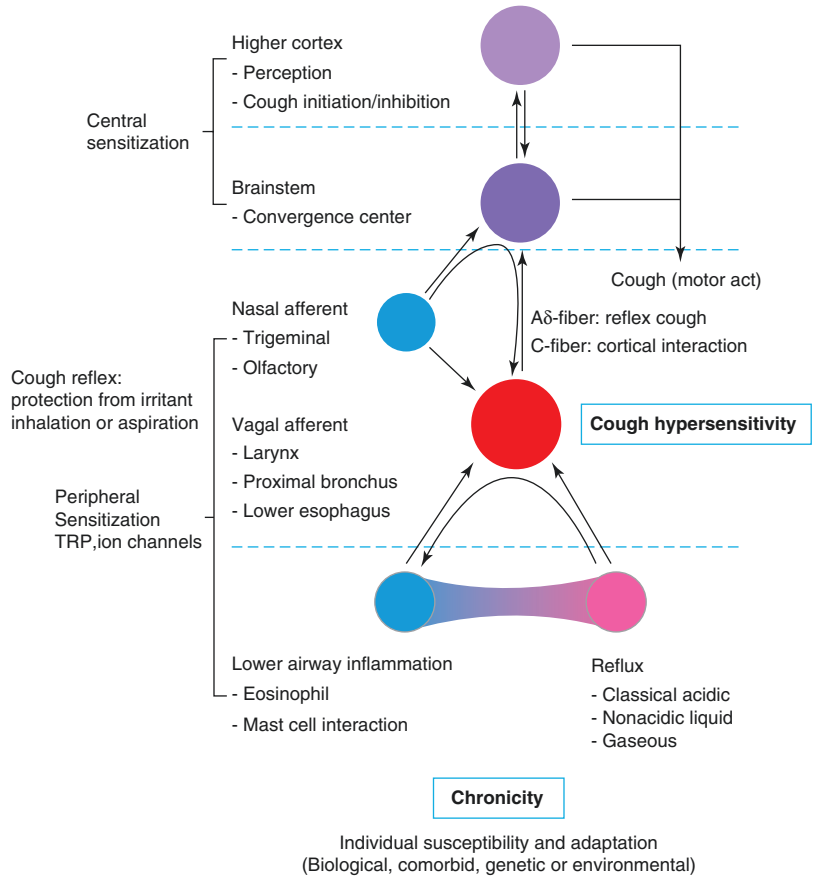

Fig. 1.2 Schematic representation of the development of cough hypersensitivity. Key event may be the development of vagal neuronal hypersensitivity in the airways. Commonly associated diseases, such as rhinitis, eosinophilic airway inflammation, or classical acidic reflux, may be triggers to lower the thresholds for peripheral cough reflex activation. Nasal afferent stimulation may not directly initiate the cough reflex, but modulate the cough reflex depending on the type of nasal stimulus. Reprinted with permission from [22]

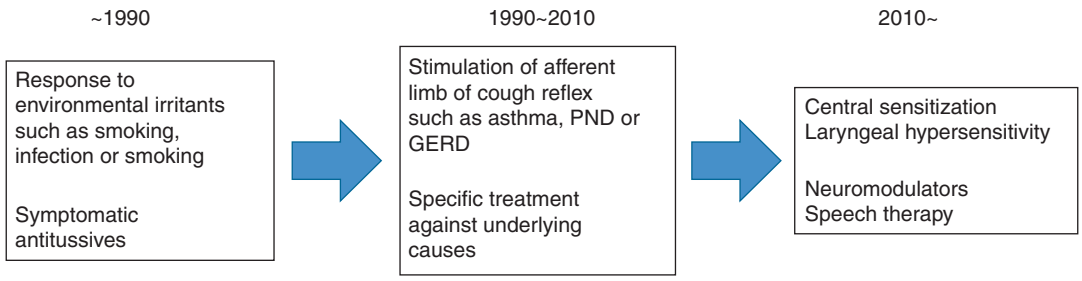

Fig. 1.3 Changing concept of pathophysiology and treatment in chronic cough [26]

upper and lower airway inflammation, and gastroesophageal reflux disease (GERD), have been emphasized [23]. The anatomical diagnostic protocol has been validated in numerous studies and has been tested in a number of clinical trials, which have demonstrated its effectiveness in diagnosing the cause of chronic cough in 54–100% of cases [19]. Moreover, this algorithm was shown to be useful in systematic diagnosis resulting in resolution of cough in more than 90% of patients [24].

Nonetheless, later studies found that about 10–40% of patients visiting specialist clinics with chronic cough did not show complete resolution despite the best diagnostic and treatment efforts [25]. The anatomical diagnostic protocol could not troubleshoot all cases of chronic cough, and it has been referred to by multiple different names, including idiopathic, unexplained, or refractory chronic cough. In fact, most adult patients with chronic cough complain that their symptom is triggered by insignificant irritations, such as cold or dry air, dust, emotional stress, talking, or eating. This indicates that the main pathophysiological feature of uncontrolled chronic cough is hypersensitivity of the cough reflex. This hypersensitivity stimulates the chronic cough in contrast to its inherent protective function. Most patients with chronic cough complain of various abnormal stimuli on their throat before a cough attack starts, such as tickling, itching, and tightness before and after coughing, also indicating hypersensitivity of the laryngeal sensory nerves. These patients usually experience emotional frustration or helplessness with various mental and social problems. Therefore, a new paradigm shift to interpret the pathophysiology and clinical approach to chronic cough began in the 2010s (Fig 1.3).

In 2014, the European Expert Group proposed a new interpretation of chronic cough as a distinct clinical syndrome characterized "by hypersensitivity to cough reflexes," rather than a symptom of other underlying diseases. This understanding of "chronic cough driven by hypersensitivity" was named "cough hypersensitivity syndrome," and this paradigm shift has been further validated by multiple clinical trials with various cough measurement tools. Through this concept, the clinical relevance of neurological processes was emphasized, and a clinical approach was suggested in the European Respiratory Society (ERS) Guidelines in 2019 [27]. The inflammatory process impacts on the nerve endings, increasing cough sensitivity, leading to peripheral sensitization. TNF-α pretreatment was shown to induce afferent activity of bronchopulmonary C-fibers in response to provocation with capsaicin, a TRPV1 activator [28]. Using fMRI, Mazzone et al. showed enhanced activity of the brain regions encoding sensation as well as abnormal responses in brain circuits that usually have descending control on primary afferent processing [20].

Although the new approach shares the basic principles of anatomical diagnostic protocols, recent practice guidelines aim to identify "cough triggering conditions" or "treatable traits" in chronic cough. Most factors that have been thought to cause chronic cough—asthma, rhinitis, sinusitis, GERD, and angiotensin-converting enzyme inhibitors (ACEi)—are now thought to be conditions that trigger chronic cough by stimulating the cough reflex [29]. In addition, traditional diagnostic naming of the underlying causes, such as asthma, rhinitis, and GERD, does

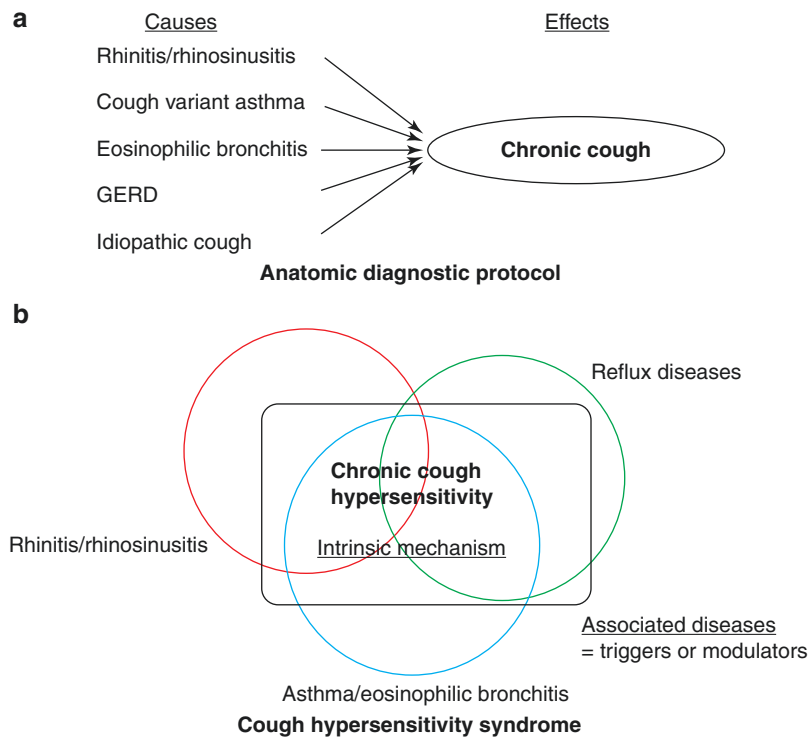

Fig. 1.4 Cough hypersensitivity syndrome. Asthma, rhinitis, sinusitis, GERD, and ACEi are cough triggers (**a**), which enhance heightened cough reflex sensitivity (**b**). Reprinted with permission from [20]

not always explain the mechanisms of cough, and identification of "treatable traits" is the key to precision medicine (Fig. 1.4).

Diagnosis of chronic cough begins with identification of possible clues for treatable traits in chronic cough. Comprehensive history taking should focus on smoking status, associated symptoms, and the current use of medications that may cause cough such as ACEi [30]. If the patient is a long-time cigarette smoker, chronic bronchitis or irritant dust are the most likely explanations of chronic cough [31]. After eliminating organic underlying conditions and cough-causing medications, further diagnostic investigations should be carried out. Chest X-ray is recommended in all patients. Additional chest imaging such as computed tomography, spirometry with or without bronchodilator, methacholine bronchial challenge test, barium esophagography, 24-h esophageal pH monitoring, and sputum analysis can be useful to evaluate possible causes of chronic cough, depending on clinical profiles of patients [32, 33]. In addition, measurement of cough hypersensitivity with citric acid or capsaicin may be potentially helpful to characterize the patients although the clinical relevance is still not confirmed [34].

It is important to perform appropriate diagnostic investigation so that the physician can continue disease- or trait-specific treatment for chronic cough. For UACS, treating allergic rhinitis, allergen avoidance, prescription of next-generation antihistamine with intranasal corticosteroids, leukotriene receptor antagonists, saline sinus irrigation, and desensitization by immunotherapy may be helpful [35]. On the other hand, along with avoidance of environmental irritants, administration of antihistamine with intranasal ipratropium bromide or corticosteroids is preferred in patients with nonallergic rhinitis or postinfectious rhinitis. Chronic cough that is related to asthma is treated with administration of inhaled corticosteroids and inhaled bronchodilators, whereas nonasthmatic eosinophilic bronchitis (NAEB)-related chronic cough patients start to respond to inhaled corticosteroids within 4 weeks in most cases. GERD is usually treated with medical therapy and lifestyle modification.

An intensive antireflux treatment, such as administration of a proton pump inhibitor to suppress acid in the stomach, is usually accompanied by prokinetic agents, such as metoclopramide [36]. This medical treatment may be synergic when combined with modification of daily lifestyle, such as the adoption of a strict diet regimen, not eating before sleeping, or binge eating. If the diet and maximal pharmacological therapy fail, evaluation of possible surgical intervention with antireflux surgery should be considered [37]. In refractory chronic cough, neuromodulatory agents such as gabapentin, pregabalin, and amitriptyline may be considered [38]. Low dose of opiates have been shown to be efficacious in randomized controlled studies. Nebulized local anesthetics may be also considered [39]. The adenosine triphosphate (ATP)-gated P2X3 receptor, a key modulator of the activation of sensory neurons central to the cough reflex, has recently been recognized as a potential therapeutic target for the treatment of chronic cough. Gefapixant, a non-narcotic, selective antagonist of the P2X3 receptor, was recently shown to have efficacy and to be generally well tolerated in clinical trials in patients with refractory chronic cough [40]. Each treatment modality will be discussed in detail in subsequent chapters.

Summary

In summary, chronic cough is a common and troublesome clinical condition, causing a considerable impact on life. In the past, the clinical significance of chronic cough has been underestimated due to a lack of understanding of its etiology, mechanism, socioeconomic impact, and diagnostic/treatment options. By thorough evaluation with validated diagnostic protocols, the physician can guide patients to proper treatment as well as accurate diagnosis. In addition, extending our understanding to chronic cough hypersensitivity will provide new targets for controlling unexplained nonspecific chronic cough that is refractory to conventional treatments. A greater understanding of the neuroinflammatory mechanisms in the peripheral and central nervous systems in chronic cough hypersensitivity will suggest more efficacious targets and contribute to the development of new drugs. This book will cover updates of all aspects of chronic cough, including diagnosis and management.

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How to Assess Cough in the Clinic

2

Peter S. P. Cho, Surinder S. Birring, and Richard D. Turner

Introduction

This chapter will address patients presenting with chronic cough as the only or predominant symptom. The content presented here aims to be applicable to a range of clinical settings. This is a challenge as the type of patients presenting in the clinic will be affected by many factors, including local disease prevalence, local health service access and organisation, health beliefs and presenting behaviour. For example, tuberculosis remains the most common cause of chronic cough in many parts of the world [1], local smoking epidemiology will largely determine prevalence of COPD and lung cancer, and at the time of writing many parts of the world have recently been affected by the COVID-19 pandemic, a disease which currently has an unknown impact on long-term lung health, including chronic cough [2].

This chapter will discuss aetiologies of chronic cough and relevant investigations only briefly; the majority are discussed in more detail elsewhere in this book.

As a minimum standard, the initial routine assessment of chronic cough should include a clinical history, an evaluation of the severity and subjective impact of the cough, a physical examination, chest radiography and spirometry [3–7]. This initial basic assessment is key to guiding further investigation and management [4, 7]. The probability of life-limiting pulmonary pathology following a normal clinical examination and chest radiograph in isolated non-productive chronic cough is low [5, 8], particularly in those who have never or rarely smoked [5].

History

The main purpose of the clinical history is to help identify a potential cause, treatable trait or aggravating factor for the cough and to ascertain potential untrialled therapeutic options [3, 4, 9] (Table 2.1). It should be remembered that chronic cough in many cases may be multi-factorial; hence the clinician should not be immediately satisfied by identifying only one possibly relevant condition, particularly if the cough persists following treatment. Features suggestive of potentially serious or significant primary pathology include haemoptysis, breathlessness, voice disturbance, a history of smoking, recurrent respiratory tract

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S. H. Cho, W.-J. Song (eds.), *Diagnosis and Treatment of Chronic Cough*,
https://doi.org/10.1007/978-981-33-4029-9_2

Table 2.1 Clinical features suggesting specific common conditions associated with chronic cough and a normal chest radiograph

Diagnosis	Clinical features	Investigation findings
Asthma		
Classical asthma	Cough with diurnal variation; worse at night/early morning Associated wheeze and dyspnoea Symptoms induced by exercise Expiratory rhonchi	Variable airflow obstruction Bronchodilator reversibility Possible raised FeNO, serum and airway eosinophilia
Cough-variant asthma	Cough as sole feature	Variable airflow obstruction Bronchodilator reversibility Possible raised FeNO, serum and airway eosinophilia
Eosinophilic bronchitis		No bronchoconstriction or bronchial hyperresponsiveness Airway eosinophilia (>3%)
Gastroeosophageal reflux disease	Cough postprandial Dyspepsia/heartburn Voice change Dysgeusia	Oesophageal dysmotility
Post-nasal drip/upper airway cough syndrome	Rhinitis/rhinosinusitis Nasal obstruction Facial pain/pressure Headache Hyposmia/anosmia	Inflamed larynx Nasal polyps
Iatrogenic	Prescription of the following drugs: –ACE inhibitor –Calcium channel antagonist –Bisphosphonate	
Chronic obstructive pulmonary disease	Breathlessness on exertion Symptoms slowly progressive with minimal diurnal variation Smoking history (>10 pack years) Hyperinflation	Obstructive spirometry without significant reversibility
Bronchiectasis	Sputum production Recurrent respiratory tract infection Fine inspiratory crepitation (alter on coughing)	Characteristic chest CT findings including airway dilatation and mucus impaction
Interstitial lung disease	Breathlessness on exertion Finger clubbing Features of associated systemic disease (e.g. connective tissue disease, sarcoidosis) Fine inspiratory crepitations (not altered by coughing)	Restrictive spirometry Characteristic chest CT findings including honeycombing and ground glass changes
Lung malignancy	Haemoptysis Breathlessness Chest pain Weight loss Risk factors (smoking history and occupational history) Finger clubbing	Focal mass lesion Lymph node enlargement

Table 2.1 (continued)

Diagnosis	Clinical features	Investigation findings
Pulmonary tuberculosis	Sputum Haemoptysis Breathlessness Weight lost Night sweats Lymphadenopathy	Infiltrates and/or cavitation on chest imaging *Mycobacterium tuberculosis* identified in sputum or other clinical samples
Cough hypersensitivity syndrome	Hypertussia[a] Allotussia[b]	Normal CXR Normal spirometry

Note relevant conditions may coexist; this is particularly the case for cough hypersensitivity syndrome alongside other aggravating conditions

ACE angiotensin-converting enzyme, *FeNO* fractional exhaled nitric oxide, *CXR* chest radiograph, *CT* computed tomography

[a]Excessive coughing secondary to a normally cough inducing stimulus

[b]Coughing secondary to a non-tussive stimulus

infection and constitutional symptoms (weight loss and fevers in particular) [3, 9].

Features suggesting conditions commonly associated with chronic cough are summarised in Table 2.1.

The clinical features of upper and lower airway conditions and of gastrointestinal disease are discussed in detail in separate chapters of this book. Asthma is probably the most frequently overlooked and treatable underlying medical condition causing cough in higher-income countries [10, 11]. It is suggested by coexisting episodic wheeze and breathlessness, nocturnal symptoms, aggravation of cough by exercise, a younger age of onset, and the coexistence other atopic conditions (e.g. eczema and allergic rhinitis), although the absence of these features certainly does not exclude asthma or other eosinophilic airway disorders [6, 11, 12].

Coexisting heartburn and indigestion are probably the most helpful features for a diagnosis of gastroeosophageal reflux-related cough [5]. Upper airway cough syndrome is probably rare as a cause of chronic cough in the absence of typical nasal or sinus symptoms [13].

Angiotensin-converting enzyme (ACE) inhibitor use is an important cause or aggravator of chronic cough and is commonly ignored [4, 9, 11, 14]. There are few reasons to continue this class of medications in any patient with persistent cough, even after years of uneventful use [5, 14, 15]. It is important to advise patients that any effect of stopping ACE inhibitors can be delayed by up to 3 months or longer [4, 15]. The use of other medications may also be relevant; in particular bisphosphonates and calcium channel antagonists may aggravate reflux-related cough [4].

A history of occupational or environmental exposures to asbestos, silica, coal dust, other mineral compounds or organic dusts may suggest interstitial lung disease, as may specific coexisting symptoms relating to other anatomical systems (e.g. arthralgia, rashes, ocular problems) [16]. A temporal relationship of symptoms to the workplace may suggest occupational asthma or hypersensitivity pneumonitis [17]. Suggested important questions to include in a basic history are shown in Table 2.2.

Rarer causes of chronic cough should be considered in the history if no other relevant associated diagnosis is apparent. These include obstructive sleep apnoea (OSA) associated with snoring [18, 19], and tracheobronchomalacia (associated with a characteristic ‘honking’ cough sound) [20], which are reviewed elsewhere [20].

Table 2.2 History taking in chronic cough

Suggested questions in history taking in chronic cough
Age
Smoking history
Past medical history
Medications (prescribed and non-prescribed, current and within the last 6 months)
Occupation; relation of presence at work to symptoms
Acuity of onset of cough
Preceding respiratory tract infection
Sputum production
Triggers of cough Exercise Cold air Aerosols Posture Eating Talking/laughing
Abnormal sensations associated with cough—tickle, irritation, itch, globus
Timing of cough
Resulting physical symptoms from cough Incontinence Syncope Chest pain Fatigue
Associated symptoms[a]
Previous trials of therapy, including dose, duration and outcome

[a]Refer to Table 2.1

In many patients with chronic cough, there are no associated apparent relevant conditions. Cough hypersensitivity syndrome (CHS) was developed as a concept to describe chronic cough that is unexplained. Up to two-thirds of patients with CHS are female, with a peak incidence of age in the 50s and 60s [4]. CHS is associated with heightened cough reflex sensitivity (CRS) [21–23]. The presence of typical triggers of cough such as strong odours and speech and abnormal laryngeal sensations that precede cough (tickle in throat, irritation, itch; laryngeal paraesthesia) may be the only clinical features of CHS. The Cough Hypersensitivity Questionnaire (CHQ) is a simple and systematic tool which can be used to assess cough triggers [24, 25]. Aside from heightened CRS, there is emerging evidence to suggest that impaired central cough suppression pathways may play a role in the pathophysiology of chronic cough [26, 27].

Subjective Effects of Cough

Chronic cough is associated with considerable physical and psychological morbidity [28–30]. This, as well as concern about potential serious underlying disease, may be the predominant reason for seeking medical attention. An important element of clinical assessment therefore includes an evaluation of the severity and subjective impact of chronic cough on the patient.

The ideal approach to measuring the subjective effects of cough should be repeatable, not clinician-dependent, and responsive to meaningful clinical improvement. Specific tools to facilitate such assessments exist. They facilitate communication with patients and between clinicians, and enable monitoring of the cough over time, particularly in response to therapy [4, 6].

Severity

The severity of cough can be evaluated in several ways. A simple verbal rating out of 10 would be the most straightforward, but the validity of this approach is not clear. Specific tools such as a visual analogue scale (VAS) or the Cough Severity Diary (CSD) are more widely advocated [4, 31]. A standardised cough severity VAS is very simple to administer, consisting of a linear scale from 0 to 100 mm marked by the patient to give a score reflective of cough severity [31–33]. A numerical rating scale (0–10) is an alternative option that has numerical gradings and descriptors of the degree of severity to promote consistency of the patient's response longitudinally [4].

Cough VAS scores are a responsive measure in patients with chronic cough [34–39], and are used extensively in both standard clinical practice and clinical trials [31, 32]. Despite this, the

cough VAS has undergone only limited robust evaluation and currently has no established minimum clinically important difference (MCID) in chronic cough [32]. Trends within individual patients may therefore be as useful as the absolute magnitude of change. Repeatability studies of VAS suggest a change of 18 mm (95% limit of agreement) is likely to be significant, but its clinical relevance has not been studied [35].

The CSD is a 7-item outcome measure with an 11-point Likert scale for each item and has a reported high internal consistency and reproducibility in subacute and chronic cough [40, 41]. Nguyen et al. reported that the CSD is responsive in chronic cough, and a reduction of ≥1.3 is considered to represent clinically meaningful improvement [41]. The CSD has more validation data available, but a comparison against the VAS has not been published. Due to its responsiveness and simplicity, the VAS is the generally preferred tool for assessing clinical severity in the clinic [4, 36–39, 42–44].

