Respiratory Medicine 170 (2020) 105939

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: http://www.elsevier.com/locate/rmed

Review article

German Respiratory Society guidelines for diagnosis and treatment of adults suffering from acute, subacute and chronic cough

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ARTICLE INFO

Keywords:
Cough
Guidelines
Chronic idiopathic cough
Chronic refractory cough
Cough diagnostic assessment

ABSTRACT

The present 2019 S2k consensus guideline of the German Respiratory Society was written for pneumologists – in contrast to the more general predecessor's S3 guidelines from 2004 to 2010 –, since 2014 the German College of General Practitioners and Family Physicians (DEGAM) published their own cough guidelines.

The guidelines contain 48 recommendations agreed upon the consensus and 16 statements, which are explained in the background text in the following nine chapters: epidemiology, physiology, classification, acute, subacute or chronic cough, diagnostics and therapy; an extra chapter was dedicated to chronic idiopathic/refractory cough. Further emphasis of the guidelines is the physiology of cough in anticipation of the introduction of new drugs, as well as detailed treatment for cough triggered by affectations of the upper respiratory tract or gastroesophageal reflux.

The guideline should provide the pneumologist with the latest knowledge for neighboring disciplines required for diagnosis and therapy of cough. The clinical chapters also contain a short summary, practical recommendations and a bibliography of their own. Three new simplified algorithms for acute, subacute and chronic cough, round off the diagnostics chapter.

Preface

The first guidelines of the German Respiratory Society (DGP) for the diagnosis and therapy of patients with acute and chronic cough was published in 2004 [1], an update followed in 2010 [2]. The German Society of General and Family Medicine (DEGAM) published cough guidelines for general practitioners in 2014 (http://www.degam.de/files/Inhalte/Leitlinien-Inhalte/Dokumente/DEGAM-S3-Leitlinien/Langfassung_Leitlinie_Husten_20140323.pdf). All three guidelines were composed using all systematic literature data and developments and assigned to level S3 guidelines of the AWMF (Association of the Scientific Medical Societies in Germany).

The scientific development of the past years requires an update. The previous guidelines for cough of the DGP (ICD 10 Classification R 05) had recommendations for all physicians treating adult patients with cough, a very common symptom or - frequently - the sole complaint. These patients are primarily treated by the general practitioner in an outpatient setting. A new version of the DEGAM guidelines for general practitioners has been announced for 2020. Moreover, the Society for Pediatric Pneumology (GPP, Gesellschaft für Pädiatrische Pneumologie) announced guidelines for children for 2021. Therefore, the DGP dedicates the present new version of its guidelines on cough in adults

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https://doi.org/10.1016/j.rmed.2020.105939
Received 18 March 2019; Received in revised form 12 March 2020; Accepted 18 March 2020
Available online 25 April 2020

primarily for pneumologists/pulmonologists and therefore setting other priorities than the DEGAM or GPP. This S2K guidelines no longer focus on a broad spectrum of diseases associated with cough, but on differential diagnostic and therapeutic issues in patients with cough referred from primary care to respiratory physicians.

Accordingly, the guidelines were developed - with participation of patient organizations - by pneumologists. Experts from neighboring disciplines were also invited to develop recommendations for cough triggered by diseases of the upper respiratory tract and gastroesophageal reflux, respectively. These chapters were presented in detail, as they are less familiar to the pneumologist, but indispensable for clarifying the cause of the cough. Particular attention has been paid to these chapters, in order to cover the need for additional information for pneumologist. In addition, a great deal of space was devoted to the physiology of the cough reflex in order to improve the understanding of the mechanism of action of new upcoming therapies. In contrast to 2010, when the last precursor version of this guideline was published, several substances are now in phase 3 trials.

Beyond an updated classification of cough, still based on the duration of the symptom, the recommended diagnostic steps are evaluated and defined in a separate chapter (#8) comprising also three algorithms for the diagnosis of cough (Figs. 8.1, 8.2 and 8.3). Chapter 9 contains the current standard of symptomatic treatment. The aim of the guideline is to help uncover the causes of cough opening the possibility for a causal treatment to eliminate or reduce health impairments as far as possible.

Since the publication of the S3 guideline of the DGP in 2010, the British Thoracic Society [3], the European Respiratory Society [4,5] and the Japanese Respiratory Society [6] have not updated their guidelines. The ACCP (American College of Chest Physicians) has been updating its 2006 guideline [7] since 2014 [8]; yet, not all chapters have been published [9-18]. However, a year after the publication of the German original of these guidelines the ERS published new guidelines for cough [19].

Another special feature of this guideline is its partition into ten independent chapters with the respective bibliographies. This is intended to provide the reader with fast, targeted access for the information needed. On the other hand, this structure produces some redundancy in the text, in the abbreviations and references.