Impact

Focusing on the severity of the cough itself is simple, but captures only a part of the morbidity of chronic cough. Health status generally can be significantly affected in chronic cough, due not only to the direct sensation of the cough itself, but resulting secondary physical, psychological and social effects. Secondary symptoms include chest pain, urinary incontinence, syncope, sleep disturbance and fatigue, whereas psychological and social effects include anxiety, low mood and excessive self-awareness in public situations [28, 30]. Evaluating these impacts of chronic cough is helpful in more fully addressing and monitoring the subjective effects of the condition [45].

Tools for the measurement of generic health status lack specificity and are often less responsive to treatments than cough-specific instruments [33, 46, 47]. The Leicester Cough Questionnaire (LCQ) and Cough Quality of Life Questionnaire (CQLQ) are two commonly used, validated and self-administered cough-specific health status measures [35, 48].

The LCQ consists of 19 items with a 7-point Likert scale for each item. Total possible summary scores range from 3 to 21, where higher scores indicate better health status [35]. It was originally well validated in terms of internal consistency, repeatability over 2 weeks and correlation with other relevant assessment measures [35]. The LCQ is responsive to therapy in chronic cough and has an established mean (SD) MCID (of 1.3 (3.2) points) in chronic cough [35, 49, 50]. It has been used very widely both clinically and in published research, in both English and a number of other languages [32, 51–53]. The CQLQ comprises 28 items with a 4-point Likert scale for each item (lower scores indicate better health status). In chronic cough, it similarly has high internal consistency, repeatability over 2 weeks, responsiveness [39, 48, 54] and an established MCID (of mean (SD) 21.89 (15.4) out of a possible total score of 112) [55, 56]. The CQLQ is probably less widely used than the LCQ, but, similar to the LCQ, has been useful in prominent clinical studies in chronic cough, including in a phase 2 study of the P2X3 inhibitor gefapixant (formerly AF219/MK-7264) [39, 48, 54].

A more comprehensive comparison of the LCQ and CQLQ is beyond the scope of this chapter and is available elsewhere [32].

Clinical Examination

Physical examination may reveal signs that are suggestive of an underlying or associated aetiology (Table 2.1). For example, expiratory wheeze and a prolonged expiratory phase would point towards obstructive airway disease, whilst inspiratory Velcro-like crackles suggest interstitial lung disease. It is imperative to look for any signs that may indicate malignancy, namely, finger clubbing, cachexia, lymphadenopathy and signs of lobar collapse or a pleural effusion. Extra-

pulmonary clinical signs may also suggest other diagnoses, such as raised body mass index and increased neck circumference in OSA, erythema nodosum in sarcoidosis, and other skin and joint changes in connective tissue disease-related interstitial lung disease.

Clinical examination, however, frequently yields no specific signs in unexplained chronic cough [8].

Investigations

Routine Investigations

A chest radiograph and spirometry should be part of the routine assessment of cough and can help to guide further investigations and management [4, 7].

Chest Radiograph

A chest radiograph is recommended universally as a standard investigation for all patients presenting with chronic cough [3–5]. It is able to identify the underlying aetiology of chronic cough in up to 30% of cases [57]. Conversely, the frequency of serious pulmonary pathology associated with chronic non-productive cough following a normal clinical examination and chest radiograph is low [6].

Spirometry

Guidelines also state that spirometry should be performed as part of the routine initial assessment [3–5]. Asthma is characterised by variable airflow obstruction, which can be detected through airflow obstruction reversible to inhaled beta-agonist. Bronchodilator responsiveness, however, has a low negative predictive value for the diagnosis when baseline spirometry is normal [58].

In patients with suspected asthma and normal spirometry with no reversibility, an inhalation challenge with either methacholine or histamine may potentially be used to assess for bronchial hyperresponsiveness [4, 5, 11]. There is, however, no consensus on the role of bronchial challenge in the investigation for asthma in chronic cough [4, 5, 11]. This is because the presence of bronchial hyperresponsiveness is not predictive of an antitussive response. Peak flow monitoring in isolated chronic cough has no role due to its poor negative predictive value [58]. Meanwhile, fixed airway obstruction is diagnostic of COPD [59].

Additional Investigations

The use of investigations in this following section should be guided by the presenting features, comorbidities and previous assessments and treatment trials of cough to date.

Thoracic Computed Tomography

There is some controversy over the routine use of thoracic computed tomography (CT) imaging in the assessment of chronic cough. Recent guidance from the European Respiratory Society takes the position that CT imaging is not routinely indicated in the absence of alarming features from the initial assessment (i.e. normal chest x-ray and nothing to suggest cancer or other significant lung disease from history and examination, particularly in the absence of a significant smoking history or strong family history of cancer) [4]. Meanwhile, some authors recommend CT imaging in patients with chronic cough which is refractory to treatment trials [7]. A CT of the thorax may identify pulmonary parenchymal abnormalities not visible on a chest radiograph [7], but the relevance of such relatively subtle changes to a persistent cough is unclear. Incidentally detected structural lung abnormalities are common; the majority are of no clinical consequence [60] and can result in unnecessary anxiety and further follow-up imaging [61]. CT imaging is also associated with considerable radiation exposure [4, 62–64]. Therefore, routine CT scanning of patients with unexplained cough should be proceeded with caution.

Bronchoscopy

The diagnostic yield of bronchoscopy in unselected chronic cough is low [65, 66]. Bronchoscopy may be useful if haemoptysis has been reported even when CT scan is normal [4]

and where the inhalation of a foreign body is suspected from the history [8]. Rarely, bronchoalveolar lavage can be used as an alternative to induced sputum to assess eosinophilic airway inflammation in patients with suspected eosinophilic bronchitis [4, 11].

Sinus Imaging and Upper Airway Endoscopy

Laryngoscopy may be used to investigate patients with upper respiratory tract symptoms, but has poor sensitivity and specificity in identifying post-nasal drip as the underlying aetiology in chronic cough in unselected patients [67, 68]. A common finding is laryngeal erythema and swelling, often thought to be secondary to laryngopharyngeal reflux. Cross-sectional imaging of the sinuses and rhinoscopy may be indicated in patients with recurrent sinus symptoms [4, 5]. However, in the absence of such symptoms, such imaging is unlikely to be warranted owing to the high prevalence of sinus abnormalities in the general population [4, 69]. This is discussed further in Chap. 4.

Markers of Eosinophilic Airway Inflammation

Airway eosinophilia (>3%) in the absence of bronchial hyperresponsiveness would suggest eosinophilic bronchitis (EB) [4]. Patients with eosinophilic airway inflammation and chronic cough may benefit from more intensified anti-inflammatory therapy [4, 11].

Fractional exhaled nitric oxide (FeNO) is non-invasive and may be used to identify eosinophilic airway inflammation which could be driving chronic cough [4]. Sadeghi et al. demonstrated that FeNO is associated with serum and sputum eosinophil counts in patients with chronic cough [70]. However, a recent review reported that FeNO measurement has a considerably wide range of sensitivity and specificity in predicting responsiveness to inhaled corticosteroids in chronic cough (53–90% and 63–97%, respectively) [71]. In addition, there is currently no consensus on a cut-off to identify patients with airway inflammation [4]. There are therefore limited data to support the use of FeNO measurement in the evaluation of unselected patients with chronic cough, and this was the view of European Respiratory Society (ERS) guidelines 2019 [4, 71].

Induced sputum can be used to obtain samples to assess eosinophilic airway inflammation directly [4, 11]. Such assessment is non-invasive and accurate, but is not readily available at most centres, and therefore is predominantly a research tool [4].

Serum eosinophil counts can be assessed with much greater ease, though there is significant diurnal and seasonal variation [9, 72], meaning that multiple assessments are required. A cut-off for a significant eosinophilia of ≥ 0.3 cells·μL^{-1} has been suggested by the ERS [4, 73]. However, as with FeNO, there is little evidence to support the predictive value of serum eosinophil counts in guiding steroid therapy for chronic cough [4]. In the authors view, the presence of elevated blood eosinophils should be followed by a review of patient adherence to asthma therapy, inhaler technique review and intensified airway anti-inflammatory medication. This is discussed further in Chap. 5.

Gastrointestinal Investigations

There is no single definitive investigation available for the diagnosis of reflux or oesophageal dysmotility in chronic cough [4]. Clinical assessment can be supplemented with the validated Hull Airway Reflux Questionnaire (HARQ) or the Reflux Symptom Index (RSI) [74, 75]. Recent European guidance suggests that routine investigation and treatment trials of proton pump inhibitors are not indicated in the absence of relevant clinical features (symptoms of acid-related heartburn) suggesting upper gastrointestinal disease [4]. High-resolution 24-h oesophageal manometry is the most sensitive and specific investigation [4, 5]. The degree of abnormality detected is however not related to cough severity [5]. Barium swallow and gastroscopy have relatively low sensitivity for reflux disease compared to manometry [4, 5]. This is discussed further in Chap. 6.

Cough Frequency

There is currently no automated cough frequency monitor commercially available in the clinical setting that analyses cough in real time and without technician input [32]. This has largely restricted the role of objective cough frequency assessment to clinical research, where it is now the clinical endpoint of choice in antitussive drug trials [39, 76]. With emerging technologies in speech recognition, ambulatory cough monitoring may become more readily available, possibly including the incorporation of cough detection algorithms into smart phone applications [32, 77].

Cough frequency monitoring could provide an objective measure of the severity of chronic cough and be used to assess responses to treatment trials. However, before such technology is more readily available, clearly no recommendations can currently be made for its routine clinical use.

Other Investigations

Skin prick tests are widely available and are relatively free of adverse effects [78]. Radioallergosorbent tests (RAST) are an alternative and measure the concentration of allergen-specific immunoglobulin E, with the advantage of not being influenced by any anti-histamines or systemic steroids [78, 79]. Both can be used to diagnose atopy in support of a diagnosis of asthma, and may identify a specific allergen leading to cough in this context.

Suspected OSA should be investigated with nocturnal oximetry or a formal respiratory sleep study according to local availability [80].

Follow-Up

Follow-up assessments of cough, after a time interval which may have included a trial of treatment, should include a re-evaluation of cough severity and impact. The extent of further investigation of chronic cough will partly be an iterative process, and will be influenced by the nature of the presenting clinical features, the results of previous investigations, the outcomes of any therapeutic trials (Chap. 3), and the impact of any residual cough on the patient. The desire of the patient and clinician to exclude pathology as much as possible is important, but a temptation to over-investigate counter to evidence or published guidance should be resisted (e.g. by avoiding investigations for upper airway or gastroeosophageal disease in the complete absence of relevant specific localising symptoms) [4]. In many cases, there may be no indication for follow-up, particularly where symptoms are mild, and there is mutual satisfaction that important disease has been excluded with sufficient certainty.

The ultimate cause of chronic cough in any patient can often be difficult to ascertain, even after positive investigations or trials of directed treatments. Chronic cough is common, as are many of the conditions associated with it, including asthma, gastroeosophageal reflux and chronic rhino-sinusitis; it is possible that these pathologies are coincidental and unrelated directly to the cough. Complicating matters further is the fact that chronic cough can resolve with no treatment, or recur periodically, and often responds well to placebo, as in the control arm of antitussive trials [10, 36, 76, 81, 82]. Chronic cough is also often multi-factorial; underlying cough hypersensitivity might, for example, be aggravated by a combination of gastroeosophageal reflux and asthma.

Summary

The assessment of chronic cough includes a basic but focused history, clinical examination and evaluation of cough severity and impact. Spirometry and a chest radiograph are recommended in all, but further investigations will largely depend on presenting features, the presence of co-morbid conditions and previous investigations and trials of treatment. Table 2.3 provides a summary of the assessment of chronic cough in the clinical setting.

Table 2.3 Assessment of chronic cough

	Assessments
Initial assessment in all	*Clinical assessment* Clinical history Physical examination *Severity* Rating out of 10, visual analogue scale (VAS) or Cough Severity Diary (CSD) *Impact* Leicester Cough Questionnaire (LCQ) or Cough Quality of Life Questionnaire (CQLQ) *Basic investigation* Chest radiograph Spirometry
Specific focused assessments guided by initial assessment	
Asthma/ eosinophilic bronchitis	Spirometry and bronchodilator reversibility testing Bronchial hyperresponsiveness (inhalation challenge) Induced sputum/broncho-alveolar lavage eosinophil count Fractional exhaled nitric oxide
Reflux/ oesophageal dysmotility	High-resolution 24-h oesophageal manometry and impedance
Post-nasal drip syndrome	Laryngoscopy Rhinoscopy Computer tomography of sinuses
Lung cancer; interstitial lung disease; bronchiectasis	Computer tomography of thorax

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3 Diagnostic and Therapeutic Trials for Chronic Cough in Adults: An Overview

Eva Millqvist

Introduction

The diagnostic and therapy of chronic cough is often a challenge and followed by uncertainty regarding which treatment path to follow. However, there are some simple steps that should always be regarded. In the recently published European Respiratory Society (ERS) cough guidelines, both the diagnostics and possible choices of therapy are discussed in detail for more profound information and knowledge [1]. The clinical picture is often complex, and thus it is important to regard how other conditions may influence and also induce chronic cough. Figure 3.1 gives a schematic image of how various factors may interplay, as well regarding diseases as for lifestyle and use of medication. History taking, physical examination, and some routine investigations may help to identify clinical traits associated with chronic cough. The aim of this book chapter is to provide an overview of diagnostic and therapeutic trials for adult patients with chronic cough. Each diagnostic test and treatment is also discussed in detail in separate chapters of this book.

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History Taking

Cough Duration and Cough Description

It is important to ask cough duration as it is useful to predict the possibility of spontaneous remission (or persistence) of cough. Daily cough for more than 8 weeks is regarded as a chronic condition, though there are some differences in this definition [3]. Cough with duration of less than 8 weeks may resolve spontaneously, whereas cough for longer than 1 year is more likely to persist. Several questions may be practically useful to initiate history taking, including the description of cough and its duration, and differentiate dangerous conditions such as malignancy, infection, or foreign body inhalation: When did the cough start and during which circumstances? Is the cough dry, or is there phlegm or haemoptysis? Any history of foreign body inhalation?

Cough Triggers

Chronic cough is often characterized by a hypersensitivity to environmental factors, normally regarded as non-toxic. The recently established concept of cough hypersensitivity syndrome (CHS) is an "umbrella" for chronic cough with vagal hypersensitivity and could be due to a variety of causes [4–7]. The patients frequently

S. H. Cho, W.-J. Song (eds.), *Diagnosis and Treatment of Chronic Cough*,
https://doi.org/10.1007/978-981-33-4029-9_3

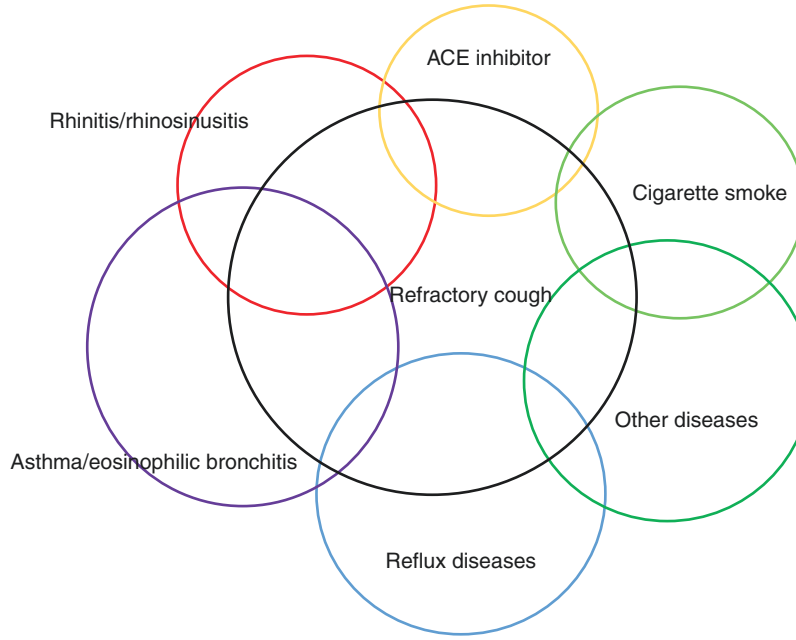

Fig. 3.1 Factors of importance in assessing chronic cough [2]

report chemicals, perfumes, or cigarette smoke as triggers. Also, cold air and exercise are common trigger factors, which may be followed by an incorrect diagnosis of asthma. The chronic cough is often worsened during common colds. However, there is no evidence whether a certain pattern of cough triggers could help differential diagnosis of chronic cough. This information may help to educate patients to recognize and avoid triggers, which may help to prevent vicious cycle of coughing.

Family History

It is not unusual that the patients report of close relatives with the same problems, though so far there are no identified genetic factors commonly associated with chronic cough.

Cough Assessment

An easy way to get an understanding of the cough's impact on the patient is to use a visual analogue scale (VAS) or simple scoring system 0–10. Simple scoring system asks the patient to score the coughing from 0 to 10. Zero is no cough at all and 10 is the worse thinkable cough. This scoring system is useful to follow up clinical responses in each patient. Cough assessment is discussed in detail in Chap. 2.

Cough Questionnaires

Validated cough questionnaires may be useful to assess cough more precisely, particularly in relation to certain aspects of chronic cough. The Hull Airway Questionnaire (HARQ) is another simple way to estimate problems induced by chronic cough [8]. The questionnaire consists of 14 items including reflux. The unweighted sum of all 14 items makes up the subject's total HARQ score, which ranges from 1 to 70. The cut-off value 13 is considered a normal value. The Leicester cough questionnaire (LCQ) is a valid, repeatable 19-item self-completed quality of life measure of chronic cough which is responsive to change [9]. Minimally important difference in the LCQ score is 1.3 in patients with chronic cough.

Cough-Associated Symptoms

Ask for symptoms from the throat and chest and for reflux and acid stomach symptoms. Predictive values of these symptoms to identify treatable traits in chronic cough are not validated but may be useful in the clinic.

Other Medical Conditions to Consider

Has the patient any other known medical condition such as heart failure? And in that case, is there any ongoing medication? Angiotensin-converting enzyme (ACE) inhibitors are since long known to induce daily cough in a sub-group of individuals and should always be excluded as a cause to the symptoms. There are a number of alternatives for ACE inhibitors.

Risk Factors

Smoking, present and earlier, should be mapped as should signs of sleep apnoea. The number of smoking pack years is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. Also overweight is a risk factor to take into account for reflux.

Physical Examination and Diagnostic Tests in Assessing Patients with Chronic Cough

Physical Examination

This includes pulmonary and cardiac auscultation; blood pressure; ear, nose and throat status; and palpation of the abdomen and lymph nodes. Ear examination may help to detect Arnold's cough reflex, which is a sign of vagal hypersensitivity.

Blood Samples

A routine blood sample will indicate other serious diseases. An increased eosinophil count in the peripheral blood may indicate a treatable trait (eosinophilia-associated cough such as asthma or eosinophilic bronchitis) and thus is a clinically valuable sign. As moderate increase is regarded a number of eosinophil granulocytes between $1.5–5 \times 10^9$/L blood and as high increase a number of $>5 \times 10^9$/L blood. When finding a value in the high range, or a value limiting to high, this may be an indication to look more specifically for a condition like asthma or eosinophilic bronchitis, to further analyse induced sputum and fractional exhaled nitric oxide (FeNO), or to try corticosteroid therapy.

Chest X-Ray

A chest X-ray should be assessed in all patients seeking health care due to chronic cough. This may exclude most serious pulmonary conditions followed by chronic cough.

Spirometry with Reversibility Testing

Spirometry is a simple method to assess lung function that should be routinely performed, though at normal values a bronchoconstriction may occur and could be revealed with reversibility testing using a bronchodilator.

Methacholine and Mannitol Provocations

When there is a suspicion of underlying asthma, a positive methacholine or mannitol provocation can indicate the presence of a treatable trait though none of the tests are prerequisite for asthma. The mannitol test may prove particularly

valuable when the patient complains of coughing induced by exercise and cold air [10], not at least to rule out an asthma diagnosis.

Capsaicin Cough Sensitivity

The CHS is characterized by sensitivity to irritating stimuli but also by increased cough sensitivity to inhaled capsaicin [5, 11]. In a few clinics, the capsaicin cough sensitivity is assessed in the diagnostics [12] but is not generally recommended for other use than in scientific studies.

FeNO

FeNO is a noninvasive, safe, and simple method of quantifying airway inflammation and related to allergic asthma and eosinophilic bronchitis [13]. However, FeNO is not diagnostic for asthma, nor does a normal FeNO measurement exclude the diagnosis of asthma. Increased FeNO may be a sign of cough variant asthma in patients with chronic cough and is an indication that treatment with corticosteroids may be valuable [14]. Today, FeNO is mostly measured at pulmonary and allergy clinics and not in primary care. The equipment for FeNO measurement is still rather expensive.

Induced Sputum

High level of eosinophils in induced sputum is a further sign of eosinophilic disease but is not needed to be performed routinely. It is technically challenging and requires experienced personnel and instruments to analyse the samples.

Chest Computed Tomography Scan (CT)

When the chest X-ray is normal and so is the physical examination and the above-mentioned physical status and diagnostic tests, the probability of diagnostic help from a CT is low. In the end, it is the decision of the individual physician to choose to go further with this investigation. Only observational (mostly retrospective) studies have reported the utility and specific findings on causal relationship with cough were not described or not likely to explain the cough [15, 16]. There is also a concern about potential cancer risk from CT radiation exposure. In summary, the ERS cough guidelines suggest that clinicians do not routinely perform a CT in patients with chronic cough who have a normal chest X-ray and normal physical examination [1].

Gastroscopy and 24 h Oesophageal pH Measurement

Several studies have shown that when a patient with chronic cough has no reflux or acid stomach symptoms, the value of anti-acid treatment is low [17, 18]. In accordance with these findings, gastroscopy and 24 h oesophageal pH measures seem to be unnecessary in most cough cases without acid stomach symptoms.

Oesophageal Motility Recording

In chronic cough patients oesophageal dysmotility is common [19] and could be identified with manometry though the use of such findings is uncertain taking in regard the lack of evidence for treatment utility.

Laryngoscopy

Cough patients with upper airway symptoms have often an inflamed and red larynx, and a laryngoscopy [20] may be useful to identify inducible laryngeal obstruction (or laryngeal hypersensitivity) but is not needed to be performed routinely.

Rhinoscopy

To exclude nasal polyps and nasal obstruction rhinoscopy may be useful in patients with upper

airway symptoms dominating but is not needed to be performed routinely.

Pathological findings during these first steps, indicating other or any serious disease, should be followed by further addressed and directed investigations and treatments in accordance to national or local guidelines.

Therapeutic Trials

When Treatable Traits Are Not Found and Risk Factors Are Excluded

In a number of cases, the physician finds no treatable traits of the chronic cough, and this may cause frustration and irritation. However, in such cases, the doctor can clearly explain to the patient that the cause to the cough *is* known; it is a hypersensitivity of vagal sensory nerves, though not always easy to treat. The good news is that no serious disease was found. Many patients fear a lung cancer or other severe illnesses to cause the coughing, which of course must be excluded. The lack of reliable test to guide the treatment is inevitably followed by a kind of "trial and error" treatment.

Though only normal findings, there are yet a number of empirical treatment options to be evaluated. *Important is to remember an evaluation of a given medication after about 1 month to assess whether to continue the therapy.*

Corticosteroids and Anti-leukotrienes

There are a shortage of evidence for the utility of corticosteroids and anti-leukotrienes in the treatment of chronic cough without treatable traits. In the literature, there is a heterogeneity regarding the efficacy of ICS in adult patients with chronic cough, probably depending on different phenotypes of cough [21]. To assess their usefulness, placebo-controlled studies are needed and also better evaluation of diagnostic tests. A short test period with oral steroids or a month with high-dose ICS or anti-leukotrienes is indicated, but the result must be *swiftly* evaluated, especially in cases without any signs of asthma and/or eosinophilic disease. There is a risk of long-drawn treatment with anti-inflammatory medicines without effects, and to a certain cost, this could be problematic as chronic cough waxes and wanes and thus therapeutic responses are often difficult to differentiate from spontaneous improvement. Though regarded as safe and with few side effects, treatment with ICS for decades cannot be regarded as completely harmless.

Neuromodulatory Agents

1. Opioids

- Morphine: One single randomized control trial of low-dose morphine (5–10 mg twice daily) in adults with chronic refractory cough found significant benefits over placebo in ameliorating chronic cough [22]. In low doses morphine can be tried in chronic refractory cough, but the risk of side effects must be regarded. The effect of morphine should be evaluated after 1 or 2 weeks since clinical experience shows that if the cough has not benefited then from the treatment, success rate is low.
- Codeine: Contrariwise, though commonly used, codeine is not suitable due to inter-individual genetic variability in drug metabolism and can be recommended only when other opioids are not available and with special awareness of side effects. Individuals with CYP2D6 gene phenotypes metabolize codeine in different ways, both slow and ultra-rapid, which may be followed by adverse codeine reactions depending on a changed CYP2D6 function [23].

2. Gabapentin and Pregabalin

In two randomized, controlled studies, gabapentin and pregabalin showed positive effects on chronic cough though adverse events were also frequently reported [24, 25]. For gabapentin the maximum tolerable daily dose was 1800 mg, and the dose used for pregabalin was 300 mg daily.

Drugs with Pro-motility Activity

In chronic cough, oesophageal dysmotility is common, and a short period of pro-motility agents can be tried (and the effect evaluated) though controlled trials are mostly lacking.

1. Macrolides
   Azithromycin or erythromycin may have effect in a sub-group of patients with chronic cough and could be tried during a shorter period though with lack of scientific evidence, and there is also a concern about macrolide resistance.
2. Other pro-motility agents
   Baclofen, metoclopramide, or domperidone improve oesophageal motility and may be considered though with lack of evidence from clinical trials.

Anti-acid Drugs

- Proton pump inhibitors (PPIs)
  In short, the use of anti-acid drugs like proton PPI in chronic cough can be recommended only when peptic symptoms or evidence of acid reflux are present. Several studies report benefit of PPIs in chronic cough provided just when acid symptoms also are present [26]. Though considered as mostly well tolerated and without serious side effects, there is a potential concern about increased risks of adverse events such as pneumonia, iron deficiency, vitamin B2 deficiency, small intestinal bacterial overgrowth, *Clostridium difficile*-associated diarrhoea, or bone fracture [27]. There is a concern of PPI overuse.

H1-Antihistamines

Though some hope of the use of H1 antihistamines in chronic cough, there is no evidence enough to recommend this medication in cough treatment in regard to the lack of adequate randomized controlled trial. The first generation of H1-antihistamines (often sedative) is supposed to have an antitussive effect depending on their action as centrally penetrant anticholinergics [28]; however, there are potential risks of central side effects from the first-generation H1-antihistamines, such as inattention, alteration in consciousness, or injurious falls, which may be of particular concerns in older patients. There is no robust evidence on the benefits of second-generation H1-antihistamines in chronic cough.

Non-pharmacological Therapy (Cough Control Therapy)

Improvements in chronic cough from therapy by a trained physiotherapist or speech therapist were reported in a couple of studies and can be recommended when such expertise is available [29].

Summary

The main message of this book chapter is to look for treatable traits in the chronic cough patient and then choose how to go further. When the "basic setup" shows no such treatable traits or worrying signs, there are a number of medications to test, but the physician must always remember to follow up and evaluate the treatment. There are today too many patients with various ongoing medications for years and years, based on negative findings and little or no improvement of the cough symptoms. It is however important to remember to inform the patient with refractory coughing that though today no effective treatment may be available, the cause of the cough is understood and future medicines are in development.

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4 Upper Airways: Assessment and Treatment for Cough

Woo-Jung Song, James H. Hull, and Kian Fan Chung

Introduction

Chronic cough is a multifactorial clinical syndrome commonly presenting as cough hypersensitivity in adults [1]. Physiologically, cough is a protective reflex that results from the irritation of sensory afferent nerve endings in the airways. Initiation of cough reflex in human is considered exclusively attributed to vagal nerve in the airways, but it is also likely affected by other sensory afferent inputs including the nose (such as trigeminal nerve) [2, 3]. In the presence of pathological conditions affecting the airway sensory nerve endings, cough reflex pathways may become dysregulated, and cough may persist for months or years. Thus, the diagnosis and treatment of such medical conditions would help to normalize cough reflex in patients with chronic cough.

Upper airway symptoms or diseases involving the nose or throat areas are frequently found in patients with chronic cough, although the prevalence may greatly vary with region or clinical setting [4–6]. Mechanistically, the causal relationships between upper airway diseases and cough in patients with chronic cough have been long suspected but they still remain controversial, as the nasal mucosa is primarily innervated by trigeminal nerve but not by vagus nerve [3]. Stimulation of the nasal mucosa using irritants or tussigens induces sneezing but not coughing [3]. However, in the clinical setting, their frequent overlap often leads physicians to establish the presence of a contribution from the nasal or laryngopharyngeal, often termed as postnasal drip syndrome or upper airway cough syndrome [7]. There are still considerable discrepancies in the approach between recent guidelines in relation to upper airway diseases and chronic cough [8–10]. The lack of international consensus may be attributed to a lack of quality evidence and also possibly to the regional differences in cough epidemiology and clinician's experience. This is further complicated because cough is prone to spontaneous remission or placebo effects; it is often difficult to differentiate them from true therapeutic responses [11, 12]. This chapter introduces the clinical evidence regarding the effectiveness of assessing and treating upper airway conditions in patients with chronic cough, with a focus on the nose and larynx, and also introduces a pragmatic clinical approach (Fig. 4.1), based on the evidence and the authors' clinical experience.

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S. H. Cho, W.-J. Song (eds.), *Diagnosis and Treatment of Chronic Cough*,
https://doi.org/10.1007/978-981-33-4029-9_4

If allergic nasal symptoms are present

- Trial of H1RA (non-sedating drug preferred)
- Trial of intranasal corticosteroids
- Allergen skin prick or specific IgE test to consult allergen avoidance or immunotherapy

If nasal polyps are suspected in clinical history

- Nasal endoscopy to confirm nasal polyps
- Further investigations for eosinophilic bronchitis or late-onset asthma

If laryngeal dysfunction is suspected in clinical history

- Challenge laryngoscopy to confirm laryngeal dysfunction
- Assessment for comorbid conditions potentially aggravating larygeal dysfunction
- Speech language and pathology therapy
- Trial of gabapentin, pregabalin, or amitriptyline

Fig. 4.1 Pragmatic clinical approach to patients with chronic cough and upper airway symptoms

Sinonasal Disease and Chronic Cough

It was previously suggested that in many patients, cough occurs directly as the result of a stimulation of sensory afferent endings in the nasal or pharyngeal mucosa. However, direct stimulation of the nasal mucosa with capsaicin or histamine induces sneezing reflex but not cough [3]. Moreover, in an observational study at a rhinology clinic, only about 10% of patients with purulent postnasal drip complained of cough in the absence of other suspected cough etiology [13]. Also, nasopharyngeal sensitivity to air puff instillation is found to be significantly lower in patients with chronic postnasal drip than in healthy controls [14]. These findings suggest that nasal inflammation or direct stimulation of nasopharyngeal mucosa by postnasal secretion may not be a major determinant in driving cough.

However, there is some evidence that nasal inflammation may modulate the cough reflex, despite the effects being likely indirect [3]. For example, in subjects with pollen allergic rhinitis, cough becomes significantly more sensitive during the pollen season [15]. This possible "nose-cough" interaction suggests the nose may play a "gatekeeper role" in host defense for the lower airways, perhaps priming the host to be more responsive to environmental triggers, and also implies that there may be a potential benefit from treating nasal inflammation to improve cough.

Diagnostic Tools

There are very few studies evaluating the utility of diagnostic tests for nasal conditions in the context of chronic cough, which is surprising given their frequent overlaps and academic interests [6, 7, 10]. In a study of 43 patients with chronic cough, using a comprehensive diagnostic protocol, the positive predictive value of sinus computed tomography (CT) was comparable to careful ear nose and throat examination in determining postnasal drip syndrome as a cause of chronic cough (67% vs. 63%, respectively) [16]. In another prospective study of 36 chronic cough patients who underwent sinus imaging, ten patients (28%)

were found to have a sinus abnormality (seven mucosal thickening and three air fluid levels or sinus opacification); however, the specificity of sinus imaging to predict the cause of cough was less than 50% [17]. These are in line with our clinical experience, in that mucosal thickening or maxillary sinus opacification is a frequent finding even in subjects without chronic cough or even nasal symptoms, particularly in adults, and such the findings of sinus change on imaging studies should not infer a causal relationship.

To our knowledge, there is no evidence on the utility of nasal endoscopy in patients with chronic cough. It is our own view that the presence of purulent nasal secretion or postnasal drip is frequent in patients without cough and thus be of little value in the evaluation of chronic cough. In a research context, it was reported that nasal fluid neuropeptide levels, such as calcitonin gene-related peptide or substance P, are significantly elevated in postnasal drip patients with chronic cough than in those without chronic cough [18]. The findings suggest that the nature of postnasal secretion or nasal inflammation may be more important than the presence; however, they are difficult to measure in usual clinical settings. Meanwhile, nasal polyps are relatively more frequent in older men and are positively associated with nasal obstruction and anosmia (or hyposmia) [19]. Of note, the presence of nasal polyps may indicate eosinophilic inflammation in the lower airways, even in the absence of atopy [20, 21]. Thus, further investigation for late-onset asthma or eosinophilic bronchitis is indicated in cough patients with nasal polyps.

Meanwhile, tests for allergic sensitization, such as allergen skin prick test or serum allergen-specific IgE measurement, may be useful in cough patients with an allergic history, such as allergic conjunctivitis, rhinitis, or asthma. This information may help to discuss preventive measures such as allergen avoidance or potentially desensitization (immunotherapy). However, in patients without a compatible clinical history, routine allergen-specific IgE tests are unlikely to be helpful because asymptomatic IgE sensitization is common in the absence of clinical relevance [22]. In summary, we suggest that routine diagnostic tests for nasal conditions, including sinus imaging, nasal endoscopy, or allergen testing, are not likely to be useful in patients with chronic cough, and any clinical decision to choose the tests should be based on a careful history taking and physical examination.

Treatment

Some early clinical trials in adults with chronic cough reported the benefit of first-generation H1-histamine receptor antagonists (H1RAs) [10]. However, the effects of H1RAs on cough may be attributable to their central effects, rather than by peripheral blockade of H1-histamine pathways. Therefore, the clinical response to first-generation H1RAs should not be used to enforce a sinonasal or allergic upper airway cause of cough. In addition, it should be noted that patients with chronic cough are frequently middle-aged or older women [23], and it is worth recalling that first-generation H1RAs can be associated with potential risk of side effects such as somnolence and neurological issues promoting a risk of falls [24].

There are several clinical trials reporting the efficacy of second-generation or non-sedating H1RAs on cough, although cough was not characterized in detail. In patients with seasonal allergic asthma and rhinitis, two trials using desloratadine 5 mg once daily reported significant improvements in cough scores compared to placebo treatment [25, 26]. In a study of 20 patients with allergic rhinoconjunctivitis and cough, treatment with loratadine 10 mg once daily was significantly more effective than placebo in reducing cough score during the pollen season [27]. However, other trials with loratadine or azelastine did not find similar benefits on cough outcome, when compared with placebo [28, 29]. Importantly, all these trials were not designed to examine cough, but also had a limitation that it assessed cough using a simple unvalidated scale (such as a scoring system of 0–3). Such differences in the unvalidated scores are difficult to interpret if the changes are clinically meaningful. Thus, overall, it is concluded that there is no convincing evidence yet in support of second-generation non-sedating H1RA treatment to

reduce cough in patients with chronic cough and nasal symptoms. Further clinical trials are warranted using validated assessment tools in key dimensions of cough, such as cough frequency or cough-specific quality of life (QoL).

It is clear that non-sedating H1RAs can be helpful to reduce nasal or ocular symptoms in patients with allergic rhinitis or conjunctivitis, regardless of cough [30]. Thus, currently, the presence of a clinical history suggesting active allergic comorbidities (such as nasal itching and sneezing) should serve to promote the choice for non-sedating H1RA in patients with chronic cough. Clinical benefits of these H1RAs are unknown in cough patients without allergic nasal symptoms. Meanwhile, patients with chronic cough are frequently middle-aged or older, and individuals in this age group may frequently have vasomotor rhinitis (which is not histamine-mediated) [31], and in our clinical experience, non-sedating H1RA are not a particularly useful treatment to relieve cough in these cases. Further clinical trials are warranted to confirm the efficacy in these patients.

There is very little evidence regarding topical treatments in patients with chronic cough. In an open pilot study of 21 patients with chronic cough and postnasal drip symptoms, cough and nasal symptom scores significantly improved after the 4-week treatments with nasal fluticasone, ipratropium bromide, and azelastine sprays [32]. In a trial of 36 patients with active nasal symptoms and stable chronic obstructive pulmonary disease, fluticasone furoate nasal spray appeared to show some benefits on cough score at 6 weeks, but not consistently throughout the 12-week trial period. Meanwhile, in a trial of patients with chronic cough and allergic rhinitis, fluticasone propionate nasal spray treatment significantly improved cough visual analogue scale (VAS) score, but not cough-specific QoL, cough symptom score, or capsaicin sensitivity [33]. However, this trial [33] used normal saline nasopharyngeal irrigation, but not placebo, as the comparison; thus these findings could not draw any robust conclusions regarding the clinical benefits of nasal steroid therapy. One interesting finding from the study [33] is that normal saline nasopharyngeal irrigation was more effective than nasal steroid in some of the cough endpoints, such as cough symptom score, cough-specific QoL, and capsaicin cough sensitivity, and the improvements in cough outcomes were significantly associated with a decrease in the levels of histamine or leukotriene C4 in the nasal lavage fluid [33]. It is clear that a placebo-controlled trial is warranted to determine the efficacy of intranasal steroid or saline irrigation in chronic cough.

Laryngeal Dysfunction and Chronic Cough

The larynx is the principal organ for lower airway protection and is innervated by vagus nerve [34]. Thus, it is not surprising that laryngeal hypersensitivity or its motor dysfunction is frequently associated with cough. Most patients with chronic cough localize their cough or urge-to-cough to throat or neck area and have some abnormal sensation in the throat, such as throat tickling, itching, or irritation [35–38]. These symptoms are often "sensory"-type features of laryngeal hypersensitivity but in some settings can be associated with motor dysfunction patterns. This laryngeal dysfunction has been described by various names in the literature, such as vocal cord dysfunction, laryngospasm, paradoxical vocal fold movement, or inducible laryngeal obstruction. It is defined by direct visualization of the altered (maladaptive or dysfunctional) movements of the larynx, including inappropriate closure of laryngeal inlet [34]. In recent studies, using endoscopic visualization of the laryngeal movements, laryngeal dysfunction was as common as 50–70% of patients with chronic cough [39, 40]. A major challenge is that the diagnostic procedure for laryngeal dysfunction is technically demanding to be used on usual clinical settings [41].

Diagnostic Tools

In typical cases, clinical history should serve to indicate the presence of possible laryngeal dysfunction [34]. Classical features include symptoms of stridor, cough, voice change, and throat or chest tight-

ness, which are highly variable, rapid onset, and repeatedly triggered by certain environmental triggers [42]. However, it may also present as dyspnea and wheeze, mimicking asthma. This complexity may delay the diagnosis of laryngeal dysfunction, sometimes leading to unnecessary corticosteroid treatment. It is notable that laryngeal dysfunction is not exclusive to asthma but is rather frequently comorbid in asthmatics (about 25%) [43].

The gold standard test to diagnose laryngeal dysfunction is flexible laryngoscopy with application of an external trigger or provocation (challenge laryngoscopy) [34, 42]. The provocation test may utilize a provocation agent selected, based on the clinical history of individual patients. Resting laryngoscopy (without a trigger provocation) is not recommended, as the laryngeal movement may be entirely normal when the trigger is not present. A specialized larynx CT protocol is also used to delineate abnormal or excessive laryngeal closure, in some research centers [44]. There are questionnaire tools that support the diagnosis of laryngeal dysfunction, including the Newcastle Laryngeal Hypersensitivity Questionnaire and more recently a throat VAS score [45, 46].

Treatment

Optimal treatment for laryngeal dysfunction in chronic cough remains to be determined. It is important to identify comorbid conditions that may potentially aggravate laryngeal dysfunction, such as asthma or gastroesophageal reflux. However, the causal relationships with comorbid conditions may be difficult to determine.

Speech pathology and language therapy is thought to be the main option for cough patients with laryngeal dysfunction (please see Chap. 8 in this book for details). It is a complex, multidimensional intervention conducted by experienced professionals, involving patient education, cough suppression exercise, vocal hygiene strategies to reduce laryngeal irritation, and psychoeducational counseling. Based on two randomized controlled trials [47, 48], it is now recommended for the management of adult patients with chronic refractory or unexplained chronic cough [8, 49].

Drugs with cough neuromodulatory effects may also have some beneficial effects in improving laryngeal dysfunction, cough, or both. In the study by Vertigan and colleagues, speech pathology and language therapy intervention with pregabalin was significantly more effective in improving cough-specific QoL and laryngeal symptom questionnaire scores in patients with unexplained chronic cough, compared to the speech pathology intervention with placebo [50]. In two retrospective cohort studies of patients with chronic cough who received gabapentin, the presence of asymmetrical vocal fold motion or laryngeal motor neuropathy was significantly associated with better gabapentin treatment response [51, 52]. A case series described that low-dose amitriptyline was effective in patients with vocal cord dysfunction [53]. Thus, these may be therapeutic options for cough patients with laryngeal dysfunction, although placebocontrolled trials are warranted to confirm the benefits of cough neuromodulators on laryngeal dysfunction. Proton pump inhibitors are often considered for laryngopharyngeal reflux, but are not recommended as a treatment for chronic cough unless there is clear evidence of acid reflux [8, 54].

Conclusion

Upper airway diseases or symptoms involving the nose or larynx are frequent in patients with chronic cough. Sinonasal diseases may not be a direct cause of cough. However, allergic nasal inflammation may sensitize cough reflex, and anti-allergic treatment may be indicated in patients with cough and allergic rhinitis. The presence of nasal polyps may indicate comorbid eosinophilic inflammation in the lower airways, which is frequently adult-onset and warrants anti-inflammatory treatment. However, there is a lack of evidence to support the routine nasal investigations in patients with chronic cough, and clinical decision whether to perform a test should be based on a careful history taking and physical examination. Pharmacological treatments targeting sinonasal diseases are not routinely indicated in cough patients without nasal symptoms, as there is no quality evidence to

support the use. First-generation H1RAs may be effective in reducing cough, but the response does not prove the causal relationship between nasal allergy and cough as the sites of actions may include central nervous system. Further placebo-controlled trials are warranted to confirm if second-generation/non-sedating H1RAs or topical agents are effective in patients with cough and nasal symptoms.

Laryngeal hypersensitivity and dysfunction may be commonly comorbid in patients with chronic cough. Flexible laryngoscopy with external trigger application (such as odor or exercise) is recommended to confirm the diagnosis; however, it is technically challenging in most usual clinical settings. Clinical history or questionnaire tools may be useful to detect the laryngeal condition. Speech pathology and language therapy is effective in patients with chronic cough and laryngeal dysfunction, but it is a complex intervention and should be performed by experienced professionals. Several drugs with neuromodulatory effects, such as pregabalin, gabapentin, or amitriptyline, may be trialed in these patients; however, further evidence is warranted to confirm their efficacy, safety, and mechanisms of action.

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5 Lower Airways: Assessment and Treatment for Cough

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Introduction

Cough reflex is initiated by stimulation of afferent limb of vague nerve and its branches, which are widely innervated in upper airways, lower airways, gastroesophagus, heart, and other systems [1]. Chronic cough is involved in a large variety of conditions, including pulmonary and extrapulmonary conditions. Common causes of chronic cough in lower airways include cough variant asthma (CVA), nonasthmatic eosinophilic bronchitis (NAEB), atopic cough, chronic bronchitis, bronchiectasis, and central bronchial cancer. Although uncommon or rare causes account for a very low proportion of chronic cough, a wide range of conditions are involved, including bronchial foreign body, relapsing polychondritis, tracheobronchomalacia, bronchial tuberculosis, ossifying bronchopathy, tracheobronchomegaly, tracheal stenosis, endobronchial hamartoma, tracheal diverticulum, tracheobronchial amyloidosis, broncholithiasis, etc. Etiological diagnosis is the key for successful therapy of chronic cough. This chapter aims to describe the current diagnostic approach and treatment in the adults with chronic cough related with lower airways.

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Assessment of Chronic Cough Related with Lower Airways Disease

The diagnostic approach of chronic cough based on the systematic evaluation has been used over 40 years, which was first described by Richard S. Irwin [2] and modified in many studies or guidelines, mainly consisting of history, examination, laboratory investigations, and specific therapy directed at potential causes. Clinical assessment involves an evaluation of the severity of cough in regard to its frequency and intensity and impact on quality of life. Objective cough frequency monitoring is being increasingly used in clinical trials. However, it is still far from the routine clinical practice. Cough Visual Analog Scales is a simple method to assess severity of cough, but may be influenced by subjectivity. A few cough-specific quality of life questionnaires, such as Leicester Cough Questionnaire and Cough-Specific Quality of-Life Questionnaire, provide a useful tool in clinical study, but may be time-consuming in routine clinical assessment. Cough Evaluation Test is a simple tool to evaluate impact of cough on physical, social, and psychological aspects in clinical practice [3]. Koo and colleagues have developed another simple cough assessment test focusing on cough frequency, limitation on daily activities, sleep disturbance, fatigue, and hypersensitivity to irritants [4]. A full discussion of cough assessment is outside of the scope of this chapter, and the evaluation of cough severity and

S. H. Cho, W.-J. Song (eds.), *Diagnosis and Treatment of Chronic Cough*,
https://doi.org/10.1007/978-981-33-4029-9_5

the investigations relevant to upper airway cough syndrome (UACS) and gastroesophageal reflux-related cough (GERC) will be dealt with in details in another chapter of this book.