This guideline developed by experts in a consensus procedure under management of a methodologist for clinical practice guidelines of AWMF is based on the published evidence and contains recommendations for respiratory physicians for step-by-step diagnostic assessment and therapy of cough. Strong and weak recommendations were formulated with “should” and labeled with ⇑⇑ or ⇑ respectively. “Can” formulations are labeled with ⇔ if evidence is uncertain and no recommendation could be made. In this case the patient must be informed, and an individual decision might be considered.

Each patient retains his or her privilege to individual diagnosis and therapy. In a specific case it may be advisable to deviate from the guidelines.

The layout of the previous version of the guidelines has been changed. Now, the recommendations and statements can be found right at the beginning, structured according to the individual chapters. The background text can be found in the respective chapters.

The German Respiratory Society (DGP) is responsible for the preparation of the guidelines. Peter Kardos (Frankfurt am Main) is in charge.

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Recommendations and Statements

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Recommendation Statement	Chapter 1: Epidemiology	Strength of recommendation
Recommendation Statement	Chapter 1: Epidemiology	Strength of recommendation
S_1	Cough due to viral infection of the upper and/or lower respiratory tract is worldwide the most common reason for a medical consultation	**Statement**
	Chapter 2: Physiology	
S_2	Cough is mediated usually by vagally sensitive afferences	**Statement**
S_3	Viral, bacterial and allergic rhinosinusitis can cause cough, mediated by trigeminal afferences.	**Statement**
S_4	Neuronal changes take place at different levels of the cough reflex arch, e.g. in peripheral and central cough receptors. The peripheral cough receptors can lead to hypersensitivity of the cough reflex due to inflammatory processes of the mucosa and/or increase in central neuronal excitability.	**Statement**
	Chapter 3: Classification	
S_5	Classification of cough is based on duration (acute up to three weeks, subacute between three and eight weeks, chronic longer than eight weeks).	**Statement**
S_6	Diagnostic assessment based on the clinical characteristics of the cough (dry, productive, etc.) is not helpful.	**Statement**
S_7	Repeated episodes of cough that occur several times a year lasting up to three weeks are referred to as recurrent acute cough.	**Statement**
R1	In the case of chronic cough, diagnosis should be initiated immediately (usually with a chest x-ray and a pulmonary function test) and completed according to the algorithm provided.	⬆⬆
	Chapter 4: Acute cough	
S_8	The most common cause of acute cough is a viral infection of the upper and/or lower respiratory tract.	**Statement**
R_2	In case of acute cough w/o alarm signals (e.g. shortness of breath, hemoptoe, severe thoracic pain, high fever, indication of pneumonia) technical examinations should not be performed.	⬇⬇
R_3	In case of acute cough with alarm signals appropriate diagnostics should be carried out without time delay, if necessary, in an inpatient setting.	⬆⬆
R_4	In case of acute worsening of the chronic cough a new diagnostic assessment should be initiated.	⬆
R_5	In case of acute cough, 4 weeks after consultation the patient should be reassessed whether the cough has subsided.	⬆
R_6	In otherwise healthy persons with acute cough, antibiotic treatment shouldn't be initiated primarily.	⬆
R_7	In common cold, drugs should be prescribed to shorten the duration and alleviate the intensity of acute cough, if their efficacy was proven in randomized controlled trials	⬇⬇
R_8	In the case of severe acute dry irritable cough Dextrometorphan should be prescribed for about 7 days.	⬆⬆
	Chapter 5: Subacute cough	
S_9	The most frequent cause of subacute cough is usually a viral infection.	**Statement**
R_9	In subacute cough, a viral and postviral rhinosinusitis and or postinfectious temporary bronchial hyperreactivity should be considered and, if necessary treated.	⬆
R_{10}	Subacute post-infectious cough due to temporary bronchial hyperreactivity should be treated with inhaled corticosteroids or with inhaled beta2-adrenergics for about two weeks.	⬆
R_{11}	Viral or post-viral rhinosinusitis (lasting up to twelve weeks) should be treated to alleviate symptoms and shorten the duration of symptoms.	⬆
R_{12}	A viral or post-viral rhinosinusitis may be treated with a nasal corticosteroid (off label use).	⇔
R_{13}	In subacute cough, 4 - 8 weeks after the first consultation the patient should be reassessed whether the cough has subsided.	⬆⬆
	Chapter 6: Chronic cough	
R_{14}	In case of chronic cough under ACE inhibitor treatment, the drug should be stopped before starting further diagnostic assessment, even if the cough may have other causes	⬆⬆
R_{15}	In chronic cough without evident cause after a chest X-ray and lung function test were done, diseases of the upper respiratory tract, cough as asthma equivalent or gastroesophageal reflux disease should be considered.	⬆⬆
R_{16}	In pertussis or well controlled asthma with refractory cough temporarily antitussives should be used	⬆
	Chapter 6.1 Chronic cough – upper airway diseases	
R_{17}	In chronic rhinosinusitis, nasal glucocorticosteroids should be prescribed, in a few individual cases also systemic glucocorticosteroids.	⬆⬆
R_{18}	In the case of chronic pharyngitis or laryngitis, therapy with inhaled glucocorticosteroids should be used. In individual cases with hypersensitive components,	⬆

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Recommendation Statement	Chapter 1: Epidemiology	Strength of recommendation
	speech therapy should be prescribed.	
S_{10}	In case of vocal cord dysfunction (VCD) usually laryngeal hypersensitivity leads to persistent laryngospasm due to different trigger factors. Cough can be both a trigger factor and a symptom.	**Statement**
R_{19}	The diagnosis of vocal cord dysfunction (VCD) can be made based on typical findings in history, laryngoscopy and if possible spirometry during an attack.	⇔
	6.3 Cough variant asthma	
S_{11}	If a patient with chronic cough is bronchial hyperresponsive without obvious bronchial obstruction and he or she responds to asthma therapy, cough variant asthma can be assumed.	**Statement**
	6.6 Bronchiectasis	
S_{12}	Intensive parenteral (if possible targeted) antibiotic therapy can alleviate cough in bronchiectasis.	**Statement**
R_{20}	At the time of first diagnosis of bronchiectasis, an etiological assessment should be carried out.	⇑⇑
R_{21}	An acute antibiotic treatment course for bronchiectasis, if necessary should last usually at least 14 days	⇑
R_{22}	For ≥3 exacerbations of bronchiectasis in a year, long-term antibiotic therapy may be considered.	⇔
	6.8 Chronic cough: Reflux	
S_{13}	For the indication "chronic cough" proton pump inhibitors (PPI) in randomized controlled trials did not prove superior to placebo.	**Statement**
R_{23}	A PPI therapy trial of a suspected gastroesophageal reflux disease with exclusively extraesophageal symptoms (i.e. chronic cough without heartburn or regurgitation) should not be carried out.	⇓⇓
R_{24}	In chronic cough associated with esophageal reflux symptoms (heartburn, regurgitation), in addition to the non-drug measures (i.e. diet, promoting weight loss in obese patients, avoiding late meals and head of bed elevation), over a period of three months an acid-inhibiting drug therapy should be prescribed.	⇑⇑
R_{25}	If the cause of a chronic cough remains unclear, endoscopy, impedance pH probe and esophageal manometry should be performed to diagnose a possible "silent" gastroesophageal reflux disease.	⇑⇑
R_{26}	In case of chronic cough without esophageal reflux symptoms but positive results of comprehensive reflux assessment, in addition to the recommended lifestyle changes, a high-dose PPI therapy with twice daily administration over 60-90 days should be performed.	⇑⇑
R_{27}	In patients with chronic cough and suspected reflux-cough syndrome lifestyle modification, diet promoting weight loss in obese patients, avoiding late meals and head of bed elevation should be performed.	⇑
R_{28}	If PPI therapy of reflux - cough syndrome is successful, the indication for surgical therapy should be evaluated.	⇑
R_{29}	If the cough is triggered by a weak acid reflux (detected by impedance pH-probe and high symptom-reflux association) surgical therapy may be considered (even if PPI therapy fails).	⇔
	Chapter 7: Idiopathic cough	
S_{14}	Chronic idiopathic or refractory cough is a diagnosis of exclusion.	**Statement**
S_{15}	With increased sensitivity of the cough reflex, inhalative stimuli (i.e. dust, smoke, perfume smell, temperature changes, telephoning) as well as laryngeal dysfunction trigger the cough reflex.	**Statement**
R_{30}	The hypersensitivity of the cough reflex is clinically diagnosed and should not be tested in clinical routine care (testing only for scientific purposes).	⇓⇓
R_{31}	Chronic idiopathic or refractory cough can be regarded as a neuropathy of the cough reflex and treated as neuropathy with gabapentin or pregabalin.	⇔
R_{32}	For the treatment of chronic idiopathic cough, respiratory physiotherapy can be performed using cough - preventing techniques (if an experienced therapist is available).	⇔
R_{33}	In laryngeal hypersensitivity with chronic irritative cough and/or throat clearing, speech therapy can be prescribed (if a experienced therapist in this field is available).	⇔
	Chapter 8: Diagnostic assessment	
R_{34}	The diagnostic assessment of cough should follow the appropriate algorithm for acute, subacute and chronic cough.	⇑⇑
R_{35}	For the diagnostic assessment of rhinosinusitis, a nasal endoscopy should be performed, in individual cases additionally computer	⇑⇑