In this chapter, we focus on clinical investigations of chronic cough related to lower airway disease, including spirometry, bronchial challenge test, induced sputum test, fractional exhaled nitric oxide (FeNO), chest computed tomography (CT) scan, and bronchoscopy. The sequence in which are ordered and the degree in which investigations are conducted depend on several factors, such as clinical features, test availability and accessibility, patient's preferences, or financial capability for the investigations. Because CVA and NAEB are the most common causes of chronic cough in lower airways, induced sputum test for differential cell counts, FeNO, spirometry, and bronchial challenge test are usually considered as first-line tests to identify treatable traits [5]. Chest CT scan and bronchoscopy are recommended to be conducted when common causes are ruled out or empirical therapy failed.

Pulmonary Function Test

Pulmonary function tests include the measurement of spirometry, bronchial reversibility, diffusing capacity, and lung volume, which are necessary to diagnose and evaluate the respiratory diseases. Patients with chronic cough commonly present with normal spirometry, diffusing capacity, and lung volume. Thus, identification of any abnormality in these parameters at baseline can help physicians make a differential diagnosis at early stage of work-up for chronic cough. For example, patients with COPD present a post-bronchodilator FEV1/FVC < 0.7. A decreased diffusion capacity might indicate the possibility of interstitial lung disease, alveolar lesions, etc. A characteristic platform changes the inspiratory phase in the F-V curve, and $FEF_{50\%}/FIF_{50\%} > 1$ supports the upper airway obstruction, indicating the possible etiology of tracheal tumors or bronchial tuberculosis [6, 7].

Additional tests can be considered to assess bronchial reversibility or hyperresponsiveness, including bronchial challenge test, the bronchodilator test, and the peak expiratory flow (PEF) test. Bronchial challenge test is the first option for patients with chronic cough since the majority of them present normal spirometry. Methacholine and histamine are the common bronchoprovocators. Exercise and inhaled mannitol may also be used [8]. A positive bronchial challenge test result refers to a fall in FEV1 from baseline of ≥20% with standard doses of methacholine or histamine or ≥15% with standardized hyperventilation, hypertonic saline, or mannitol challenge. The presence of bronchial hyperresponsiveness usually indicates CVA. It should be noted that the patient with postviral cough may also have dyspnea and wheezing and a positive bronchial challenge test result due to transient, viral upper respiratory tract infection-induced bronchial hyperresponsiveness [9]. Given its higher negative predictive power, the bronchial challenge test is more useful to exclude CVA from the differential diagnosis of chronic cough. NAEB shares similar airway eosinophilic inflammatory features with CVA; however, if a patient with chronic cough is characterized as normal spirometry, airway eosinophilia, and lack of airway hyperresponsiveness, the diagnosis of NAEB should be considered in priority [5].

A positive bronchodilator reversibility test result refers to an increase in FEV1 of 12% and >200 mL from baseline, 10–15 min after 200–400 mcg albuterol or equivalent. Since the spirometry of CVA is generally normal, the utility of bronchodilator reversibility test in diagnosing CVA is limited. Monitoring the average PEF variation overtime is recommended when the provocation test is not available. The excessive variability in twice-daily PEF over 2 weeks refers to an average daily diurnal PEF variability >10% for adults and >13% for children. However, due to its low sensitivity and specificity, PEF monitoring is not suggested as a routine diagnostic method for CVA [7].

Induced Sputum Test

Induced sputum test for differential cell counts is a noninvasive and well-tolerated method for identifying etiologic diagnosis and airway inflammatory patterns of chronic cough [5]. Sputum induction is performed using nebulization of hypertonic saline. A single-concentration (3% or 4.5% hypertonic saline) or a step-up concentration method (3%, 4%, and 5% hypertonic saline) is recommended; however, repeated induced sputum tests within 48 h should be avoided [5]. Sputum eosinophilia is a major treatable trait in chronic cough or a defining feature of NAEB, but is also common in patients with CVA or other eosinophilic diseases such as hyper-eosinophilic syndrome or eosinophilic granulomatosis with polyangiitis. Induced sputum for differential cell counts can be used to monitor response to corticosteroids, helping management of cough and prediction of the prognosis in patients with chronic cough. Patients with sputum eosinophilia are more likely to respond to corticosteroids. CVA with high sputum eosinophil counts is more likely developing classic asthma [10, 11]. In addition, persistent sputum eosinophilia after treatment is a risk factor of relapse of NAEB [12, 13]. Follow-up assessment of sputum eosinophil counts after the initiation of corticosteroid treatment may help guide the treatment duration. Asthmatics could benefit from tailoring asthma interventions based on sputum eosinophils in reducing the frequency of asthma exacerbations [14].

Fractional Exhaled Nitric Oxide

FeNO measurement is a quick, easy, and noninvasive method to assess the airway inflammation. The FeNO value is largely determined by airway epithelial iNOS expression with little contribution from other isoforms including neuronal NOS (NOS1) and endothelial NOS (NOS3) [15]. T helper 2 cell (Th2) inflammation can upregulate iNOS expression in airway epithelium via a STAT6 pathway [16]. The FeNO value is modestly associated with eosinophilic airway inflammation. Several factors can affect FeNO level including the age, sex, height, smoking, nitrate food, environmental exposure, etc. [17–20]. Previous studies showed that the FeNO levels in patients with CVA or NAEB are higher than other causes of chronic cough. A high level (>31.5 ppb) of FeNO indicates more likelihood of corticosteroid-responsive cough (including CVA, NAEB, and atopic cough), with a moderate sensitivity of 54.0% and specificity of 91.4%, respectively. But the sensitivity is insufficient to rule out a diagnosis of corticosteroid-responsive cough if chronic cough patients are with FeNO < 31.5 ppb [21]. In a meta-analysis of 15 studies involving 2187 adult with chronic cough [22], FeNO measurement shows a moderate diagnostic accuracy in predicting CVA in patients with chronic cough while may not be useful to predict NAEB in nonasthmatic patients with chronic cough [23]. In addition, using FeNO as a single surrogate to predict airway eosinophilia which induced sputum was frequently used as the reference standard could lead to a substantial number of false positives or false negatives [24, 25]. Nevertheless, FeNO could be used as an important supplement for induced sputum in the diagnosis of the cause of chronic cough, the assessment of airway inflammation, and the guidance of corticosteroids usage, particularly in usual clinical settings without specialized facilities for induced sputum tests. Its predictive value for airway eosinophilic inflammation and treatment response in chronic cough still needs further study [26].

Chest CT

Chest CT scan can be of use in patients with persistent cough of uncommon causes in whom other routine tests including simple chest X-rays are normal [27]. Lesions anterior and posterior to the mediastinum, thickening and calci-

fication of trachea, enlargement of mediastinal lymph nodes, and other mild abnormalities of the thorax can be revealed by chest CT. Chest CT is helpful for the early diagnosis of interstitial pulmonary diseases, lung cancer, atypical bronchiectasis, and other rare conditions like broncholithiasis, diffuse panbronchiolitis, and relapsing polychondritis.

Bronchoscopy

Bronchoscopy is an invasive method of assessing airway condition. However, it is not routinely recommended for chronic cough except for the etiology that is not identified by other more targeted investigations or patients who fail to response to the treatment for common causes of cough [27]. Bronchoscopy is an important tool for the diagnosis or exclusion of uncommon airway disease associated with cough, including bronchopulmonary carcinoma, tuberculosis, tracheal stenosis, foreign body, and tracheobronchial amyloidosis.

Treatment of Chronic Cough Related with Lower Diseases

Corticosteroids are first-line treatment for cough related to airway eosinophilic inflammation including CVA and NAEB. Corticosteroids and antihistamines are the treatment options for atopic cough. Antibiotics are recommended for the treatment of acute exacerbation of chronic bronchitis and bronchiectasis. Antitussive agents can be prescribed when severe dry or frequent cough impacts daily life. Mucolytic agents can be used in patients with productive cough. More importantly, successful treatment of chronic cough depends on etiologic diagnosis. Due to the limitation of space, we will describe mainly the clinical features, diagnosis, and treatment in CVA, NAEB, and atopic cough since the three conditions account for about a half of patients with chronic cough.

Cough Variant Asthma

CVA presents solely with cough without obvious chest tightness, wheezing, or dyspnea. Cough-predominant asthma presents with cough as the predominant symptoms, while wheeze and/or dyspnea is also accompanied. It is characterized as airway eosinophilia and airway hyperresponsiveness. CVA is an atypical form of asthma as well as one of the most common causes of chronic cough [28]. Previous studies showed the prevalence of CVA ranged from 10 to 40% in adult patients with chronic cough [29–33].

The etiology of CVA is caused by a combination of genetic and environmental interactions like classic asthma. A family history of allergic diseases is the predisposing factor of CVA. Allergens, dust, and cigarette smoke are the common exposure to induce coughing. Similar to classic asthma, bronchial hyperresponsiveness and airway inflammation contribute to the pathogenesis of CVA. CVA shared comparable eosinophilic airway inflammation (e.g., eosinophil infiltration, FeNO, IgE, Th2 cytokines) and airway remodeling (e.g., subepithelial thickening, goblet cell hyperplasia, and vascular proliferation) to classic asthma [34–38]. On the other hand, CVA showed the heightened cough sensitivity and milder airway hyperresponsiveness compare to the classic asthma, which might be the mechanism of patients with CVA present only coughing without obvious wheezing [39–41].

CVA is characterized by recurrent episodes of irritating dry cough particularly at night and early morning. The coughing often gets worse once exposure to the allergen and other stimulus (e.g., cold air, dust, cigarette smoke, perfume). Some patients with severe cough may also present chest tightness, wheezing, and dyspnea. A history of recurrent coughing in childhood, comorbidities of allergic disease (e.g., allergic rhinitis, eczema), and family history of allergic diseases are the predisposing factors of CVA.

Diagnosis is based on history, physical examination, the bronchial challenge test, and the response to anti-asthmatic treatment. Sputum

eosinophilia and elevated FeNO level suggest a diagnosis of CVA. The following diagnostic criteria for CVA are recommended: (1) chronic cough as the solely symptom, usually with irritating dry cough particularly at the night and early morning; (2) bronchial hyperresponsiveness; (3) normal chest radiograph; and (4) response to anti-asthmatic treatment.

The therapeutic strategies for CVA are similar to classic asthma. It should be noted that a definitive diagnosis of CVA can only be confirmed after anti-asthmatic treatment. The ACCP cough guideline recommends the administration of inhaled corticosteroids (ICS), leukotriene receptor antagonist (LTRA), and/or beta-2 agonists in the treatment of CVA. ICS is recommended as the first-line treatment [42]. Although the optimal treatment course remains unknown, it is generally recommended that the treatment should last for more than 8 weeks, and for some patients, long-term treatment may be required [5]. The treatment strategy should follow the stepwise principle. Most patients show a good response to treatment, while those patients who have recurrent symptoms require long-term maintenance treatment. If the response to ICS treatment is incomplete, the patients should be evaluated again. The poor inhaler technique, medication adherence, and persistent environmental exposure can affect the efficacy. A multiple cause of chronic cough (e.g., UACS, GERC) should be considered. Meanwhile, an incorrect diagnosis including a false-positive bronchial challenge test or the existence of comorbidities, such as early-stage eosinophilic granulomatosis with polyangiitis and hypertension, should be concerned [5]. After reconsideration of alternative causes of cough, it is suggested to step up the ICS doses and/or consider a therapeutic trial of LTRA. Beta-2 agonists could also be considered in combination with ICS [42]. A short-term oral corticosteroid (10–20 mg/day, 3–5 days) is also recommended if patients are refractory to ICS treatment [5].

About 30–40% patients with CVA will develop classic asthma. A longer cough duration, severe airway hyperresponsiveness, persistent sputum eosinophilia, and atopy are risk factors for developing classic asthma [10, 11]. Early and long-term administration of ICS is helpful to prevent CVA from developing into classic asthma [11, 43].

Nonasthmatic Eosinophilic Bronchitis

NAEB, characterized by irritable dry cough, sputum eosinophilia, being responsive well to corticosteroids, and without airflow obstruction and airway hyperresponsiveness, was originally described by Gibson and colleagues [44]. NAEB has been reported as one of the most common causes of chronic cough, accounting for about 7–33% of cases [30, 45–47]. In addition, NAEB was also an important cause of subacute cough [48].

The etiology of NAEB may be associated with allergy and air pollution. About 30–40% patients of NAEB are accompanied with allergy, including dust mites, pollen, and the mushroom spores [49]. Several case reports showed that occupational exposures to certain sensitizers (e.g., bucillamine, latex gloves, acrylate, and styrene) could induce NAEB [50–53]. Our previous study found that traffic-related air pollution could induce non-allergic eosinophilic inflammation of airways in guinea pigs, indicating eosinophilia-related chronic cough might be related with air pollution [54].

NAEB shares similar eosinophilic inflammation with asthmatics. Similar degrees of eosinophils, T lymphocytes, and mast cells in airway lumen and a similar degree of basement membrane thickening in bronchial biopsy specimens were presented in both conditions. NAEB also shows increased airway inflammatory mediators, cytokines such as IL-5, histamine, cysteinyl-leukotrienes, and eosinophilic cationic protein as asthma. However, there is no variable airflow obstruction and airway hyperresponsiveness in NAEB; the mechanism is not fully understood. The difference of inflammatory cells location and inflammatory mediators might result in vari-

ant clinical phenotype of NAEB from asthma. It was found that the number of mast cell on airway smooth muscle was significantly higher in asthmatics than that in subjects with NAEB [55]. There was higher concentration of prostaglandin E2 in patients with NAEB [56], which could induce cough, and exert dilation of airway smooth muscle and decrease proliferation of smooth muscle cell. In addition, the increased expression of IL-13, a key cytokines associated with bronchial hyperresponsiveness, was showed in asthma compared with NAEB [57, 58].

NAEB could occur in any age of patients, but it is more prevalent in middle-aged population. The patients often present irritable dry cough as sole symptom or with slight production of white mucoid sputum. Their cough could last for several months, even for years. Half of them were presented with cough hypersensitivity, being triggered easily by cigarettes smoke, cooking-oil fumes, dust, odors, cold air, etc. However, to date there exist no reliable clinical characteristics to discriminate between NAEB and other causes of chronic cough. Physical examination usually shows unremarkable findings.

On the basis of the Chinese Cough guideline (2018) and ACCP evidence-based clinical practice guideline (2020), the following diagnostic criteria are recommended: (1) chronic cough, characterized by irritable dry cough or with bit amounts of sticky sputum; (2) normal chest radiograph; (3) normal pulmonary function tests, a lack of airway hyperresponsiveness, and normal average weekly PEF; (4) eosinophil count ≥3% in sputum (≥2.5% in China); and (5) response to corticosteroids.

Patients with NAEB usually respond well to corticosteroids. Cough resolves rapidly by corticosteroid treatment. Initial treatment can be conducted with a short course of oral prednisone (10–20 mg/day for 3–5 days) followed by more than 8 weeks of treatment with ICS [5]. A longer duration of treatment (more than 8 weeks) will reduce the relapse rate significantly [13]. If response to ICS is incomplete, stepping up the inhaled corticosteroid dose or a therapeutic trial of a leukotriene inhibitor is recommended [42]. Considering persistent sputum eosinophilia was a risk factor of relapse after treatment [13], tailoring interventions based on sputum eosinophil may be beneficial in patients with NAEB. Other diseases related to sputum eosinophilia, such as hyper-eosinophilic syndrome and eosinophilic granulomatosis with polyangiitis, should be considered especially when the patients are accompanied with high blood eosinophil count and show no response to the treatment with low-dose corticosteroids.

Though M.A. Berry and colleagues found that the most common outcome in 32 patients with NAEB with longitudinal data of greater than 1 year is continuing disease, complete resolution is rare [59]. Park et al. found that 3 of 24 patients showed gradually decline in lung function (FEV1) during 6–48 months follow-up, and more studies showed that the overall prognosis of NAEB is generally quite good [12, 60, 61]. We enrolled 143 patients with NAEB and followed up for 10 years [12]. Despite the fact that 59.6% of patients had a relapse after treatment, only eight patients (5.7%) developed mild asthma. FEV1, FVC, and FEV1/FVC of patient were stable during long-term follow-up, though the proportion of small airway dysfunction was increased.

Atopic Cough

Atopic cough is one of the common causes of chronic cough in Chinese and Japanese studies [29, 30, 62]. It should be noted that the concept of "atopic cough" in Japan Respiratory Society embodies induced sputum eosinophilia which means atopic cough reported in Japan overlap with NAEB [63]. However, in Chinese Thoracic Society guidelines, atopic cough is an entity that is characterized by chronic cough, atopy, and response well to corticosteroids or antihistamines, but no sputum eosinophilia and airway responsiveness [5]. ICS should be prescribed to last for more than 4 weeks, and oral corticosteroids can be used initially for a short period (3–5 days) for treatment.

Summary

Chronic cough relates to numerous lower airway diseases, and etiological diagnosis is the key for successful therapy of chronic cough. Induced sputum test, FeNO, spirometry, and bronchial challenge testing are first-line measurements for assessing chronic cough. Comparison of cough character, diagnostic tests, and therapeutic options among CVA, NAEB, and AC are summarized in Table 5.1.

Table 5.1 Comparison of clinical, inflammatory, pathophysical features, and therapeutic options among CVA, NAEB, and AC

	CVA	NAEB	AC
Cough timing	Nocturnal and early morning	Daytime	Daytime
Cough character	Dry cough	Dry cough	Dry cough
Atopy	– ~ ++	– ~ ++	+ ~ ++
FeNO	– ~ +++	– ~ ++	– ~ +
Eosinophil			
Sputum	– ~ +++	+ ~ +++	–
Bronchial mucosa	++	+	– ~ +
BALF	++	+	–
Blood	– ~ ++	– ~ ++	– ~ ++
Pulmonary function			
FVC	Normal	Normal	Normal
FEV_1	Normal/↓	Normal	Normal
FEV_1/FVC	Normal/↓	Normal	Normal
PEF	Normal/↑	Normal	Normal
BHR	+	–	–
Capsaicin cough sensitivity	– ~ +	– ~ +	– ~ +
Treatment option	ICS, ICS+LABA, LTRA	ICS, LTRA	ICS, Anti-histamine

Notes: *AC* atopic cough, *NAEB* nonasthmatic eosinophilic bronchitis, *CVA* cough variant asthma, *FeNO* fractional exhaled nitric oxide, *BALF* bronchoalveolar lavage fluid, *FVC* forced vital capacity, *FEV1* forced expiratory volume in 1 second, *PEF* peak expiratory flow, *BHR* bronchial hyperresponsiveness, *ICS* inhaled corticosteroid, *LABA* long-acting beta-agonists, *LTRA* leukotriene receptor antagonist

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6 Gastrointestinal Tract: Assessment and Treatment of Cough

Qiang Chen and Zhongmin Qiu

Introduction

The gastrointestinal tract is closely associated with respiratory diseases since it is anatomically adjacent to respiratory structures and shares the oropharyngeal passage with the respiratory tract. Gastroesophageal reflux is defined as a backflow of gastric acid and other non-acidic stomach contents into the esophagus or higher locations up to or beyond the laryngopharynx. The fluid refluxate can injure tissues it flows by, leading to gastroesophageal reflux disease with symptoms including regurgitation, heartburn, and chest pain. Chronic cough is a common extraesophageal symptom that occurs in 33–43% patients with gastroesophageal reflux disease [1, 2], whereas gastroesophageal reflux-induced chronic cough (GERC) can be elicited by both acidic and non-acidic reflux, is a specific type of gastroesophageal reflux disease with a predominant cough, and is also called reflux–cough syndrome [3]. GERC is increasingly recognized, and its management has been discussed in the international guidelines for the diagnosis and treatment of cough [4–6].

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Prevalence of GERC

In patients with chronic cough lasting more than 8 weeks without abnormal findings on chest radiography, common causes include cough-variant asthma, upper airway cough syndrome, eosinophilic bronchitis, and GERC. In western countries, GERC is the third most common cause of chronic cough, after upper airway cough syndrome and asthma, accounting for 10–40% of chronic cough cases [7]. GERC is a less common cause of chronic cough in East Asian countries. In China, GERC accounts for 5–20% of chronic cough cases and ranks fourth or fifth among causes of chronic cough [8, 9]. Nevertheless, the diagnoses of GERC have been increasing in the regions, as the awareness increases and the lifestyle and dietary habit changes due to social and economic development, accompanied by the increase of obesity [9].

Mechanisms of GERC

The mechanisms underlying GERC remain unclear. Two theories have been proposed to explain its pathogenesis: reflux theory and reflex theory (Fig. 6.1) [7]. The reflux theory proposes that the refluxates go up to the laryngopharynx and then are microaspirated into the lower airway, inducing cough by irritating receptors innervating the hypopharynx and lower airway. The

S. H. Cho, W.-J. Song (eds.), *Diagnosis and Treatment of Chronic Cough*,
https://doi.org/10.1007/978-981-33-4029-9_6

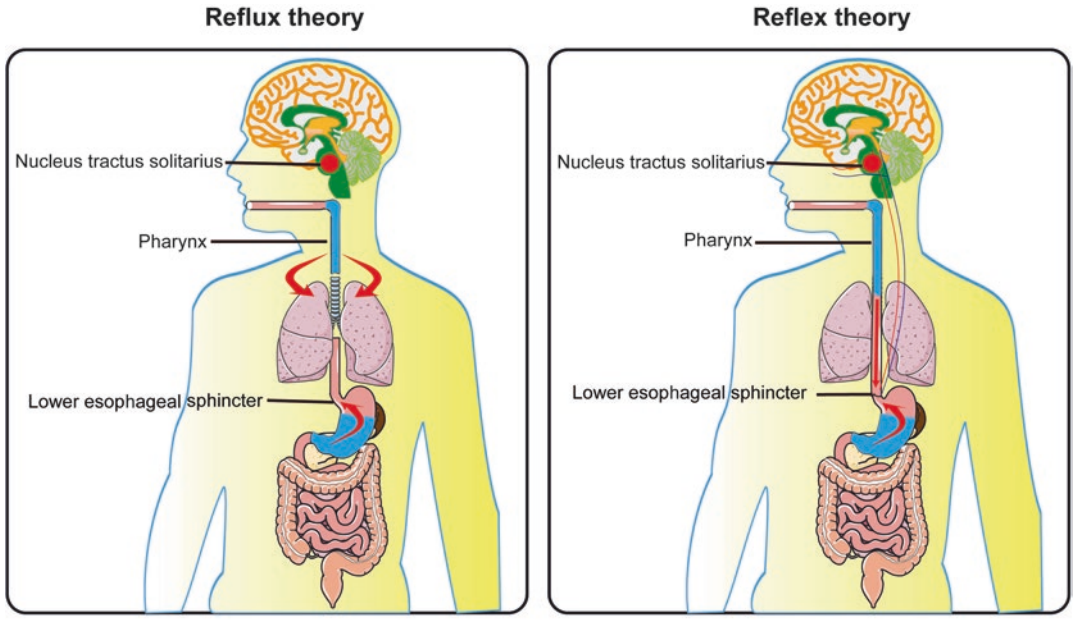

Fig. 6.1 Mechanisms underlying cough due to reflux

terminology employed to describe this kind of proximal esophageal reflux includes laryngopharyngeal, supraesophageal, and extraesophageal reflux, which Morice et al. termed airway reflux [10]. However, reflux to the proximal esophagus is present in only 32–37% of patients and cannot explain the majority of GERC cases [2, 11]. The reflex theory suggests that distal esophageal reflux causes cough through vagally mediated esophageal–bronchial reflexes that excite the cough center or sensitizes cough reflex. Due to the prevalence of reflux to the distal esophagus, reflex theory is far more important than reflux theory in GERC pathogenesis.