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Recommendation Statement	Chapter 1: Epidemiology	Strength of recommendation
	tomography or digital volume tomography.	
R_{36}	For the diagnostic assessment of pharyngitis or laryngitis, a pharyngo- laryngoscopy should be performed, in individual cases additionally videostroboscopic diagnostic.	⇑⇑
R_{37}	For the diagnosis of cough as asthma equivalent in case of normal lung function an inhalative provocation test with metacholine should be performed.	⇑⇑
R_{38}	Diagnostic assessments using CT and/or bronchoscopy should only be performed after the most frequent trigger factors have been excluded.	⇑⇑
R_{39}	For the diagnosis of suspected bronchiectasis, a multislice chest computed tomography with 1 mm reconstructions without contrast medium should be performed.	⇑⇑
R_{40}	If after completing the appropriate algorithm the cause of cough remains unexplained patients should undergo bronchoscopy.	⇑
R_{41}	In chronic cough, 8-12 weeks after treatment initiation the success of therapy should be assessed.	⇑⇑
	Chapter 9: symptomatic therapy	
R_{42}	Before initiating therapy for chronic cough, the cause of the cough should be assessed.	⇑⇑
R_{43}	A symptomatic therapy should only be initiated if no causal therapy available or until onset of the effect of the causal therapy.	⇑
S_{16}	When secret retention leads to coughing, the promotion of expectoration is the central principle in physical and drug therapy. Antitussives are only indicated in exceptional cases, e.g. at night for cough attenuation in combination with mucoactive drugs during the day.	**Statement**
R_{44}	To relieve the intensity and shorten the duration of cough due to common cold/acute bronchitis herbal remedies with proven efficacy in RCT's or ambroxol should be given.	⇑
R_{45}	Inhalative or nasal corticosteroids should be prescribed only for the following indications: cough variant asthma, eosinophilic bronchitis or rhinosinusitis.	⇑⇑
R_{46}	Opiates with central antitussive effect should be prescribed in low doses (e.g. daily 1-2x10 mg morphine retard) for distressing irritable cough. Side effects (i.e. respiratory depression, sedation, constipation, addiction) must be considered.	⇑⇑

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Recommendation Statement	Chapter 1: Epidemiology	Strength of recommendation
R_{47}	Opiates (except dextrometorphan) should not be used for cough in acute cold as they are no better than placebo.	⇓⇓
R_{48}	Dextrometorphan has an antitussive efficacy in common cold as documented in RCT's and should be considered for irritative cough. .	⇑

Chapter 1

Epidemiology of cough

Cough is one of the most common symptoms worldwide that leads to a medical consultation [1]. This is mainly due to acute cough that occurs in the course of common colds. Many people also suffer from chronic cough, a common symptom of almost all respiratory diseases and some extrapulmonary diseases [2].

A neuronal hypersensitivity of the cough reflex plays an important role in triggering the cough. Cough is an important protective reflex of the respiratory tract. It can also contribute to the spread of infectious diseases. Chronic cough impairs the quality of life [3].

No reliable data are available on the prevalence of cough in Germany. One reason for the lack of these data is that epidemiological studies on cough based on questionnaires are difficult to interpret. The prevalence of coughing measured in this way is strongly dependent on the research question. In addition, unlike shortness of breath or thoracic pain, many patients perceive cough not necessarily as symptom of a disease, so that timely contact with a physician will not take place.

Systematic evaluation and analysis of the published studies on cough in adults have shown that chronic cough occurs worldwide with a prevalence of 9.6% (cough $>$ 3 months at 7.9%), more frequently in Europe (12.7%) and America (11%) than in Asia (4.4%) and Africa (2.3%) [4]. Different prevalences are also reported within Europe. An ethnic or genetic difference in the cough reflex is not solely responsible, but environmental factors such as urbanization and lifestyle can partly explain the regional differences in the prevalence of chronic cough [4-6].

As an example, the prevalence of chronic cough in England was 12%, with smoking, gastroesophageal reflux and lower social status being considered strict predictors [7]. In the United States, cough is the most common complaint to visit a general practitioner or hospital outpatient clinic, which means about 30 million visits per year [8,9].

The prevalence of cough depends not only on exogenous noxae but also on age and sex. The sensitivity of the cough reflex increases during childhood and puberty, is more pronounced in girls and women than in boys and men, and decreases again at an advanced age [10,11]. A questionnaire survey showed that in 66% of the cases no other disease was known to the patient apart from the chronic cough [12].

Chronic cough means for the health system an enormous socio-economic burden with high direct and indirect costs and for the individual patient a great burden often with social isolation. Therefore, further systematic epidemiological studies with worldwide uniform international standards and definitions are needed to investigate the prevalence of cough with its complex heterogeneity and etiology.

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Chapter 2

Physiology

The anatomical and physiological processes involved in the initiation and regulation of the cough are complex and at first glance do not appear to be of importance to the physician working in the practice or inpatient settings. However, an understanding of the complexity of the cough reflex is helpful in clarifying the etiology of the cough and in the search for new therapeutic concepts (Fig. 2.1).

2.1. Characteristics of sensory airway innervation and its involvement in cough reflexes

The cough is mediated by sensory nerve fibers which originate bilaterally in the vagus nerve from the two vagal-sensory ganglia (jugular ganglion and ganglion nodosum) and innervate the pharynx, the trachea, the carina and the two main bronchi down to the small bronchioles. These vagal-sensory nerve fibers differ from each other in their anatomical, embryonic, chemical, mechanical and physiological properties [1,2]. Their nerve endings, the so-called cough receptors, which are located everywhere in the epithelium of the respiratory tract, throat, larynx, trachea and bronchi, are activated by mechanical and chemical stimuli as well as by released inflammatory mediators (bradykinin and prostaglandins). The stimulus reaches the brain stem via the Aδ and C fibers through the vagus nerve. The cough receptors can be divided into three groups with regard to their electrophysiological configuration, namely into the two mechanosensitive, acid-sensitive, myelinated Aδ fiber types “fast-adapting (RAR) mechanoreceptors” and “slow-adapting (SAR) mechanoreceptors” (leading speed of 14–23 m/s and 3-5 m/s, respectively) and the non-myelinated C fibers (leading speed (0.3–2 m/s) [3]. The perikarya of the mechanoreceptors is in the ganglion nodosum, that of the C-fibers in the ganglion jugulare [4].

C-fibers represent the largest part of the N. vagus, the bronchopulmonary vagal sensory airway innervation. They differ from the Aδ fiber types in their insensitivity to mechanical stimulation. However, activation can occur by inhalation of allergens, bradykinin, capsaicin, chemical irritants, hypertonic saline solution, ozone, proinflammatory mediators, dry cold air and cigarette smoke. C-fibers are responsible for the mediation of scratchy, irritant, slowly rising cough (“urge-to-cough sensation”). A strict functional difference between Aδ and C fibers does not exist between the two fiber types, as new results provide evidence of interaction between Aδ and C fibers in their common course [1,2,5].

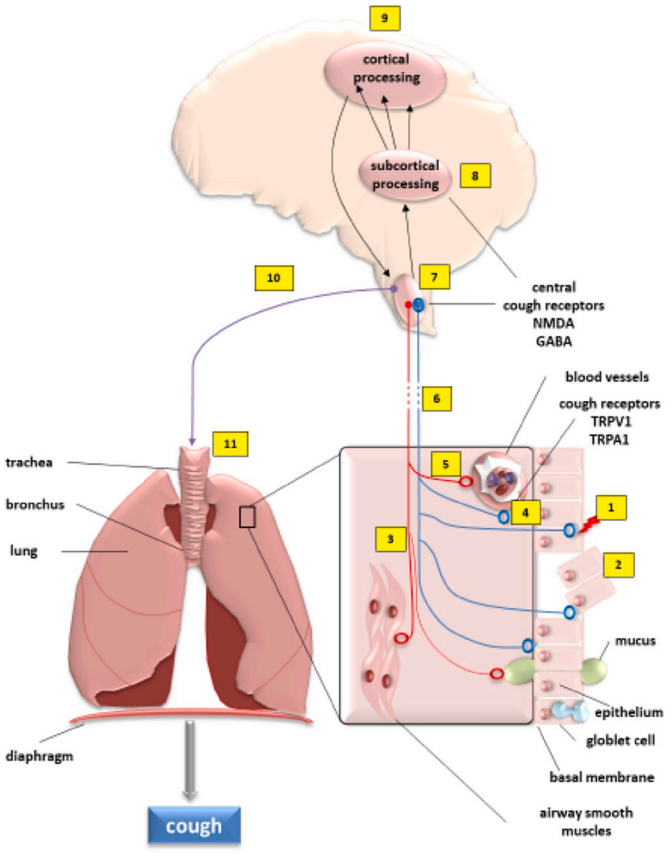

Fig. 2.1. Physiology of the cough reflex.
Legend: (1) The cough reflex can be triggered by activation of the peripheral cough receptors by various noxae such as inflammation in asthma, COPD, chronic and acute infections, mechanical irritation by foreign bodies, chemical irritation (gastric acid) and inhalation of tobacco smoke. Epithelial damage (2) with the release of inflammatory mediators such as histamine, prostaglandins and TNF-α can also increase the activity of cough receptors (3). Different cough receptor types (4) such as C-fibers (5) SAR (slowly-adapting mechanoreceptor) and/or RAR (rapidly-adapting mechanoreceptor) are activated by different stimuli. (6) Via the N. vagus, the stimulus passes through the ganglia jugulare and nodosum into the cough center located in the medulla oblongata (7). Subcortical regions (8) and several cortical centers (9) can influence the motor activation of the cough. (10) Spinal afferents, the phrenic nerve and the laryngeal recurrent nerve (11) innervate the diaphragm, the abdominal, intercostal and laryngeal muscles and trigger the cough (modified according to [1]).