Why does chronic cough only affect some patients with gastroesophageal reflux disease? It may be related to cough or esophageal hypersensitivity. In the latter case, gastroesophageal reflux, as a subthreshold or irrelevant cough stimulus, can cause an exaggerated or violent cough response and lead to GERC [12]. Studies have shown that only patients with GERC present with airway neurogenic inflammation and cough hypersensitivity, which is not observed in healthy volunteers or patients with cough-free gastroesophageal reflux disease, even though gastroesophageal reflux is detected among all the subjects [13]. Therefore, GERC may be due to multiple factors.

Cough and gastroesophageal reflux can have a bidirectional cause–effect relationship. An increase in intra-abdominal pressure induced by coughing may precipitate or aggravate reflux, which in turn exacerbates cough or cough hypersensitivity, creating a vicious, self-perpetuating reflux–cough cycle [7].

Assessment of GERC

When patients with chronic cough present with typical reflux-associated symptoms such as regurgitation, heartburn, hoarseness, and dysphagia, or when other common causes are excluded after a sequential laboratory workup according to the existing diagnostic algorithms, or when the therapy specific to the other common causes of chronic cough fails to resolve the cough, the possibility of reflux-induced cough should be considered. Also since 40–75% of patients with cough due to reflux do not have concomitant regurgitation and heartburn, the absence of

Table 6.1 Laboratory investigations related to reflux and their usefulness for GERC

Laboratory test	Indications	Evaluation
Barium radiography	Not recommended for GERC diagnosis unless evaluating dysphagia	Extremely low sensitivity and high specificity
Upper endoscopy	Not recommended for GERC diagnosis; useful for the detection of erosive esophagitis but not non-erosive reflux disease	Low sensitivity and high specificity
Detection of lipid-laden alveolar macrophages	Indirect biomarker of microaspiration	Low sensitivity and specificity
Detection of pepsin in sputum and saliva	Indirect biomarker of microaspiration and laryngopharyngeal reflux	High sensitivity and low specificity
Gastroesophageal reflux disease questionnaire	Able to measure the frequency and intensity of typical reflux-associated symptoms	Low sensitivity and high specificity
Ambulatory 24-h esophageal pH monitoring	Able to detect acid reflux but not non-acid (weakly acidic and alkaline) reflux	Relatively high sensitivity and modest specificity
Multichannel intraluminal impedance–pH monitoring	Able to detect both acid and non-acid reflux	High sensitivity and modest specificity
Esophageal high-resolution manometry	Not recommended for GERC diagnosis; able to assess the morphology and function of the esophagogastric junction and the esophageal peristalsis	Low sensitivity and relatively high specificity

GERC gastroesophageal reflux-induced chronic cough

typical reflux-associated symptoms cannot rule out GERC [7, 14].

On the basis of comprehensive analysis of patients' symptoms and signs, it is crucial to obtain objective evidence of abnormal reflux and establish a temporal relationship between reflux and cough before diagnosing GERC. The laboratory investigations related to reflux are listed in Table 6.1.

1. *Ambulatory reflux monitoring*

The recommended first-line assessments are 24-h ambulatory esophageal pH monitoring and esophageal impedance–pH monitoring. The former can detect abnormal acid reflux and provide information regarding reflux–cough association, while the latter can identify gas, liquid, or mixed reflux and distinguish reflux as acidic or non-acidic. Diagnostic accuracy may be further improved with simultaneous acoustic cough recording. Esophageal impedance–pH monitoring is superior to 24-h ambulatory esophageal pH monitoring in that it can detect both non-acidic and acidic reflux, so it is considered the gold standard for reflux episode detection and characterization, as well as the most sensitive and specific diagnostic tool for GERC [15, 16]. Chinese Thoracic Society cough guidelines recommend either abnormal acid reflux (indicated by a positive DeMeester score) or a temporal association between cough and detected reflux (indicated by positive symptom-associated probability) as one of the diagnostic criteria of GERC [4]. It is surprising that no other international cough guidelines have attempted to set up a diagnostic standard of GERC related to ambulatory reflux monitoring. It may be due to the fact that there is no consensus on how to best interpret the results of 24-h ambulatory esophageal pH monitoring and esophageal impedance–pH monitoring. In the Lyon Consensus, the proposed criteria for abnormal reflux detected by esophageal impedance–pH monitoring include esophageal acid exposure time >6%, symptom-associated probability >95%, and reflux episodes >80 per 24 h [16]. Nevertheless, it remains unclear how these parameters are associated with GERC.

2. *Esophageal high-resolution manometry*

The main indication for high-resolution esophageal manometry is to locate the lower

esophageal sphincter and accurately place pH–impedance electrode catheters during esophageal impedance–pH monitoring. Besides determining the pressure, length, relaxation, and motility of the lower esophageal sphincter, esophageal high-resolution manometry can assess the morphology and function of the esophagogastric junction, as well as the peristaltic function of the esophageal body contributing to reflux. These abnormalities are more likely to induce cough and have a less robust response to reflux management because of the high esophageal reflux burden and incomplete clearance of refluxates that define GERC [16]. To reflect the new understanding of esophageal dysmotility relevant to GERC, esophageal high-resolution manometry is first incorporated into the assessment flow chart for chronic cough according to European Respiratory Society cough guidelines [6].

3. *Laryngopharyngeal reflux monitoring*

Laryngopharyngeal reflux monitoring such as with the Dx–pH detection system can detect the liquid or vapors of acid reflux that reach above the upper esophageal sphincter and is helpful to define reflux laryngitis. Since it cannot identify reflux to the distal esophagus, its application is restricted [17].

4. *Upper endoscopy*

Upper endoscopy has been widely used in clinical practice as it can assess lesions on the esophageal mucosa under the direct vision. If high-grade esophagitis (LA grade C or D) is present, it is strong evidence for a GERC diagnosis [18]. Although it has high specificity, upper endoscopy only reveals positive findings in <50% of patients [3]. Patients with cough related to nonerosive reflux disease might be underdiagnosed due to the gross appearance of normal esophageal mucosa. Thus, upper endoscopy is not the standard diagnostic test for GERC; rather, it is an alternative when ambulatory esophageal reflux monitoring is unavailable. Negative upper endoscopy findings do not exclude GERC.

5. *Barium esophagography*

Barium esophagography is a radiologic evaluation of gastroesophageal reflux. It can demonstrate reflux through the fluoroscopic observation or recording of barium entering the esophagus from the stomach, and it is more effective when combined with provocative maneuvers, especially the water-siphon test. Barium reflux and reflux esophagitis in barium esophagography are important indicators for GERC diagnosis. However, barium esophagography is insensitive for reflux assessment and can only identify a minority of patients with symptomatic gastroesophageal reflux. The reported sensitivity and specificity for barium esophagography identification of GERC are 37.0% and 82.4%, respectively [19]. Therefore, barium esophagography has limited diagnostic value and is not commonly used for evaluation of GERC.

6. *Biomarker detection*

Under normal conditions, pepsin is absent in the saliva, sputum, and bronchoalveolar lavage fluid. The appearance of pepsin in these samples can be used as a biomarker of microaspiration and reflect laryngopharyngeal reflux [20]. Similarly, the presence of lipid-laden alveolar macrophages in sputum or bronchoalveolar lavage fluid also indirectly indicates supraesophageal and laryngopharyngeal reflux [21]. Although biomarker measurement is simple, rapid, and low cost, it is still rarely used in clinical practice because of its low sensitivity and specificity.

7. *Questionnaires*

Apart from cough, typical reflux-associated symptoms such as regurgitation and heartburn may be present in some patients with GERC. Quantitative analysis of the frequency and intensity of these symptoms with questionnaires may be helpful for GERC diagnosis and assessment. The gastroesophageal reflux disease questionnaire is a simple, patient-centered, self-reported diagnostic instrument vali-

dated for gastroesophageal reflux disease. It consists of six symptom-related items that patients answer using a 4-point scale ranging from 0 to 3 for positive predictors and from 3 to 0 for negative predictors. The total scores range from 0 to 18. The gastroesophageal reflux disease questionnaire has a modest sensitivity and a higher specificity in identifying potential GERC when the cut-off score is set at 8.0, with a higher score indicating a greater possibility of GERC [22]. However, it is not useful if patients with GERC have no obvious regurgitation or heartburn.

GERC Treatment

The principles of treatment are to reduce the time and frequency of reflux episodes, eliminate factors that stimulate reflux, relieve cough, and improve patients' quality of life. Favorable response to the therapy is also an important step to confirm the cause–effect relationship between reflux and cough.

1. *Lifestyle modification*

Lifestyle interventions are part of GERC therapy [23] and are important for long-term management [24]. Weight loss is recommended for patients who are overweight or have had recent weight gain. Tobacco and alcohol cessation are mandatory. Patients are counseled to avoid late-night meals and stop consuming foods that can potentially aggravate reflux symptoms including acidic, spicy, and fatty foods and drinks such as coffee, strong tea, or acidic beverages. Medications that can trigger reflux such as calcium antagonists, theophylline, and progesterone should be avoided during GERC treatment. Head elevation during sleep may also help reduce reflux [25].

2. *Pharmacological anti-reflux therapy*

The main drugs include antacids and prokinetics for more than 3 months [6]. Acid-suppressive therapy can obviously decrease refluxate acidity and pepsin activity; it also reduces mucosal damage and irritation in esophagus, laryngopharynx, and lower airway, which help relieve cough [26]. Proton pump inhibitors are preferred because of their faster symptom relief and lower relapse rate [26]. Commonly used drugs include omeprazole, lansoprazole, rabeprazole, and esomeprazole. With the exception of esomeprazole, which has stronger acid suppression and longer-lasting effects, there are no major differences in efficacy [23]. A relatively high dose of proton pump inhibitors is recommended for treatment of GERC (e.g., omeprazole 20–40 mg or equivalent of the other proton pump inhibitors), and they should be taken 30–60 min before meals orally twice a day.

Proton pump inhibitors can reduce the acidity and volume of refluxates but not the frequency or duration of reflux episodes, and they have no therapeutic effect on weakly alkaline refluxates in patients with non-acid reflux. The effectiveness of proton pump inhibitors on GERC in clinical observations [7, 26] was not corroborated in two randomized double-blind clinical trials [27, 28]. Moreover, a meta-analysis demonstrated that the antitussive therapeutic gain of proton pump inhibitors is greater in patients with pathologic esophageal acid exposure [29]. Therefore, the overall benefits of proton pump inhibitors for GERC are controversial and need further evaluation. Recent guidelines for cough management are against the universal use of proton pump inhibitors and advocate rigorous patient selection [5, 6]. As cough is one of the extraesophageal symptoms of gastroesophageal reflux disease, it is not as easy to establish a cause–effect association with reflux as regurgitation and heartburn since reflux may or may not be related to chronic cough. Nevertheless, proton pump inhibitors are still the first choice for treating GERC with concomitant typical reflux symptoms or excessive acid reflux confirmed by 24-h ambulatory esophageal pH monitoring or esophageal impedance–pH monitoring [5, 6, 29]. Even for GERC caused by weak acidic reflux without previous antacid therapy, a trial of proton pump inhibitor therapy may be beneficial since a small increase in the pH of the refluxates might decrease acid signal trans-

duction in the hypersensitive esophagus, leading to cough resolution [13].

Prokinetics can increase the pressure of the lower esophageal sphincter, promote esophageal peristalsis, and augment gastric emptying, making it a suitable option for anti-reflux therapy. The dopamine receptor antagonists metoclopramide and domperidone are usually taken 10 mg orally three times a day 30 min before meals. Mosapride is another prokinetic agent that enhances acetylcholine release at the gastrointestinal neuromuscular junction by promoting serotonin (5-HT4) receptor activity and is widely used in clinical practice. The usual adult dose is 5 mg orally three times daily. At present, the efficacy of prokinetic therapy for GERC is still presumptive, but there are little to no data available to verify the clinical benefit. Prokinetics are not recommended to be used alone; they are usually combined with antacids to treat patients with esophageal dysmotility and gastric emptying disorder or those who do not adequately respond to acid-suppressive therapy [23, 26].

If patients fail to respond to an 8-week course of routine anti-reflux therapy, the possibility of refractory GERC should be considered. After further assessment and confirmation of possible cough–reflux association, intensified anti-reflux therapy may be tried, which includes optimization of proton pump inhibitors and add-on therapies with histamine H2 receptor antagonists and neuromodulators [30].

When aggravated suppression of acid, by doubling the dose of proton pump inhibitors or combining with histamine H2 receptor antagonists, does not yield a therapeutic gain in patients with suspected refractory GERC, neuromodulators may be considered as an add-on therapy. The commonly used neuromodulators are baclofen and gabapentin. There is limited evidence to support their application because both drugs ameliorate chronic refractory cough due to reflux [31, 32]. In addition to its non-specific antitussive effect, baclofen can inhibit transient lower esophageal sphincter relaxation and reduce both acid and non-acid reflux. In contrast, gabapentin mainly exerts its therapeutic effect through suppressing the hypersensitive cough center. The usual doses are 10–20 mg three times a day for baclofen and 200–300 mg three times per day for gabapentin. Studies have demonstrated that baclofen and gabapentin achieve similar therapeutic successes for refractory GERC at 53–58% [33–35]. However, their usage may be limited by central nervous system side effects including drowsiness, dizziness, and fatigue, and gabapentin may be preferable because it is better tolerated [35]. In our experience, drug-related adverse effects usually decrease within 3 weeks in most patients. Only a few have to discontinue baclofen and gabapentin due to severe dizziness and drowsiness. Gradually increasing the doses of baclofen and gabapentin over 1–2 weeks may help decrease the incidence and severity of side effects [30, 33–35]. However, the efficacy of neuromodulators is suboptimal, and a considerable number of patients with refractory GERC do not respond to baclofen or gabapentin. Identifying a way to screen patients with refractory GERC to determine suitability for gabapentin or baclofen may improve therapeutic success.

3. *Anti-reflux surgery*

Anti-reflux surgery is a promising curative treatment for intractable and refractory GERC that artificially reconstructs the mechanical barrier between the esophagus and stomach to block gastroesophageal reflux [23, 36]. The most commonly employed surgical options for GERC is laparoscopic fundoplication, which has a reported success rate of 85% [37]. However, the surgical response to laparoscopic fundoplication decreases over time; maintenance of cough resolution decreases to 71% within 5 years postoperatively [38]. Because of its invasiveness and uncertain efficacy in cases without a definite reflux–cough association, the indication of anti-reflux surgery should be strictly limited to carefully selected patients. Radiofrequency augmentation to the lower esophageal sphincter, silicone injection into the lower esophageal sphincter, endoscopic suturing of the lower esophageal sphincter, and transoral incisionless fundoplication radiofrequency have reported advantages of high short-term efficacy, simple operation techniques, minimal inva-

siveness, high safety, and few complications [39]. However, their long-term efficacy remains to be verified, and more clinical evidence is needed before they become widely accepted therapeutic approaches [23].

Conclusion

GERC can be elicited by both acidic and non-acidic reflux and is an increasingly recognized etiology of chronic cough. The interaction between reflux and cough may lead to a vicious self-perpetuating cycle. At present, esophageal impedance–pH monitoring is the gold standard for detection of abnormal reflux and a most sensitive and specific diagnostic tool for GERC. The favorable response to the anti-reflux treatment is essential to definitely confirm GERC. When lifestyle modification is important for long-term management of GERC, pharmacological anti-reflux therapy is a first-line choice, and anti-reflux surgery may be a promising option for cure in the future.

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Pharmacological Management of Cough

7

Kayleigh Brindle and Alyn Morice

Introduction

The drug treatment of chronic cough (cough with a duration of >8 weeks) remains a challenge to many medical professionals. This is despite dramatic advances over the last decade in our understanding of the pathophysiology of cough hypersensitivity and its aetiology. This is, in part, due to the recent realisation that chronic cough is a separate, distinct, clinical entity [1, 2]. The historically poor understanding of the aetiological mechanisms underlying chronic cough has resulted in poor treatment decisions, based on therapy for other diseases such as asthma which have led to a significant healthcare burden [3].

The recent publication of international guidelines on the diagnosis and treatment of chronic cough provides healthcare professionals with evidence-based guidance on current pharmacological treatments [4]. Substantial advances are on the horizon with several new, effective and novel therapies in phase 2 and 3 clinical trials which will see the first effective drugs to treat this cohort of patients in over 40 years.

Historically the research into the pharmacological treatment of chronic cough has produced little in the way of effective therapies [5]. This is despite the clear signal on need, in that OTC remedies are a multi-billion pound industry [6]. These therapies, such as codeine, dextromethorphan and diphenhydramine, may provide some benefits in acute cough [7] but have little or no clinical evidence in chronic cough. This lack of robust evidence alongside the compounds' prominent side effects such as sedation and the risk of addiction has resulted in such therapy being no longer recommended for long-term use in cough (Footitt & Johnson, 2009). To a greater extent, this can be applied to codeine which is still one of the most widely used antitussives even though many well-controlled studies show its lack of efficacy in reducing cough in man [8].

The first challenge healthcare professionals face when deciding on suitable pharmacological therapies for chronic cough lies in the correct diagnosis of any underlying cause. Previously the paradigm of the three causes of cough—the so-called cough triad which consisted of asthma, GERD/GORD and postnasal drip—was adopted as the underlying cause [9]. However many patients with classic asthma do not have a prominent cough, and patients with an asthmatic phenotype, i.e. those with eosinophilic bronchitis, do not respond well to conventional asthma treatments. Similarly GERD, when diagnosed as acid reflux, does not respond in terms of cough to high-dose acid suppression [10]. Finally postna-

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S. H. Cho, W.-J. Song (eds.), *Diagnosis and Treatment of Chronic Cough*,
https://doi.org/10.1007/978-981-33-4029-9_7

sal drip is a sensation rather than a disease [11] and was adopted as a cause of cough because patients sometimes respond to first-generation antihistamines. Thus each diagnostic box did not reflect the totality of the population presenting to specialist cough clinics.

Observational studies have shown that there is a unique phenotype of patients with chronic cough who are predominantly middle-aged women [1, 2]. Their main complaint being a hypersensitivity to external stimuli such as a change in temperature, strong smells, bleaches and perfumes. The concept thus arose that patients have an underlying neurological abnormality characterised by hypersensitivity of vagal afferents [12]. This resulted in a unifying diagnosis of cough hypersensitivity syndrome. This is defined as "a clinical syndrome characterised by troublesome coughing often triggered by low levels of thermal, mechanical or chemical exposure" [1, 2].

It is, however, imperative that differentiation is made between those presenting with an eosinophilic or neutrophilic inflammation by first looking into a patient's eosinophilic biomarkers, e.g. blood eosinophils, exhaled nitric oxide or sputum eosinophilia. This is in order to prescribe the correct treatment to target the specific pathology of this treatable trait [13].

Pharmacological Managements

Targeting Eosinophilic Airway Inflammation

Patients presenting with evidence of eosinophilic airway inflammation, which has a variety of different labels such as late-onset asthma, cough variant asthma or eosinophilic bronchitis, should be treated with a specific anti-inflammatory pathway. Although this subset of patients (perhaps 20%) presenting with chronic cough was first recognised by Gibson et al., in 1989, it is often overlooked or misdiagnosed as classic asthma despite the lack of airway obstruction or hyperresponsiveness [14].

The presence of eosinophil inflammation must be recognised before commencing other treatments as not only is it a treatable cause of chronic cough, but the treatment used is significantly different from that advocated in classic asthma. Since there is little or no bronchoconstriction, bronchodilator therapy is ineffective. It is this subset of patients who respond to inhaled corticosteroids (ICS) [15]. A short 2–4-week trial of ICS is recommended after which, if no clinical benefit is seen, treatment should be stopped [16]. The evidence of the efficacy of inhaled corticosteroids in this cohort of patients is varied; Chadhuri et al. [17] report significant decrease in cough severity compared to placebo when patients were prescribed a 2-week high dose of ICS, whereas Boulet et al. [18] and Pizzchini et al. [19] saw lack of clinical significance in improving cough outcomes compared to placebo when using ICS. As expected the reported adverse events (AEs) in all three trials were low. Due to the possible clinical benefit and the low risk of adverse events, the recommendation of ICS prescribed at high doses is advocated as a treatment trial in recent ERS guidance [4]. It is likely that because of the different distribution of eosinophilic inflammation between classic asthma and cough-related eosinophilic bronchitis that topical therapy such as ICS may be less effective [15]. A short course of oral prednisolone is advocated by some as a therapeutic trial to confirm the diagnosis. Even then some patients do not respond to systemic therapy by corticosteroids.

In eosinophilic patients, a recommendation for an oral leukotriene antagonist such as montelukast may be warranted. A therapeutic trial of 2–4 weeks is based on results from placebo-controlled RCTs on the use of the leukotriene receptor antagonist zafirlukast [20] and the effectiveness of montelukast [21].

Cough Neuromodulators

Currently there are few treatment options directed at cough hypersensitivity itself. The hypothesis that hyperexcitability of afferent sensory neurons

plays a role in the aetiology of chronic cough is supported by evidence of increased sensitivity to challenge agents such as capsaicin and citric acid [22]. There is a large overlap of sensitivity in the normal population with some individuals not coughing at all, even at high concentrations. It is thus impossible to have a "normal range" with cough patients uniformly being excessively sensitive. The location of this hypersensitivity depends on the individual patient. There is clearly a major element of peripheral nerve hypersensitivity since inhalational challenge with rapidly metabolised agents such as ATP and distilled water have been shown to be decreased by blockade of the P2X3 receptors [16]. Interestingly capsaicin and citric acid are not diminished by blocking this pathway inferring that there is much diversity and redundancy within the afferent neural pathways.

Whilst peripheral neuronal blockade does demonstrate clinically meaningful reduction in cough hypersensitivity, central activity is also clearly important. Recent studies using fMRI have demonstrated descending cortical pathways which inhibit cough sensitivity and when absent, for whatever reason, excessively coughing results [23]. Replacement of these inhibitory pathways with agents such as opiates and first-generation antihistamines allows treatment for patients with cough hypersensitivity who have reduced cortical inhibition of the cough reflex.

Opiates have long been advocated as an antitussives with their use first discussed in literature by Mudge in 1778 [24]. However, randomised controlled data was only provided more recently. This study provided evidence of significant benefit of slow-release morphine (MST) vs placebo in reducing cough (by 40%) and improving cough-specific quality of life [25]. In clinical practice, it seems that this benefit is restricted to some patients and not others. Patients either respond to opiates or not. A short-term trial of 1-week therapy should suffice to determine whether the patient is a responder or not. There is no point in increasing the dose if the patient does not respond because, unlike pain, higher doses do not seem to be increasingly efficacious. Concerns have been raised regarding the side effect profile of MST including constipation and drowsiness, but in that study it was found to be well tolerated [25]. The effectiveness of MST has recently been supported by a study by Al-Shekly et al. [26]. This double-blind RCT of low-dose MST was performed in patients known to be opiate responders. It showed that MST provides clinically significant reductions in objective cough and cough-specific quality of life vs placebo. Morphine continues to be the neuromodulator of choice in treating chronic cough, and its use is recommended in the ERS guidelines [4]. Uptake may be limited by the anxieties of patients willing to take it and medical professionals willing to prescribe it. In certain countries, this has led to limited use outside specialist clinics because of its status as a controlled drug [8].

Other neuromodulators used in cough treatment pathways include gabapentin and pregabalin. The similarities between the proposed mechanisms of chronic pain and chronic cough led to the research into these compounds for this indication [8]. Caution must be taken however, when using gabapentin or pregabalin due to the paucity of RCTs using these compounds. A single RCT comparing 1800 mg of gabapentin versus placebo highlighted small but statistically significant improvements in quality of life outcomes, cough frequency and cough visual analogue scales [27]. A further study from the same group of pregabalin (maximum dose 300 mg daily) combined with speech therapy showed significant improvement in quality of life outcomes; however, this trial has major limitations due to the low subject numbers and the fact the control group also received speech therapy with pregabalin having no statistically significant effect in lowering cough frequency in comparison to speech therapy only [28]. There was a high incidence of AEs shown in both of these studies including cognitive changes, drowsiness and blurred vision [27]. This raises questions as to how well these compounds are tolerated in the long term.

Promotility Agents

Patients with chronic cough can present with elevated markers of neutrophilic inflammation including in induced sputum. The use of the macrolide therapy such as azithromycin is therefore advocated based on the benefits seen in a number of airway diseases such as COPD [29], asthma [30], cystic fibrosis [31] and bronchiectasis [32]. It has been suggested that this broad spectrum of activity is due to hypothesised properties as an anti-inflammatory and anti-neutrophil alongside its broad spectrum antimicrobial activity [33]. However, azithromycin is a potent agonist of the hormone motilin [34] and has been shown to improve oesophageal motility [35], and we believe that this underlies its therapeutic effects in this diverse collection of airway diseases. A reduction in exacerbation events is the main outcome in the studies, and this infers that reflux and aspiration are major precipitants of deterioration in these conditions.

We have shown that patients with chronic cough have a greater than 80% incidence of oesophageal dysmotility [36]. However the use of azithromycin has yet to be conclusively shown to be of benefit in such patients. The best evidence is from studies in chronic cough in COPD with azithromycin resulting in a clinically significant reduction in cough-related quality of life versus placebo in a controlled RCT [37]. In an 8-week study using low-dose azithromycin three times a week in patients with isolated chronic cough, a placebo-controlled RCT showed clinical important reduction in cough quality of life but did not produce a clinically significant reduction ($p = 0.12$) in objective cough counting [33]. The lack of significance in this study may be explained by lack of power (only 22 patients in azithromycin arm) and the use of a low dose, that is, azithromycin 250 mg three times a week. Clinical experience has shown many patients report improvement in chronic cough with azithromycin 250 mg daily. There is therefore an area that clearly warrants further investigation. Currently, however, the ERS Task Force only recommend routine use of macrolide therapy in a chronic cough in patients with a productive cough, refractory to other treatments [4].

Novel Treatments

ATP Story

The serendipitous finding that P2X3 inhibitors decrease cough counts in patients with severe chronic cough could be the biggest breakthrough in the pharmacological treatment of this condition. ATP is released in response to tissue injury and acts on afferent sensory nerves leading to a state of cough hypersensitivity [38].

The role of ATP in chronic cough has now been explored in numerous clinical studies. The direct role of ATP in chronic cough is supported by the work of [39], who demonstrated that inhalation of exogeneous ATP evokes cough in both healthy volunteers and chronic cough patients. These findings support the hypothesis that the hyperexcitability of sensory nerves in chronic cough is caused by the increased release of ATP into the extracellular space during airway inflammation.

Early clinical trials in the use of the prototypic P2X3 antagonist, gefapixant, showed a reduction of cough by up to 75% vs placebo in patients with chronic cough [40] and was the foundation for the concept that ATP was a major mediator of hypersensitivity in chronic cough. The success of gefapixant has since been strengthened by phase 2 clinical trials (Fig. 7.1). A placebo-controlled study looking at ATP-evoked cough demonstrated that a single dose of gefapixant 100 mg

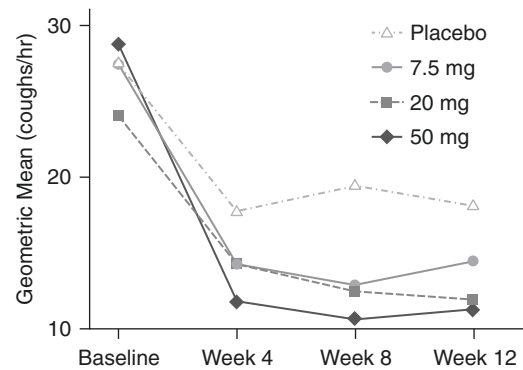

Fig. 7.1 The P2X3 antagonist gefapixant. Effect on awake cough frequency (primary endpoint) in phase 2b study

inhibited ATP-induced cough resulting in statistically significant reductions in cough challenge sensitivity in both healthy volunteers and chronic cough patients when compared to placebo [16]. Interestingly, this study found no effect of gefapixant on citric acid and capsaicin challenge inferring that there are at least two different pathways in man. One is an irritant pathway sensitive to acid and TRPV 1 stimulation by capsaicin and another pathway responsible for the pathophysiology of cough hypersensitivity. This finding infers that P2X3 antagonist may be safer than conventional antitussives since they target only the pathophysiological pathway and preserve the vital irritant pathway which protects the airway from aspiration. In this study up to 75% of healthy volunteers and 67% of chronic cough patients report dysgeusia [16].

Further studies have taken place exploring the efficacy and tolerability of various doses of gefapixant over a longer duration. Smith et al. [41, 42] report the use of gefapixant in a two double-blind placebo-controlled, two period crossover, dose escalation studies with dosage ranging from 7.5 mg to 200 mg over 16 days in both arms. Clinical significance was seen across both studies in reducing awake cough as well as cough over a 24-h period but only with doses of 30 mg and above. A statistical improvement was also seen in cough-related quality of life and patient-reported outcomes.

A phase 2b double-blind, parallel group, placebo-controlled trial exploring the tolerability and efficacy of gefapixant over 12 weeks supports its use as an antitussive with significant improvements shown in cough frequency and patient-reported outcomes in the 50 mg dose vs placebo. It also demonstrated a positive safety profile although again, this dose saw 48% of patients reporting dysgeusia resulting in some patient discontinuation [41, 42]. The results of two phase 3 studies of this compound have been recently published an abstract form and confirm the efficacy of gefapixant at 45 mg. These are the first large-scale chronic cough studies with a positive outcome.

Although gefapixant appears to be at the forefront of chronic cough therapeutics, some doubt may be cast over the patients' tolerability of dysgeusia over the long term. The results of follow-on studies investigating the tolerability of gefapixant in these phase 3 trials are awaited. The AE of taste disturbance can be explained through ATP serving as the key neurotransmitter for the peripheral taste system requiring the heterotrimer of the P2X2/3 receptor for the sensory transmission within this system [43]. It is for this reason several new agents, deemed to be more selective for the P2X3 homotrimer rather than the P2X2/3 receptor, are currently being evaluated in phase 2 clinical trials.

Bayer: The lead compound currently in phase 2 studies is BAY1817080. Results from a recently completed double-blind, placebo-controlled, randomised crossover study comparing BAY1817080 at doses of 10 mg, 50 mg, 200 mg and 750 mg BD versus placebo show a dose-related inhibition of cough (Fig. 7.2). As a potent P2X3 receptor antagonist, this compound has been well tolerated with a low number of taste disturbances whilst reducing 24 h cough count against placebo and significantly reducing patient-reported cough severity with dosing of 50 mg and above [4]. This compound is currently being studied in phase 2b RCTs to test its efficacy in a larger population over a more prolonged period.

Bellus: BLU-5937 is a selective P2X3 antagonist which has recently completed an initial phase 2 study. This small molecule has been shown to

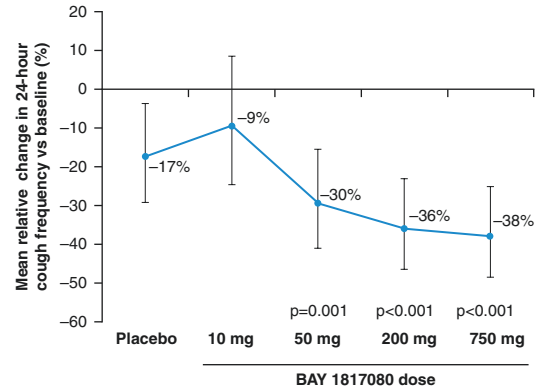

Fig. 7.2 The effect of 1817080 on cough frequency in a phase 2 study. Mean relative change in 24-h cough frequency vs baseline. Duration of treatment was 1 week with each dose of BAY 1817080

be a potent, selective and noncompetitive P2X3 homotrimeric receptor antagonist which in preclinical and animal studies has shown to have a low incidence of taste disturbances likely due to its higher selectivity [44]. Although the phase 2 study did not reach a statistically significant reduction in its primary endpoint of awake cough counts, this was mainly due to the early termination of the study because of the onset of COVID-19 restrictions. When the study was terminated, a number of patients had only completed a single arm of this crossover study. If the per protocol population is considered, then the results on cough counting and other parameters are significant. It is only the intention-to-treat population in which these metrics do not reach significance.

Shionogi: Recruitment into a large phase 2 RCT of S-600918 is currently ongoing. Results from a small phase 2 trial in 33 Japanese patients show promise for S-600918 an oral P2X3 receptor antagonist as an effective antitussive. Again, due to its high selectivity for the P2X3 homotrimer, early indications show a low incidence of taste disturbance with this compound at 150 mg although the ongoing study is exploring the efficacy of 50 mg, 150 mg and 300 mg daily vs placebo [45].

Neurokinin Story

It was first suggested in 1987 that substance P may have a role in cough reflex sensitivity since it is broken down by angiotensin-converting enzyme and accumulation may occur with ACE inhibition [46]. Substance P acts on the NK-1 receptor, and overpitant, a NK-1 antagonist, has been developed as a possible antitussive. It has been assessed in both phase 1 and phase 2 clinical trials. Results from an open-label pilot study using 30 mg daily for 4 weeks showed that not only was the drug safe and well-tolerated within this small cohort of patients, but significant improvement was seen in cough frequency as well as patient-reported outcomes [41]. Further exploration of this compound in a phase 2b double-blind, placebo-controlled trial using doses of 10 mg, 20 mg and 30 mg showed statistically significant results in patient-reported outcomes, but unfortunately significance was not seen in the reduction of awake cough due to a high placebo response [41, 42]. In a subgroup analysis, significant benefit was seen in those patients whose baseline cough counts were greater than the median. Because it has a different, presumably central, mode of action, it is likely that a different profile of cough responses will be seen with NK-1 antagonists. In many ways it is similar to the response of opiates where patient-reported outcomes predominate in the beneficial effects. There was no effect on cough challenge in either of the two studies for morphine.

ACE Inhibitor

Whilst the focus seems to be on adding in therapy to treat chronic cough, a review of existing therapy should be the first line of management. Experience working in a specialist cough clinic has shown that approximately 10% of patients will present with a long history of chronic cough that correlates with the commencement of an ACE inhibitor. It is over 35 years since ACE inhibitor cough was first described by Sesoko and Keneko in 1985. Discontinuation of the therapy will result in cessation of the persistent cough in as little as a few days although because ACE inhibitors cause cough by resetting the sensitivity of the cough reflex (Fig. 7.3), it can take many months for this hypersensitivity to return to normal [47].

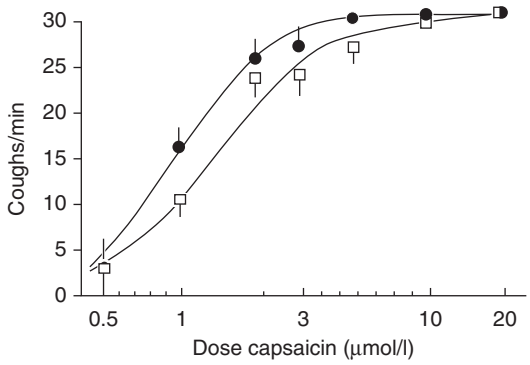

Fig. 7.3 The effect of the ACE inhibitor captopril on cough reflex sensitivity as demonstrated by inhalational challenge with capsaicin. Open squares placebo, closed circles captopril

Conclusion

The future of the pharmacological treatment of chronic cough is an area with a huge amount of promise with compounds such as M8 agonists and sodium channel blockers being explored for their antitussive properties. With the novel therapies described within this chapter programmed to finish phase 3 studies in the coming years, this nascent field of medicine will have specific licensed therapies to treat a neglected patient population. Collaborations such as NEUROCOUGH [5] will also promote future multinational and multidisciplinary collaborations to ensure that further research is geared towards improving the care of chronic cough patients with the overall aim of addressing their currently unmet needs.

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8 Non-pharmacological Control of Cough

Anne Vertigan

Non-pharmacological approaches to cough are broadly classified into two groups—those required for cough augmentation in patients with absent or ineffective cough and those for cough control in patients with hypersensitive cough [1]. This chapter will largely focus on management of hypersensitive cough using behavioural techniques.

Non-pharmacological approaches are described by various names such as speech pathology treatment for chronic cough, behavioural cough therapy, cough control therapy, breathing retaining physiotherapy and speech and language therapy intervention (PSALTI) and behavioural cough suppression therapy [2]. These terms attempt to describe the goals of treatment such as *cough suppression*, the profession providing the treatment, for example, *speech pathology*, and to distinguish it from pharmacologic treatment [3].

Non-pharmacological Approaches for Chronic Cough

Non-pharmacological approaches to cough have been described in the medical, speech pathology, psychology and physiotherapy literature. There are many similarities between these approaches. For example, both speech pathology treatment and PSALTI contain similar components. However while the macrostructure of the therapy is similar, it is possible that speech pathology has greater focus on laryngeal function, while physiotherapy has more focus on breathing pattern disorder. Speech pathology treatment intervention for chronic cough was originally developed from approaches used to treat hyperfunctional voice disorders, such as muscle tension dysphonia. The treatment teaches patients to develop voluntary control over their urge to cough while simultaneously reducing irritants and phonotraumatic laryngeal behaviours that trigger cough.

Components of Non-pharmacological Treatment Approaches

Speech pathology intervention for chronic cough is multidimensional and targets four areas: (1) education, (2) cough suppression, (3) laryngeal irritation and (4) psychoeducational counselling (Table 8.1) [4]. The laryngeal irritation and cough suppression components aim to improve the patient's voluntary control over their cough, while the education and psychoeducational counselling aim to improve the patient's understanding and adherence to the behavioural treatment.

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S. H. Cho, W.-J. Song (eds.), *Diagnosis and Treatment of Chronic Cough*,
https://doi.org/10.1007/978-981-33-4029-9_8

Table 8.1 Non-pharmacological treatment of cough

Components of treatment	Examples
Education	Cough is not always necessary Cough can be brought under conscious control The cause of cough may not be found in all individuals
Laryngeal irritation	Improve hydration Reduce exposure to dehydrating substances Desensitisation Reduce phonotraumatic vocal behaviours
Cough suppression	Identify urge to cough and substitute with competing response Reduce laryngeal constriction Promote vocal fold abduction during respiration Anticipate and inhibit co-existing vocal cord dysfunction episodes (if present)
Psychoeducational counselling	Acknowledge concerns Support adherence to therapy Internalise control over coughing behaviour

1. *Education*. Patients need a rationale in order to understand the goals of non-pharmacological approaches to therapy. The education component in the treatment program involves explanation of cough mechanisms, abnormal laryngeal movement and laryngeal hypersensitivity. It is important for patients to understand that cough has become sensitised to be triggered by non-tussive stimuli or low levels of tussive stimuli in the absence of a physiological need to cough. The discrepancy between an urge to cough and a physiological need to cough can be challenging for patients to understand even if they employ continued effortful coughing in attempt to expectorate. Some patients are keen to ascertain the cause of their cough; however the cause of cough may not be identified in many patients despite extensive medical investigation [5, 6]. Education also addresses the role of voluntary control over coughing episodes so that patients understand that it is physiologically possible to exert control over cough.
2. *Cough suppression*. The aim of cough suppression exercises is to identify the precipitating sensation to a cough and to substitute with an alternative and less phonotraumatic behaviour. These strategies can prevent or interrupt the cough. Cough suppression strategies can range from simple distraction or swallowing exercises to more complex breathing and laryngeal reposturing techniques. These techniques promote efficient and coordinated airflow during phonation and breathing and release supraglottic laryngeal constriction that can be a precursor to or a result of cough. Exercises are taught in a hierarchy beginning with the clinical setting, to asymptomatic periods outside the clinical setting, then employing techniques during symptomatic periods and finally during deliberate exposure to triggers. It is essential that correct technique is used when performing the exercises and therefore ongoing monitoring by the speech pathologist is required. Chronic cough commonly coexists with other laryngeal disorders, namely, muscle tension dysphonia and inducible laryngeal obstruction (ILO). Laryngeal reposturing techniques such as laryngeal deconstriction or PVFM release breathing used in the treatment of these conditions may be needed in some patients.
3. *Laryngeal irritation*. Vocal hygiene strategies are employed in attempt to reduce laryngeal irritation. These strategies involve increasing surface and systemic hydration while reducing exposure to laryngeal irritants such as alcohol, reflux and oral breathing. Phonotraumatic vocal behaviours can also exacerbate laryngeal irritation and trigger coughing and may need to be addressed as part of the speech pathology treatment. Desensitisation, involving deliberate exposure with coaching through cough suppression strategies, may also be helpful for some patients with cough triggered by specific irritants.
4. *Psychoeducational counselling*. Psychoeducational counselling is implemented to improve motivation and adherence to therapy. It encourages patients to internalise control over their coughing behav-

iour so that coughing is something they are doing in response to irritation rather than something that is happening to them. Non-pharmacological approaches require commitment from patients over a period of weeks or months, and patients may need support to develop realistic goals for therapy. Some patients need support to recognise emotional issues as a trigger for cough.

Suggestion therapy has been described as a stand-alone treatment for habit cough that can be delivered in a single session [7]. Suggestion therapy is described as a treatment for functional habit cough in children and adolescents and involves concentrating on holding back the urge to cough. There are case series reporting successful outcomes; however further research is needed including randomised control trials of the therapy using standardised outcome measures [8].

There are emerging reports of expiratory muscle strength retraining in chronic cough. In a case series of 19 patients with chronic cough, Cough Severity Index scores improved in 17 patients, and maximum expiratory pressure improved in 18 [9]. This treatment is thought to reduce glottal airway resistance and reduce high chest breathing and high larynx position in chronic cough [9]. Improvement may be related to rebalanced breathing. Further evidence involving randomised treatment trials is needed to confirm the efficacy of expiratory muscle strength training for chronic cough as well as the extent to which it needs to be combined with other components of speech pathology intervention.

Evidence for Non-pharmaceutical Approaches

The efficacy of speech pathology treatment for chronic cough has been confirmed in two single-blind randomised control trials [10, 11]. The first randomised 87 patients with chronic cough that was refractory to medical management, to receive either 4 sessions of speech pathology treatment for their cough as described above or 4 sessions of healthy lifestyle education [10]. Treatment for both groups was conducted by a qualified speech pathologist. This study found greater improvement in in cough, breathing, voice and upper airway symptoms in the treatment group than the control group. This study was replicated by another research group approximately a decade later and used a similar study design [11]. This study, which also involved physiotherapists in the treatment, found improved cough quality of life and reduced cough frequency which was sustained up to 3 months. The results of these studies suggest that behavioural intervention for chronic cough can be effective.

Mechanisms for Non-pharmacological Approaches

The mechanisms underlying improvement following non-pharmacological approaches to cough are not fully understood [1]. Speech pathology intervention is multimodal [12] and targets both laryngeal irritation and voluntary control over cough symptoms. The treatment process has been standardised to enable replication between therapists [10, 11]. Despite this, it is unknown which of the elements is the most effective, whether they could be effective in isolation or whether specific components need to be emphasised for certain individuals.

Our understanding of the physiology of cough sheds some light on the mechanisms for successful behavioural treatment of cough. Patients with chronic cough have increased sensitivity to low levels of tussive stimuli as well as sensitivity to non-tussive triggers such as talking or cold air. Chronic cough is associated with an abnormality of neuronal pathways [13, 14] with increased peripheral and central sensitisation [15–18]. Hypersensitivity is encoded peripherally (cough sensory nerves) and centrally (brain stem and higher centres) [14]. Increased hypersensitivity causes innocuous stimuli to activate the afferent pathway of the cough reflex. The afferent pathway feeds into two medullary nuclei, the nucleus of the solitary tract and the paratrigeminal nucleus, and is perceived as an *urge-to-cough* via the cerebral cortex.

Cough can be either reflexive or under volitional control, the latter dependent upon the perception of an urge-to-cough which allows for voluntary initiation or suppression of the cough. Central inhibition of cough is impaired in chronic cough. Frequent coughing, in turn, exacerbates laryngeal hypersensitivity so that the process becomes repetitive. In addition to laryngeal hypersensitivity, cough reflex sensitivity and enhanced urge to cough [19], the laryngeal motor response is enhanced as evidenced by increased cough frequency and increased laryngeal constriction during respiration and phonation leading to dyspnoea and dysphonia [19]. Increased laryngeal motor responses may also be the result of decreased activation of the cough-suppression brain network [15].

There are three possible mechanisms of action for non-pharmacological approaches: reduced hypersensitivity, improved laryngeal motor control and enhanced activation of the central cough suppression network. Cough reflex sensitivity has been shown to decrease following speech pathology treatment [20]. In contrast, other studies of neuromodulator treatment do not show a significant change in cough reflex sensitivity compared to placebo which suggests that these treatments have different mechanistic targets. Speech pathology treatment is also associated with changes in patient reported laryngeal hypersensitivity [21], although the relationship between laryngeal hypersensitivity and cough reflex hypersensitivity requires further exploration.