2.2. Central regulation of the cough reflex

The cough stimulus reaches the brain stem via the various cough receptors of the Aδ and C fibres of the N. vagus, initially mainly in the nucleus tractus solitarius. Under the influence and modulation of the central pattern generator, an accumulation of inspiratory and expiratory neurons located in the ventrolateral region of the medulla oblongata, cough is induced by reflex via the motor neurons [1-3,6]. In addition to the sensory, motor and cognitive cortical centers, the subcortical regions such as the insula and the anterior cingulum also influence the cough. The influence of these brain areas, e.g. the cerebral cortex, can be seen in the case of arbitrary cough or suppression of the cough [7] and in the

absence of cough during general anesthesia [8,9].

2.3. Extrapulmonary regulation of the cough reflex

Allergic, viral and bacterial rhinosinusitis can cause coughing, although the nose and sinuses have no vagal afferent nerves.

- The classical assumed pathomechanism is mucus running down into the pharynx and larynx (postnasal drip syndrome) with activation of the cough receptors present there.
- The hypothesis preferred today is an activation of trigeminal sensory nerve fibers of the nasal and sinus mucosa, which influence the threshold of the central cough reflex. Trigeminal sensory nerve fibers can both strengthen and relieve the cough [2,10,11]. Nasally applied menthol, eucalyptus and camphor have a calming effect on the ion channels, TRPM8 [12] [13], which may be activated by the transient receptor potential (TRP). The pharynx has vagal and afferent innervation via the glossopharyngeal and trigeminal nerves [14].

Inflammatory processes with mediator release lead not only to an increased neuronal excitability and activation of sensory nerve fibers, but also to their phenotypic changes due to an altered gene expression in the sense of neuronal plasticity.

2.4. The role of TRP ion channels, N-methyl-D-Aspartate (NMDA) and γ-aminobutyric acid (GABA) receptors in cough reflexes

A reduction of the excitability of sensory nerve fibers in patients with chronic cough, an inhibition of the interaction between the cough mediating sensory nerve fibers and neurons at the central level and a modulation of the cough receptors by blocking the TRPV1, TRPA1 and NMDA receptors and/or stimulation of the GABA receptors are potential pharmacological targets for long-awaited new treatment strategies of chronic cough.

The family of Transient Receptor Potential (TRP) ion channels, including TRPV1, TRPV4, TRPA1 and TRPM8, are expressed on cell membranes of nerve fibers and neurons. The activation of the TRPV1 and TRPA1 receptors leads to an increased excitability of the vagal-sensory nerve fibers with the triggering of the cough reflex [15,16]. Antitussive effects of menthol suggest stimulation of the TRPM8 receptors that suppress the cough reflex. N-methyl-D-aspartate (NMDA) receptors are cation channels on the cell membrane of nerve cells activated by glutamate. γ-Aminobutyric acid (GABA) is an important neurotransmitter, and GABA and GABA receptors are widely distributed in the CNS and peripheral nerve system. Some NMDA receptor blockers and GABA agonists such as baclofen have a more effective antitussive effect in animals than in humans [17].

2.5. Cough induced by inflammatory mediators

Inflammatory mediators, such as tachykinins, bradykinin and prostaglandins, which are produced more frequently in mucosal viral or bacterial inflammations, can increase the excitability of the vagal-sensory nerve fibers via various mechanisms. These can also have a direct sensitizing effect on the cough receptors of the respiratory tract, initiate and intensify the cough. Bradykinin activates the TRPV1 receptor, prostaglandin (PGE2) activates Gs protein-coupled prostaglandin E2 receptors (GsPC-PGE2-Rs) and thus initiates an activation of the signaling cascade that eventually leads to phosphorylation of the TRPV1 receptor. Activation of the TRP ion channels leads to increased excitability of the sensory respiratory neurons [15].