Speech pathology treatment also targets laryngeal muscle tension and laryngeal motor control, and palpation of the laryngeal muscles during voice assessment is commonly practiced. Many voice therapy techniques aim to reduce intrinsic and extrinsic laryngeal muscle tension which can be present at rest or during phonation. Therapy also aims to increase voluntary control over coughing and respond to an urge to cough by substituting cough behaviour for a competing response and reducing exposure to irritating stimuli. A recent study has shown that up to 69% of patients with chronic cough have paradoxical vocal fold movement on laryngoscopy typical of ILO [22], and laryngeal constriction could be a precursor to coughing episodes. Therapy promotes greater voluntary control of vocal fold abduction by targeting co-existing ILO.

Speech pathology treatment may enhance activation of the central cough suppression network by altering cortical control over cough. Evoked reflexive cough is not solely a brainstem-mediated reflex response to irritation of the airways, but rather requires active facilitation by cortical regions, and is further regulated by distinct higher order inhibitory processes [23]. Activation of the cough suppression brain network is impaired in chronic cough as demonstrated by functional magnetic resonance imaging (fMRI), and reduced activity in the cough suppression network correlates with reduced ability to suppress coughing [15, 24]. fMRI studies have shown that inhalation of capsaicin reliably evokes an urge-to-cough which in turn requires increasing behavioural suppression of cough as the stimulus magnitude increases. This urge-to-cough is associated with activations in a variety of brain regions including the insula cortex, anterior-mid cingulate cortex, primary sensory cortex, orbitofrontal cortex, supplementary motor area and cerebellum [25]. The urge to cough can be responded to by avoiding or suppressing cough [1], implementing a strategy to reduce the urge to cough or producing a cough. It is possible that these same processes are involved in voluntary suppression of cough following non-pharmacological intervention.

When Should Non-pharmacological Approaches Be Used for Chronic Cough?

Non-pharmacological approaches for chronic cough are typically used when cough is refractory to medical management, that is, cough persisting despite guideline-based treatment. The only evidence for non-pharmacological treatment has been with patients with refractory cough rather than the broader chronic cough population. Is this approach appropriate?

Non-pharmacological approaches should not be considered as a first-line treatment for cough

due to serious medical diseases such as lung cancer, cardiac disease, foreign body aspiration or uncontrolled asthma. Practitioners of non-pharmacological approaches are likely to vary in their knowledge of these disease processes and are often not suitably qualified to diagnose or treat. Embarking on non-pharmacological approaches without considering serious medical disease may delay appropriate diagnosis and treatment of the underlying medical condition.

While medical management is required before non-pharmacological approaches, the extent of medical management requires consideration. Some medical conditions associated with cough, such as rhinosinusitis or gastroesophageal reflux disease, are not life-threatening. To what extent do these conditions need to be investigated and treated before considering non-pharmacological approaches? Patients with chronic cough can experience delayed access to treatment with multiple tests and consultations leading to patient frustration. One study reported an average cough duration of up to 37 months before speech pathology treatment was implemented, and yet once commenced, it was successful in 87% of patients [2]. Cough duration and associated negative side effects could have been considerably decreased in these patients if earlier referral for speech pathology treatment had been made.

Non-pharmacological approaches have the advantage of relatively few side effects and are relatively cost-effective. Training has been standardised and many speech pathologists across the world are able to implement the treatment. Despite this, non-pharmacological approaches have not been universally incorporated into cough guidelines.

Non-pharmaceutical approaches to cough secondary to lower airway disease has not been formally investigated. Cough can be secondary to lower airway diseases such as lung cancer, cystic fibrosis, idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease. Further, cough is vital for airway clearance in diseases such as bronchiectasis and cystic fibrosis. It is possible, however that cough can become hyperfunctional or hypersensitive in these lower airway diseases particularly for the dry irritated component of the cough. Treatment could encourage cough to expectorate phlegm but employ cough suppression strategies for dry irritated coughing. While this approach sounds plausible, there is limited safety and efficacy data available. Furthermore, it should be emphasised that non-pharmacological approaches are symptomatic treatments and that additional treatment of the underlying lower airway disease is vital.

Non-pharmacological Combination Approaches

Non-pharmacological approaches can be combined with other treatments. A randomised trial compared combined speech pathology and 300 mg pregabalin with combined speech pathology and placebo medication [26]. The results showed improvement in cough frequency, cough quality of life, cough severity and cough reflex sensitivity in both groups; however there was greater improvement in cough quality of life and cough severity in the combined speech pathology and pregabalin group [26]. Speech pathology treatment for cough could be considered as an adjunct in studies of new pharmacological treatments.

Slovarp has also investigated desensitisation using capsaicin in five healthy controls over five to six treatment sessions. Participants were exposed to increasing doses of aerosolised capsaicin while simultaneously implementing the behavioural cough suppression strategies. This study showed improvement in C2 and C5 over the course of treatment [27]. These results suggest a potential role for incorporating desensitisation with non-pharmacological interventions; however further research is needed to confirm the benefits of therapy.

Conclusion

Non-pharmacological approaches for chronic cough are useful for patients whose cough has persisted despite medical management. These treatments are an adjunct rather than a substitution for

medical treatment although the degree of medical treatment required before considering speech pathology intervention requires further consideration. The mechanisms underlying improvement are not fully understood but are likely to involve reduced laryngeal hypersensitivity, improved cortical control of cough and improved laryngeal motor control.

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Chronic Cough in Children

9

Daejin Song

Introduction

Cough is the most common reason for parents to seek medical advices for their children [1]. Most acute cough is associated with viral upper respiratory tract infections (URTIs). However, cough can be very distressing to watch if it persists and/or interferes with daily activities, including child and parents' sleep. In addition, cough may present as a symptom of serious underlying pulmonary or extrapulmonary diseases. Therefore, attention should be paid to persistent cough, and, in some cases, active investigations for underlying etiology may be necessary.

While the physiology of the respiratory systems may be similar across age groups, there are also distinct differences in airway, respiratory muscle and chest wall structure, lung mechanics, and respiratory control between children and adults [2, 3]. Therefore, it is not surprising that adult diagnostic and therapeutic approaches should not be applied to children.

However, it is often difficult to diagnose and treat children with chronic cough due to lack of solid data and parents' concerns. Therefore, to determine whether to initiate additional investigations or empirical treatments accordingly, a systematic approach to find out clues suggesting underlying disease is necessary, in consideration of the patient's age and medical resources.

Definition of Chronic Cough in Children

There is no consensus on the duration of cough which defines chronic cough in children, whereas cough lasting ≥8 weeks is commonly used to define chronic cough in adults. However, chronic cough in children aged ≤14 years is usually defined as a cough lasting ≥4 weeks based upon expert consensus [4]. The rationale behind the decision is that most acute URTIs in children resolve within this time frame [5, 6].

Meanwhile, British Thoracic Society (BTS) guideline suggests the same definition as adults based on the observation that acute cough due to URTIs could last more than 3 weeks in about 10% of children and could last up to several months in some children who showed repeated cough receptor hypersensitivity after respiratory viral infection [7]. However, the guideline still encourages careful individualized management, including warnings that investigation before 8 weeks is warranted if the child shows any signs of chronic lung disease or when the cough becomes worse. Indeed, 17.6% of children with chronic cough had a serious underlying disease (bronchiectasis, aspiration, or cystic fibrosis) in a multicenter study using a standardized

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S. H. Cho, W.-J. Song (eds.), *Diagnosis and Treatment of Chronic Cough*,
https://doi.org/10.1007/978-981-33-4029-9_9

cough management pathway [8]. Therefore, most guidelines including the American College Chest Physicians (ACCP) guideline define chronic cough in children as a cough lasting ≥4 weeks [9–12]. Although this approach may potentially lead to unnecessary investigations, it calls for earlier attention on child with prolonged cough to prevent possible damage caused by delayed diagnosis and treatment. However, these guidelines also recommend "watchful waiting" for patients without any specific symptom and/or sign suggesting underlying diseases.

It still remains unclear what age should be used to stratify into child and adult in applying the definition of and approach for chronic cough. Although there are many differences in underlying etiologies, outcome measures, and feasible investigatory tests between children and adults, none of the guidelines provide a robust evidence regarding the cutoff age of such stratification. However, it is reasonable to use adult guidelines for adolescents 15 years and older since the causes of chronic cough in this age group are fairly similar to those in adults [3, 13, 14].

Common Causes of Chronic Cough in Children

Although asthma, upper airway cough syndrome (UACS), and gastroesophageal reflux disease (GERD) are known to be major cough-triggering conditions in adults with chronic cough [15], common causes in children are reportedly variable, due to the heterogeneity in study design, chronic cough definition, age range of study populations, practice settings, or cough epidemiology across regions. Although there are few prospective studies based on a standardized management protocol, recent multicenter studies suggested that the most common causes of chronic cough in children are asthma, protracted bacterial bronchitis (PBB), UACS, and nonspecific cough (that resolves spontaneously or is likely post-infectious cough) [8, 16].

Asthma

Variable airflow obstruction in asthma leads to typical symptoms such as wheezing, dyspnea, and cough. Asthma is rarely a cause of "isolated" cough in children; therefore, the evaluation for chronic cough in children should include careful medical history about other suggestive findings of asthma, and, if possible, spirometry and assessment of response to bronchodilators and bronchial challenge test [17, 18].

However, typical symptoms of asthma may not be present initially, and cough can be the sole symptom, called as "cough variant asthma (CVA)" [19]. CVA may present as a nonspecific chronic cough in children. Thus, the possibility of asthma should be considered even in a child with chronic cough presenting no other apparent asthma symptoms. The cough associated with asthma is typically dry, but a wet cough alone cannot exclude asthma since other diseases or infections may coexist.

Protracted Bacterial Bronchitis

PBB is one of the most common causes of chronic wet cough, especially in preschool children [20, 21]. It accounted for approximately 40% of children under 18 years referred with chronic cough in a prospective multicenter study [8]. PBB may therefore be more common than previously thought [8, 20]. Although much skepticism regarding the existence of PBB has been raised, this disorder is now widely accepted and incorporated into most cough guidelines [22–24]. However, PBB has remained largely unrecognized and is often misdiagnosed as asthma.

Although the original diagnostic criteria for PBB included positive bronchoalveolar lavage (BAL) fluid cultures for respiratory bacterial pathogens, it was changed to more pragmatic one since performing BAL using a bronchoscopy on every child with a chronic wet cough is impractical. Now, PBB is usually diagnosed by a chronic wet cough (>4 weeks) without any symptoms

or signs of an alternative cause and responds to 2–4 week course of appropriate antibiotics [10, 25]. Chest radiographs are often normal or reveal only minor abnormalities such as peribronchial wall thickening. Pulmonary function tests are also usually normal. PPB is frequently associated with airway malacia [25]. *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis* are the most common pathogens isolated in the BAL fluid culture from children with PBB. Most widely used first-line empiric antibiotic is oral amoxicillin-clavulanate, which is active against beta-lactamase-producing strains based on a randomized controlled study [26, 27].

Timely diagnosis has been emphasized due to the potential risk that PBB may progress to chronic suppurative lung disease or bronchiectasis. However, each case should be carefully assessed to exclude alternative causes of chronic cough since the proposed diagnostic criteria of PBB may lead to overdiagnosis and unnecessary prescription of antibiotics.

The optimal duration of treatment of PBB is still unknown. The ACCP and European Respiratory Society (ERS) guidelines recommend 2-week course of antibiotics followed by 2 weeks if cough does not resolve, while the BTS guidelines recommend an initial course of 4–6 weeks [7, 9, 10]. If the wet cough has not improved substantially by this time, other causes should be considered. Chest CT scan is needed in the case of chronic productive or wet cough unresponsive to 4 weeks of antibiotics, recurrent (>3 times per year) PBB, and other key symptoms of bronchiectasis (e.g., hemoptysis, persistent pneumonia, or chest pain) [22].

Nonspecific Cough That Resolves Without Specific Treatment (or Post-infectious Cough)

Post-infectious cough is mostly self-limiting and usually resolves with time. Although the specific pathogen causing the post-infectious cough in most cases remains unidentified, respiratory viruses (particularly respiratory syncytial virus, influenza, parainfluenza, and adenovirus), *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Bordetella pertussis* may be the pathogens that may potentially lead to chronic cough [28–31]. Although the pathogenesis of the post-infectious cough is not fully understood, prolonged and excessive stimulation from extensive disruption of epithelial integrity and exposure of sensory nerve endings in the airway lining are considered to contribute to the development of post-infectious cough [31]. Cough receptors and peripheral and central neural circuits are also involved in post-infectious cough [32, 33].

Respiratory viruses are supposed to be the most common pathogens related with post-infectious cough and can be managed with reassurance. Substantial number of children with chronic cough had a serologic evidence of recent pertussis infection despite full immunization, but the classic features of pertussis infection (repetitive paroxysmal coughing episodes, inspiratory whoop, and posttussive vomiting) may not be seen in infants and older children [34]. Thus, post-pertussis cough should be considered in children with chronic cough regardless of immunization status. *M. pneumoniae* is also a common cause of post-infectious cough, and although *C. pneumoniae* is less common than *M. pneumoniae*, symptoms may be more severe. Post-infectious cough is often difficult to distinguish from PBB, and this may complicate therapeutic decisions.

Upper Airway Cough Syndrome

UACS, formerly termed as posterior nasal drip (PND) syndrome, includes a variety of disorders such as allergic rhinitis, non-allergic rhinitis, rhinosinusitis, and adenoiditis if associated with cough. The diagnosis of UACS in children is often made clinically based on symptoms, physical examination, and a response to therapy with antihistamines. The reported proportion of UACS varies widely (3–38%) in children with chronic cough depending on diagnostic algo-

rithms [13, 20, 35]. It also seems to be age-dependent. A low proportion was reported when the age of study population was young and ENT examination and allergy tests were not included in the diagnostic workup. However, whether PND is the cause of chronic cough in children is controversial and the pathophysiologic mechanism is still debated [36, 37].

Gastroesophageal Reflux Disease

Although it remains controversial whether GERD is common cause of chronic cough in children, chronic cough may be a presentation of GERD. There is also evidence suggesting a role for non-acid reflux in triggering chronic cough [38–41]. However, GERD is not commonly identified as the cause of "isolated" chronic cough in children (i.e., absence of gastrointestinal GERD symptoms) [9]. Thus, only for children with chronic cough who have gastrointestinal GERD symptoms, it is recommended investigations and treatment for GERD following pediatric GERD guidelines.

Tic Cough (Habit Cough) and Somatic Cough Disorder (Psychogenic Cough)

Tic cough describes a dry repetitive "tic-like" cough. It is usually not very disruptive and has habitual features similar to a vocal tic [42]. Meanwhile, somatic cough disorder shows bizarre honking cough. It is very disruptive to daily life and brings some secondary gain to the child. These coughs become worse in front of the caregivers or medical staffs and often disappear during sleep or engrossment. The coughs are very loud, but the patients themselves are often indifferent (la belle indifference). Although typical clinical characteristics are usually evident, a diagnosis can be made after other possible causes have been excluded. Non-pharmacological trials of hypnosis or suggestion therapy or combinations of reassurance, counseling, or referral to a psychiatrist are suggested in tic cough and somatic cough disorder in children [42, 43].

Other Causes of Chronic Cough in Children

Possible other causes of chronic cough in children are listed in Table 9.1. As the causes of chronic cough in children are so diverse across pulmonary and extrapulmonary diseases, this list outlines only some of the relatively common encounters. *The child's age can help narrow the list of possible causes. Asthma, UACS, and GERD, reported as the most common causes of chronic cough in adults and adolescents, are not much common in preschool children. Instead, PBB, post-infectious cough, and bronchiectasis may account for most of the causes in this age group* [20]. Therefore, the sequence of evaluation is guided by the age and accompanying symptoms/signs of each child.

Clinical Approach (Fig. 9.1)

Chronic cough in children may be representative of a simple, self-limiting cough or a serious underlying disease. In this regard, chronic cough has been classified into specific and nonspecific cough. Specific cough refers to a chronic cough that suggests a specific underlying disease and needs further investigations to confirm a diagnosis. Whereas, nonspecific cough refers to a chronic cough that does not suggest identifiable cause after a reasonable evaluation. To distinguish these two types of cough, it is crucial to find out clues that suggest underlying diseases through focused history, physical examination, and tests that can be easily performed in an outpatient setting (chest radiography or pulmonary function tests). However, specific cough may not be easily distinguished from nonspecific cough

Table 9.1 Specific cough pointers suggesting underlying causes in children with chronic cough

Specific cough pointers	Possible causes
Neonatal onset	Congenital malformations of airway such as tracheobronchomalacia or tracheoesophageal fistula
Onset after choking episode	Retained foreign body inhalation
Disappear during sleep	Tic cough (habit cough)
Associated with exercise, cold air	Reactive airway disease
Associated with feeding	Aspiration, tracheoesophageal fistula, gastroesophageal reflux
Throat clearing	Posterior nasal drip
Night cough	Reactive airway disease, rhinosinusitis
Seasonal cough	Reactive airway disease, allergic rhinitis
Exertional dyspnea	Asthma, any severe airway or parenchymal disease, cardiac disease
Chest pain	Asthma, arrhythmia, pleuritis
Hemoptysis	Bronchiectasis, tuberculosis, vascular abnormalities, retained foreign body inhalation
Feeding difficulty	Aspiration, laryngeal or trachea disorders
Neurodevelopmental abnormalities	Aspiration
Recurrent pneumonia	Immunodeficiency, suppurative lung disease
Medication	Angiotensin-converting enzyme inhibitor use
Environmental exposure	Asthma (allergen), irritant (active or passive smoking, pollutants)
Cough characteristics	
Paroxysmal cough	Pertussis and parapertussis
Staccato cough	Chlamydia
Barking or brassy cough	Tracheomalacia, tic cough (habit cough)
Honking cough	Somatic cough disorder (psychogenic cough), tic cough (habit cough)
Wet/productive cough	Protracted bacterial bronchitis, chronic suppurative lung disease, bronchiectasis, aspiration
Auscultatory findings (wheezing, crepitation)	Asthma, bronchopulmonary dysplasia, bronchiolitis obliterans, foreign body aspiration, secretions in airway, parenchymal disease such as interstitial disease
Chest wall deformities	Chronic lung disease, neuromuscular disease
Digital clubbing	Bronchiectasis, interstitial lung disease, cardiac disease
Abnormalities in chest radiograph or spirometry	Pulmonary and/or cardiac disease

after initial evaluation. Thus, children with a nonspecific chronic cough should be reevaluated until cough is spontaneously resolved or a specific cause is identified.

When managing children with chronic cough, most guidelines recommend a similar systematic approach, which was shown to significantly improve clinical outcomes in a multicenter randomized trial [4]. Remaining uncertainties about this approach are whether the management algorithm should depend on the duration or severity of chronic cough and the cutoff age for child-specific guideline to be applied.

Clinical History and Physical Examination

Many children experience recurrent acute cough which parents will not readily distinguish from chronic cough. So, first of all, it is necessary to confirm whether the patient's cough is truly chronic. Then, the history and physical examination focuses on identifying symptoms or signs suggestive of a specific cause of cough (specific cough pointers; Table 9.1).

Age and circumstance at onset of cough can help identify the cause. Neonatal onset, espe-

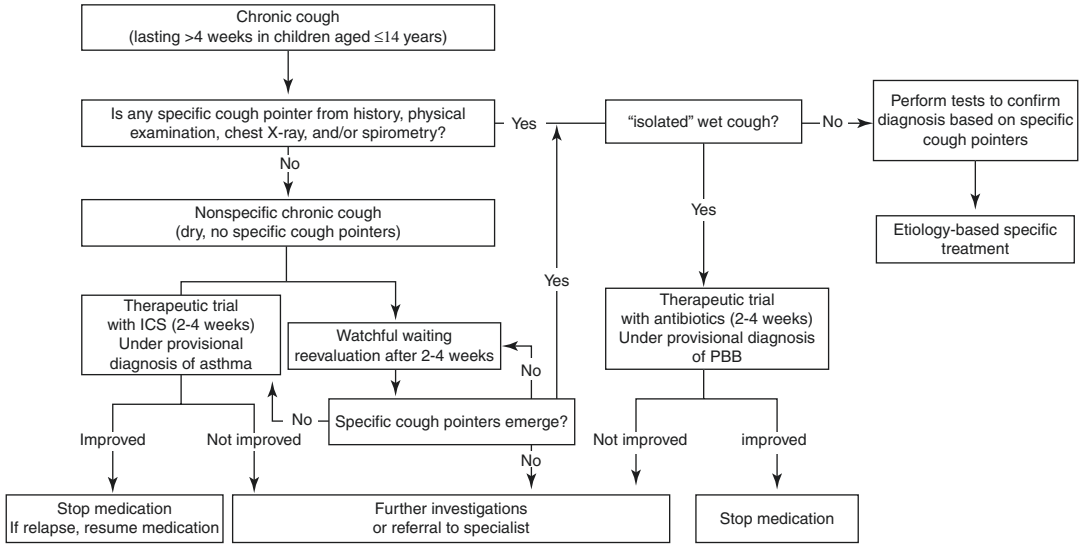

Fig. 9.1 Clinical approach for children with chronic cough. *PBB* protracted bacterial bronchitis

cially within a few days or weeks of birth, can be associated with congenital malformations of airway such as tracheobronchomalacia or tracheoesophageal fistula, so an immediate diagnostic process should be followed to reveal the underlying disease. In toddlers, sudden onset or onset after choking episode while playing or eating should raise suspicion of a foreign body aspiration. Sometimes, the characteristics of cough may be easily recognizable in the clinical history, which can provide diagnostic clues to underlying etiology. This is diagnostically less useful in adults [44]. Severe paroxysmal cough accompanied by vomiting or inspiratory "whoop" suggests an infection with pertussis or parapertussis. Chronic paroxysmal cough triggered by exercise and/or cold air is often seen in patients with asthma. Barking or loud brassy cough suggests lesions of proximal airway such as airway malacia or foreign body inhalation. Staccato cough in young infants suggests chlamydia infection, and honking cough that disappears during sleep or engrossment in something suggests a tic cough (habit cough) or somatic cough disorder (psychogenic cough). A chronic productive cough (wet cough) suggests suppurative process such as infection, bronchiectasis, cystic fibrosis, or immune deficiency, whereas dry cough suggests airway irritation, inflammation, or a non-airway cause of the cough.

Past medical history including perinatal period and family history relevant to chronic cough should be taken. History about cough-triggering factors can also provide helpful information. Environmental exposure to allergens (e.g., pollen, pets, dust) or irritants (e.g., active or passive smoking, environmental pollutants) that may cause cough should be evaluated.

Medications also should be reviewed carefully. Any current medications that can induce cough (e.g., angiotensin-converting enzyme (ACE) inhibitors) and a response to prior therapy may yield diagnostic clues.

All children with chronic cough need close physical examination, including overall health, growth, development, and nutritional state. As with medical history, physical examination should focus on identifying any signs suggesting underlying etiologies. If possible, listening to the patient's spontaneous cough can help to identify the characteristics of cough. Since other organs besides the lungs can be an origin of chronic cough, it is necessary to have a full physical examination, including an otorhinolaryngological examination as well as a chest examination.

Initial Diagnostic Tests

Chest Radiography

Although a definitive diagnosis is rarely made on the radiographic findings alone, chest radiography should be obtained as a part of initial workup. It can provide important information about the overall condition of the lungs and the need for additional diagnostic tests. However, a normal chest radiograph cannot exclude the possibility of underlying pulmonary diseases as a cause of cough, including bronchiectasis, airway abnormality, and interstitial lung disease. Therefore, additional imaging studies such as chest CT scan may be necessary if certain pulmonary diseases are suspected in medical history and physical examination.

Pulmonary Function Tests

Spirometry provides an important overview for lung volume and airway caliber, so, if available, it is recommended in children over 5–6 years who can cooperate. An obstructive pattern in the spirometry indicates obstructive lung diseases such as asthma and emphysema, while a restrictive pattern reflects restrictive lung diseases such as interstitial lung disease, pulmonary fibrosis, and neuromuscular disease. Bronchodilator responsiveness or bronchial challenge tests (direct or indirect) can help to diagnose asthma. However, a normal spirometry does not fully exclude these conditions.

Classification into Specific and Nonspecific Cough

After the patient's chronic cough has been classified into a specific and a nonspecific cough with an initial evaluation, the specific cough should be further investigated to diagnose the suspected specific disease and then managed with etiology-based treatment. In the case of nonspecific cough, reassurance and "watchful waiting" can be a reasonable option because it usually resolves over time without any specific treatment. However, some patients with specific or nonspecific cough may require an empirical treatment for diagnostic purpose. Parental expectations and concerns should be considered when determining whether to initiate empirical treatments.

Empirical Treatments in Children with Chronic Isolated Cough (Cough Without Any Other Specific Cough Pointer)

When empirical treatments are trialed, the placebo or "period effects" should be considered since the spontaneous resolution of cough over time is common [45]. To avoid lasting unnecessary treatments, reassessment of the patients is emphasized in 2–4 weeks that is usual time to response for most medications [9].

Chronic Isolated Dry Cough Because of an imprecise definition of asthma and lack of available tests to confirm the diagnosis in young children, asthma cannot be easily excluded in young children whose cough is the only symptom. Thus, when the cough is dry and objective testing cannot be undertaken, empirical treatment with inhaled corticosteroids (ICS) under provisional diagnosis of asthma may be considered. However, before starting ICS therapy, a period of the empirical treatment (e.g., 2–4 weeks) and objective end points should be pre-determined. The use of high-dose ICS in this situation must be balanced against well-known potential adverse events including growth deceleration, adrenal suppression, and pulmonary infection. Asthma medication should not be continued unless the diagnosis of asthma can be made with confidence. In children who responded to ICS, an early relapse of cough after the cessation of ICS may be a clue for the diagnosis of asthma.

Chronic Isolated Wet Cough Chronic wet cough is a specific cough pointer that needs further investigations to find out an underlying etiol-

ogy. However, empirical antibiotics for 2–4 weeks can be trialed in isolated wet cough under a provisional diagnosis of PBB. Although treatment with amoxicillin-clavulanate is usually effective, antibiotic selection should be based upon regional sensitivity patterns. If chronic wet cough fails to respond to antibiotics, then further investigations (see additional tests below) are required to rule out other suppurative lung diseases.

Empirical treatments targeting GERD or UACS are not usually recommended in children with chronic isolated cough, unless they have specific symptoms or signs for the diagnosis. These two disorders are not common cause of isolated cough, and there is no convincing evidence supporting that these empirical treatments are effective in children with chronic isolated cough.

Additional Diagnostic Tests

Additional investigations depend on the provisional diagnosis after initial evaluation and the clinical course of cough with or whiteout treatments.

Chest CT Scan

Chest CT scan is useful for the diagnosis of pulmonary parenchymal or central airway disease. High-resolution computed tomography is considered as a standard diagnostic method for structural changes in the small airways because it is more sensitive than pulmonary function tests. However, chest CT scan should be selectively performed only for patients with other accompanying symptoms/signs suggestive of underlying pulmonary diseases in consideration of the risk associated with radiation.

Bronchoscopy

Sometimes, chronic cough itself can be an indication for bronchoscopy in children [46]. However, considering that bronchoscopy is an invasive test and medical conditions requiring bronchoscopy are relatively rare, it is desirable to first perform noninvasive tests for common diseases. In children with chronic cough, indications for bronchoscopy are (1) a suspicion of tumor or structural abnormality in the central airway, (2) suspected retained foreign body inhalation, (3) suspected bronchial tuberculosis, (4) localized changes on chest radiography, and (5) bronchoalveolar lavage for bacteriological examination.

Sputum Testing

In most children with chronic wet/productive cough, it is difficult to obtain the sputum necessary for the examination, but if possible, culture with susceptibility testing and viral PCR should be performed.

Allergy Testing

Allergy testing is usually not recommended in the assessment of every child with chronic cough. However, a skin prick test or serum-specific IgE test can help to diagnose asthma or allergic rhinitis in children with a family or personal history of allergies or with any symptoms or signs for respiratory allergic diseases.

Esophageal pH or Multichannel Intraluminal Impedance Monitoring

In selected children who have GERD symptoms (e.g., acid regurgitation, heartburn) with chronic cough, esophageal monitoring may be undertaken to determine if the cough episodes are associated with reflux events.

Fractional Exhaled Nitric Oxide

Fractional exhaled nitric oxide (FeNO) is a quantitative, noninvasive, and simple method for measuring airway inflammation that provides a

complementary tool for diagnosing and monitoring asthma. FeNO levels have been shown to well reflect the degree of airway eosinophilic inflammation and to predict corticosteroid responsiveness in patients with respiratory symptoms [47, 48]. Thus, FeNO measurement may be particularly useful for younger patients and adults who find it difficult to perform the bronchial challenge test [49].

However, it should be noted that FeNO levels alone do not directly indicate a diagnosis of a specific disease. Many factors such as ethnicity, age, height, dietary intake, atopy, and tobacco smoke exposure can influence FeNO levels [50, 51]. Although ATS recommended FeNO levels >35 ppb in children aged ≤12 years and >50 ppb in children aged >12 years as cutoff to define presence of clinically important eosinophilic inflammation, there are still substantial discrepancies in the optimal cutoff value for defining abnormality among studies [52].

Treatment of Chronic Cough in Children

Making the correct diagnosis and then managing the underlying etiology is the key to treatment of chronic cough in children. There is little evidence supporting the benefit of treatments without a clear diagnosis. It is also important to ensure that children with chronic cough are not exposed to tobacco smoking and other pollutants.

Nonspecific cough can be managed with reassurance, watchful waiting, and reevaluation. If an empirical treatment is trialed, a regular reassessment for the treatment response and diagnosis is recommended with a predefined time frame. Further investigations with specialist referral are warranted if cough has not resolved with therapeutic trials or specific cough pointers have emerged. Specific cough should be managed with etiology-based treatment except empirical antibiotics in chronic isolated wet cough under provisional diagnosis of PBB. Management of each specific etiology is beyond the scope of this chapter and should follow the specific guidelines for each disease.

Summary

Chronic cough in children is usually defined as a cough lasting ≥4 weeks. Although the most common causes of chronic cough in children are reportedly variable, asthma, PBB, UACS, and nonspecific cough are suggested as common causes. When managing children with chronic cough, most guidelines recommend a similar systematic approach, which was shown to significantly improve clinical outcomes. In this regard, chronic cough has been classified into specific and nonspecific cough. To distinguish these two types of cough, it is crucial to find out clues that suggest underlying diseases through focused history, physical examination, and tests that can be easily performed in an outpatient setting. Additional investigations depend on the provisional diagnosis after initial evaluation and the clinical course of cough. Nonspecific cough can be managed with reassurance, watchful waiting, and reevaluation, whereas specific cough should be managed with etiology-based treatment. If empirical treatments are trialed due to parental concerns and/or diagnostic purpose under provisional diagnosis of asthma (isolated dry cough) or PBB (isolated wet cough), a reassessment is recommended in predefined time frame (e.g., 2–4 weeks). If the cough has not improved substantially by this time, other causes should be considered.

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Chronic Cough in Older Adults

10

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Introduction

Cough is a vital physiologic mechanism for protecting the lower airways against aspiration [1]. However, cough may become hypersensitive in the presence of pathologic conditions affecting the cough regulation pathways. Viral infection is a common exogenous trigger for sensitizing the cough reflex, and virus-induced cough may resolve within a few weeks. However, cough may persist for months or years in some individuals, and cough persisting for longer than 8 weeks is defined as chronic cough in adults [2–4].

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Chronic cough is a prevalent condition with a considerable impact on quality of life (QoL) [5]. One important finding from epidemiological studies is that chronic cough is more prevalent in older adults (≥65 years) than in adolescents or young adults [6]. The reason for this age-related prevalence pattern remains unknown, although roles of comorbidities have been postulated [6]. Older adults are prone to drug side effects and may have diseases in the central nervous system which may impair protective cough reflex. Thus, the management of chronic cough should be more challenging in older adults. Given the trends of rapid global population aging, chronic cough is likely to become a more significant medical issue. In this chapter, we review several issues of chronic cough in older adults, with the aim of addressing the following topics: (a) epidemiology, (b) clinical characteristics, and (c) therapeutic considerations including drug safety issues.

Epidemiology

Chronic cough is a prevalent condition affecting about 10% of general adult populations [7], but is reportedly higher in older adults (Fig. 10.1) [8–13]. In the Korean National Health and Nutrition Survey (KNHANES) 2010–2012, the overall point prevalence of chronic cough was estimated as 2.6%, but was 5.5% in older adults [8]. Also, the impact of chronic cough on QoL is larger in

S. H. Cho, W.-J. Song (eds.), *Diagnosis and Treatment of Chronic Cough*,
https://doi.org/10.1007/978-981-33-4029-9_10

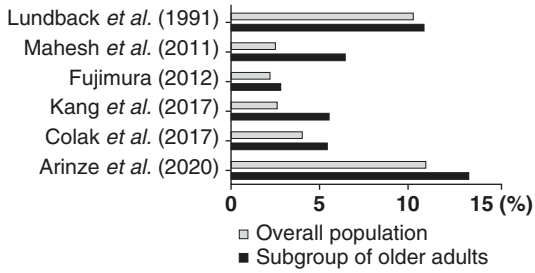

Fig. 10.1 Reported prevalence of chronic cough in older adults [8–13]. Prevalence of chronic cough, from population-based studies, was higher in a subgroup of older adults, compared to the overall population. Six studies reported the prevalence of chronic cough in the elderly to range from 2.8% to 13.3%

the aged group, particularly elderly women [14]. In an Internet-based survey of 10,505 subjects in Japan, the prevalence of chronic cough was 2.2% in general, but increased with aging, being the highest in older adults with 2.8% [9]. A postal survey for respiratory symptoms in 6,610 adults living in northern Sweden reported that 11% of adults aged 65–66 years had long-standing cough [10]. The Rotterdam study reported the period prevalence and incidence of chronic cough with 6-year follow-up [11]; of the 9,824 adult participants (≥45 years), the prevalence and incidence rate of chronic cough was 10.9% and 11.6 per 1000 person-years. Of note, the prevalence of chronic cough increased with age and peaked in the eighth decade with 13.8%, but the incidence rate of chronic cough decreased with age [11]. These findings suggest the relationships between aging and chronic cough may not be linear, which might be attributed to the age-related occurrence of disorders in central nervous systems.

Clinical Characteristics

The evidence is scare, but it has been suggested that natural aging process itself is unlikely to cause the impairment of cough reflex [15]; certain diseases affecting central nervous system such as dementia, Parkinson disease, or stroke may impair the protective function of cough reflex and increase the risk of aspiration pneumonia [16, 17]. On the contrary, respiratory and non-respiratory conditions stimulating the vagus sensory nerve terminals in the airways may be more frequent and various in older adults, and thus these complexities may make the clinical picture being more complicated.

In the literature, two studies compared the etiologies of chronic cough between younger and older adult patients visiting referral clinics. The study by Smyrnios et al. was the first to explore the causes and treatment responses in older adults with chronic cough [18]. They found generally similar characteristics across age groups; the disease triad (upper airway disease, asthma, and gastroesophageal reflux disease [GERD]) consisted of 85% of all causes of chronic cough in older adults and 100% in those without current smoking, angiotensin-converting enzyme inhibitor (ACEi) use, and abnormal chest X-rays [18]. In a study of 287 Chinese patients, asthma and upper airway cough syndrome were common causes both in the elderly and non-elderly groups, but ACEi-induced cough and GERD were more prevalent in older adults than in younger adults [19].

In population-based studies, different clinical conditions were associated with chronic cough in older adults, although the causal relationships remain undetermined. In the Korean Longitudinal Study of Health and Aging, a community-based elderly population cohort study, smoking status, asthma, allergic rhinitis, constipation, and uncontrolled diabetes mellitus (HbA1c ≥ 8%) were positively associated with chronic cough in older adults [20]. The association between diabetes mellitus and chronic cough was similarly observed in the KNHANES 2010–2012 study participants [8]. The Copenhagen General Population Study found that abdominal obesity, asthma, airflow limitation, bronchiectasis, and GERD were related with chronic cough in their middle-aged or older adult population [12]. In the prospective Rotterdam cohort, current smoking, GERD, asthma, and chronic obstructive pulmonary disease (COPD) were independent risk factors for chronic cough, with high shares of those aged 60 years or older [11].

Although the prevalence is low or undetermined, there are more clinical conditions that are potentially related to chronic cough in older adults. Cardiac diseases, such as left heart failure, endocarditis, or cardiac arrhythmia, were reported to be potential causes of cough [21–23]. In the study by Smyrnios et al., the following conditions were reported to be the etiologies of chronic cough in older adults, including bronchiectasis, chronic bronchitis, Zenker's diverticulum with aspiration, ACEi use, left ventricular failure, and bronchogenic carcinoma [18]. ACEi is one of the most well-known causes of chronic cough; however, small case reports described that other drugs, such as calcium channel blocker, sitagliptin, topiramate, methotrexate, or mycophenolate mofetil, might also cause cough [24] (Table 10.1).

Therapeutic Considerations

Management of chronic cough follows the same general principles for all adults, but more safety considerations are required in older patients. Commonly prescribed drugs, such as H1-histamine receptor antagonists (H1RAs), corticosteroids, or anti-acid drugs, may have higher risk of adverse reactions in older patients, as they are prone to cognitive dysfunction, injurious fall, or pneumonia. Thus, these patients should be informed of potential risks and benefits of each therapeutic drug, prior to commencing treatment.

H1RAs are one of the most prescribed drugs for managing adult patients with chronic cough in some regions. They are primarily indicated for the patients with nasal symptoms or signs; but first-generation H1RAs are also considered for those without such evidence, which is partly because of their central actions and possible antitussive effects [4]. However, importantly, older adults are vulnerable to unwanted side effects of first-generation H1RAs, such as cognitive dysfunction, behavior disturbance, voiding problems, or even injurious fall and fracture [25, 26]. Second-generation H1RAs are generally more tolerable, but there is no quality evidence to confirm or refute their benefits in patients with chronic cough (please see Chap. 4 for more details).

Inhaled corticosteroids (ICSs) and oral corticosteroids (OCSs) are used to manage cough variant asthma and eosinophilic bronchitis (please see Chap. 5 for more details). ICS is usually considered safe in adults, but may increase the risk of steroid-induced complications in older adults, such as osteopenia, fracture, cataract, adrenal insufficiency, hyperglycemia, infection, or pneumonia [27]. Local complication such as oral candidiasis is also frequent [28]. Fluticasone-based inhalers were associated with the risk of pneumonia in patients with COPD [29]. In population-based studies, there were significant associations between ICS use and tuberculosis or non-tuberculous mycobacterial lung diseases [30, 31]. However, it is unknown if these findings can be extrapolated to patients with chronic cough.

OCSs are also often considered for diagnostic trials or rapid symptom relief in patients with chronic cough [32]. However, repeated or long-term use of OCS may increase the risk of various systemic complications, even at low dose [33]. Population-based study in the USA found that a short-term use of OCS (even at a prednisolone-equivalent dose of less than 20 mg/day) was associated with the risk of sepsis, venous thromboembolism, or fracture [34]. A retrospective cohort study of asthmatic patients documented deleterious effects of short-term OCS treatment, including osteoporosis, hypertension, obesity, diabetes mellitus, cataract, or fracture [35]. These findings indicate that OCS should be used carefully in older adults with chronic cough.

Proton pump inhibitors (PPIs) are considered in cough patients with symptoms or signs of acid reflux (please see Chap. 6 for more details) [4, 32, 36]. However, the use of PPIs has dramatically increased over the years, and there are global concerns about their overuse [37]. According to the 2004 National Nursing Home Survey from the USA, about 27% of 355,600 elderly nursing home residents received at

least one episode of PPI treatment, and 48.6% of the use was not evidence-based [38]. It is notable that chronic cough was significantly associated with the non-evidence-based use of PPI (adjusted odds ratio [OR]: 2.10, 95% confidence interval [95% CI]: 1.12–3.96) [38]. Also, although the risk is modest, PPI use was positively associated with complications, such as osteoporosis-related fractures, iron deficiency, vitamin B12 deficiency, hypomagnesemia, *Clostridium difficile* infection, dementia, or community-acquired pneumonia, which are elderly prone conditions [39].

Chronic refractory cough (or unexplained cough) is frequent in older patients, and antitussive drugs are indicated to control cough (please see Chap. 7 for more details). Codeine, a prodrug of morphine, is one of the most well-known antitussive drugs, presumably acting on the medullary cough center [40]. There is no proper RCT to confirm the efficacy of codeine in patients with chronic refractory cough, but clinical experience suggests that it is likely effective in about half of patients with chronic refractory cough [41]. Common side effects are nausea and constipation, which may also occur in about half of the patients; but there is a concern about codeine dependence. The risk of codeine dependence may be higher in subjects with vulnerability to dependence [42]. Another issue with codeine is that its metabolism is dependent on cytochrome P450 2D6 (CYP2D6) in the liver [43]. Thus, the efficacy and safety of codeine are dependent on CYP2D6 genetic polymorphisms and may be unpredictable in usual clinical practice.

Morphine is not affected by inter-individual variability in CYP2D6 metabolism, and thus the biological effects of morphine are more predictable than those of codeine [41]. Morphine is about tenfold more potent than codeine, and low-dose slow-release morphine treatment (5 mg twice daily) was significantly more effective than placebo treatment in improving cough-specific quality of life and reducing cough severity in patients with chronic refractory cough [44]. In clinical experience, the proportion of codeine or morphine responders is supposed to be about 40–50% among patients with refractory cough, and the responders are likely to respond rapidly (within a week) and also well to even lower dose. In the clinical trial by Morice and colleagues, slow-release morphine therapy was associated with constipation and nausea, but no serious events [44]. However, there are concerns and anxiety about the safety of morphine, including respiratory depression, drowsiness, and addiction. Thus, the use of morphine is restricted to patients with cough otherwise uncontrollable.

Gabapentin or pregabalin may reduce cough and improve cough-specific quality of life in patients with chronic refractory cough [45, 46]. However, side effects are common and sometime intolerable, such as fatigue, dizziness, sedation, or cognitive changes, which may increase the risk of injurious fall in older patients.

Conventional antitussives, such as codeine/morphine, gabapentin, or pregabalin, are primarily developed or used for pain and neuropathic conditions. Therefore, as discussed above, they have limitations with efficacy and safety. There are recent clinical successes with novel antitussives, such as P2X3 antagonists [47] (also please see Chap. 7). A first-in-class drug, gefapixant, which recently completed phase 3 trials, is expected to be available in the near future. Gefapixant is generally well tolerated, but may cause taste disturbance at high dose, which is likely related to the inhibition of P2X2/3 channels in taste buds [48]. Interestingly, gefapixant appears to have minimal effects on cough responses to citric acid or capsaicin inhalation [49], suggesting that it may preserve the vital cough response to irritant inhalation, although clinical observations are warranted to confirm the safety (Table 10.2).

Table 10.1 Clinical conditions associated with chronic cough in older adults[a]

Common conditions	Other conditions
• Upper airway diseases [18–20] • Asthmatic cough [18–20] – Cough variant asthma – Eosinophilic bronchitis • Gastroesophageal reflux disease [18, 19]	• Chronic bronchitis [18] • Chronic obstructive pulmonary disease [11] • Bronchiectasis [12, 18] • Bronchogenic carcinoma [18] • Constipation [20] • Diabetes mellitus [8, 20] • Obesity [12] • Zenker's diverticulum [18] • Heart failure [18] • Endocarditis [22] • Cardiac arrhythmia [21] • ACE inhibitors [18, 19] • Calcium channel blockers [24] • Sitagliptin [24] • Topiramate [24] • Methotrexate [24] • Mycophenolate mofetil [24]

[a]Causal relationships with cough may be unclear

Table 10.2 Common therapeutic drugs and potential adverse reactions in older adults with chronic cough

Drugs	Indications	Adverse drug reaction
H1-histamine receptor antagonists (particularly first-generation drugs)	• Upper airway disease-associated cough (or upper airway cough syndrome)	• Cognitive decline [25] • Behavior disturbance [25] • Urinary dysfunction [25] • Injurious falls or fracture [26]
Inhaled corticosteroids	• Asthmatic cough – Cough variant asthma – Eosinophilic bronchitis	• Oral candidiasis [28] • Pneumonia [27, 29][a] • Osteopenia [27] • Fractures [27] • Cataract [27] • Adrenal insufficiency [27] • Mycobacterial infections (tuberculous or non-tuberculous) [30, 31]
Oral corticosteroids	• Asthmatic cough – Cough variant asthma – Eosinophilic bronchitis	• Sepsis [34] • Cataract [35] • Skin diseases involving bruising and striae [33] • Venous thromboembolism [34] • Fracture [34, 35] • Osteoporosis [35] • Hypertension [35] • Diabetes mellitus [35] • Obesity [35]
Proton-pump inhibitors	• Acid reflux-induced cough	• Osteoporotic-related fractures [39] • Iron deficiency [39] • Vitamin B12 deficiency [39] • Hypomagnesemia [39] • *Clostridium difficile* infection [39] • Dementia [39] • Pneumonia [39]
Opioids (codeine or morphine)	• Chronic refractory or unexplained cough	• Nausea [44] • Drowsiness [44] • Constipation [44]
Gabapentin or pregabalin	• Chronic refractory or unexplained cough	• Dizziness [45, 46] • Somnolence or sedation [45, 46] • Fatigue [45, 46] • Drowsiness [45] • Nausea [45] • Gastric discomfort [45]

[a]Possible risk of pneumonia in COPD patients (not proven in cough patients without COPD)

Summary

Chronic cough in older adults is an emerging issue with high prevalence. Clinical considerations for these patients should be more complex and challenging because they have more comorbidities. They are prone to adverse reactions to commonly prescribed drugs such as H1RAs, corticosteroids,

PPIs, or antitussives. Thus, these patients should be informed of potential risks and benefits of each therapeutic drug, prior to commencing the treatment. A comprehensive approach is essential to improving clinical outcomes and understanding the clinical heterogeneity of chronic cough problems in the older adult population.

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