2.6. Hypersensitivity of the cough reflex

Increased sensitivity of cough receptors in peripheral afferents in inflammatory processes and/or altered central coughing processes may lead to hypersensitivity of the cough reflex. In central hypersensitivity, neuronal changes, the so-called plasticity of the cough reflex - little is known about the more precise molecular pathophysiology - play a central role. Regarding the hypersensitivity of the cough reflex, the involvement of neuronal TRP channels (transient receptor potential channels TRPV1 and TRPA1) and ATP-triggered P2-purino receptors P2X3 is suspected. An increased expression of TRPV1 in nerve fibers in patients with chronic cough, of TRPV1 and TRPA1 in neurons after viral infection have been demonstrated as well as antitussive effects of the P2X3 receptor antagonists (e.g. MK 7264. Gefapixant). Neuronal changes may occur at different levels of the cough reflex arch: Peripheral afferents, ganglia in the expression of "cough receptors" (TRPV1, TRPV4, TRPA1 and P2X3) up to subcortical and/or cortical structures (opioid receptor, histamine receptor 1, GABA or NMDA receptor) may be involved. However, new pharmacological substances against TRPV1 and TRPA1 other than P2X3 [18,19] do not appear to have any clinically relevant antitussive effects. Results from clinical studies support the assumption of hypersensitivity of the neuronal cough reflex, since all effective antitussive drugs such as opioids, gabapentin, pregabalin, and an antagonist of P2X3 receptor have neuromodulatory properties [20-22]. Today the hypersensitivity of the cough reflex is clinically regarded as the cause of chronic idiopathic or refractory cough. Diseases such as bronchiectasis, reflux, rhinosinusitis, COPD, asthma, eosinophilic bronchitis and pulmonary fibrosis are considered triggers of chronic cough [23]. (Fig.2.2).

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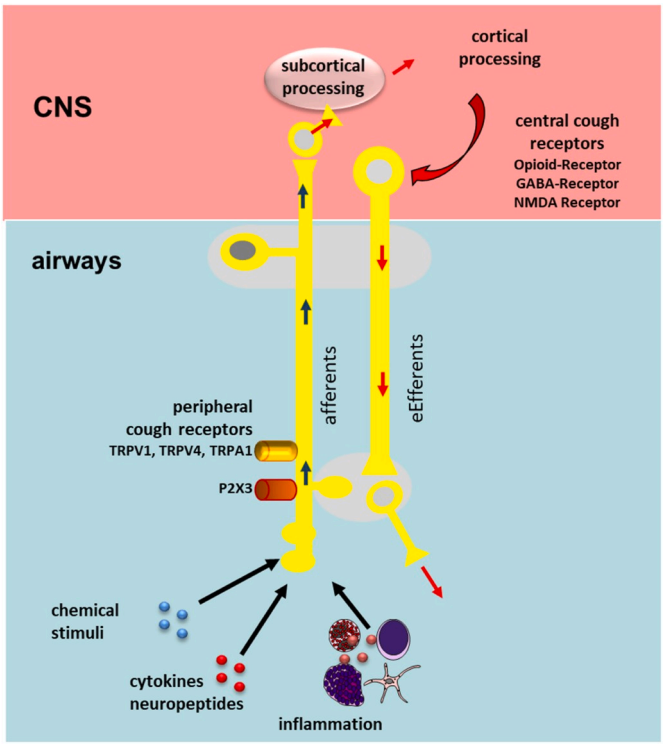

Fig. 2.2. Hypersensitivity of the cough reflex (modified according to [24])
Legend: see text above.

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Chapter 3

Classification and clinical causes of cough

Cough is a very common symptom of various diseases. For the purpose of diagnostic assessment and therapeutic intervention, it is most appropriate to classify the cough according to its duration [1].

3.1. Characteristics of classification

The most common cause of cough is an acute, self-limiting viral disease of the upper and/or lower respiratory tract ("common cold"). The *acute cough lasts up to three weeks*. If the doctor is consulted at all, only the history should be taken, and a physical examination carried out. Each further assessment burdens the health service with unnecessary costs and the patient with potential complications. (see the initiative choosing wisely/"Klug entscheiden"/of the German Society for Internal Medicine [2]).

Chronic cough lasting longer than 8 weeks is the common and sometimes the only symptom of a broad spectrum of diseases with different prognoses and different therapeutic approaches. Therefore, diagnostic clarification of the cause of the chronic cough is of utmost importance.

Considering the need for a detailed diagnostic assessment of chronic cough, *cough lasting three to eight weeks - is classified as subacute cough*, which like acute cough usually does not require any technical examinations. The subacute cough is often the result of a prolonged but still self-limiting infection (e.g. pertussis).

The classification "acute, subacute and chronic" largely corresponds to international guideline recommendations [3] [4] [5]. However, the transitions between categories and causes are continuous.

In about 20% of patients with chronic cough no clear cause or trigger for the cough can be determined (chronic idiopathic cough, CIC).

3.2. Productive and non-productive (irritant, dry) cough

Another characteristic frequently used to classify cough is the distinction into productive and dry (irritant) coughs, although the boundaries between the two categories are fuzzy. Productive cough is defined as a phlegm production of 30 ml (equivalent to two tablespoons) or more in 24 h. Furthermore, it is difficult to estimate the amount of sputum as it is often overestimated by the patient. The subjective differentiation of bronchial secretion from saliva is also challenging. Mucus coating on the bronchial mucosa can trigger cough as a mechanical stimulus in chronic bronchitis, COPD, bronchiectasis or in the early phase of a common cold infection. However, the irritable cough - a consequence of the hypersensitivity of the cough receptors - is often perceived by the patient as "phlegm" [6] [7] [8]. Also, from a therapeutic point of view, the distinction between productive and irritable cough is not important. The effect of secretolytics, mucolytics and mucoactive drugs on cough is not evidence based. Frequently used substances such as ambroxol [9] or N-acetylcysteine have also anti-inflammatory [9] or antioxidant action that may explain some efficacy. Guaifenesin as an "expectorant" acts on the virally induced hypersensitivity of cough receptors in acute bronchitis [10]. However, treatment techniques of the respiratory physiotherapy (see chapter 9.1) may differ in case of productive and non-productive cough.

Characteristics of the sputum.

- mucous: slimy, modified in viscosity and elasticity
- serous - foamy: with high liquid content of the secretion, e.g. in pulmonary edema; occasionally in chronic bronchitis ("bronchorrhoea")
- purulent or putrid (yellow and green): in infections, but also in asthma or eosinophilic bronchitis, bronchiectasis
- bloody (hemoptoe, hemoptysis): In infections, necrosis, tumor, bronchiectasis, coagulation disorder
- bronchial cast: Allergic bronchopulmonary aspergillosis, bronchiectasis, uncontrolled asthma and COPD

3.3. Acute, subacute and chronic cough

The spontaneous course of the acute cough in common cold in adults lasts on average two weeks [11] but can also last longer: Adenoviruses and mycoplasma pneumoniae [12] usually cause cough for six to eight weeks; after infection with B. pertussis [13] the patients cough even longer (see Table 3.1). Postviral rhinosinusitis [14] or infection-induced temporary bronchial hyperreactivity [11] may also cause a longer

Table 3.1
Clinical classification and causes of cough.

Acute (<3 weeks)	Subacute (3-8 weeks)	Chronic (>8 weeks)
Airway diseases: • upper airways: - (viral) common cold - allergic rhinoconjunctivitis • asthma • aspiration: common in children 1-3 y.o. • inhalative intoxication: accident, fire ***Diseases of the lung/ pleura*** • pulmonary embolism • pneumothorax ***Extrapulmonary diseases***: • acute congestive heart failure	***Airway diseases*** • postviral rhinosinusitis • postinfectious cough with temporary bronchial hyperresponsiveness • pertussis, adenovirus- or mycoplasma pneumoniae infection ***Diseases of the lung/ pleura*** • pneumonia • pleuritis	***Airway diseases*** • chronic upper airways' diseaases • chronic bronchitis, COPD • eosinophilic diseases: Asthma, NAEB • tumors of the lung • obstructive sleep apnea syndrome • chronic infections, e.g. tuberculosis • ciffuse parenchymal lung diseases – systemic diseases with lung involvement • inhalative events (Aspiration, RADS) • bronchiectasis, bronchomalacia • cystic fibrosis • rare localized diseases of the tracheobronchial system ***Extrapulmonary diseases*** • gastroesophageal reflux disease • drug-induced cough: e.g. ACE inhibitor • cardiac diseases: - all with lung congestion. • endocarditis ***Chronic refractory/ idiopathic cough***

COPD: chronic obstructive pulmonary disease.
RADS: reactive airways dysfunction syndrome.
ACE angiotensin converting enzyme.
NAEB: non-asthmatic eosinophilic bronchitis.

lasting but spontaneously resolving cough, which is defined as subacute cough (3-8 weeks). It is advisable to wait eight weeks before starting the step-by-step diagnosis of the cough if a typical history of an acute respiratory infection and a suitable physical examination result have been established [15]. If there are special circumstances (Table 3.2) which are not consistent with an acute trivial infection of the respiratory tract, diagnosis should be initiated immediately [1].

The arbitrarily drawn limit of eight weeks for differentiating acute/ subacute from chronic cough marks the obligatory start of detailed diagnostic assessment.

The exact diagnosis of the chronic cough should be established before starting a treatment in order to treat the cause. The diagnosis will always be difficult to make if both the chest X-ray and the lung function findings are none-contributory and the cough is the only symptom. In the English literature such cases are summarized as "chronic cough" or "chronic persistent cough" [16] or "chronic unexplained cough" [17]. In this guideline, we use chronic idiopathic and chronic refractory cough (CIC, CRC) respectively to facilitate diagnostic work-up in clinical practice.

Table 3.2
Red flags in acute cough.

Shortness of breath at rest, cyanosis
Hoarseness
Suspicion of pneumonia
Fever ≥38.5° C
Suspected tbc: residence in countries with high tbc prevalence, tbc contacts, homeless people
Malignancies in the history
Immunodeficiency, HIV infection, immunosuppressive therapy
Extremely heavy smokers >35 pack-years
Acute heart failure
Acute intoxication by inhalative noxious agents

1977 Irwin et al. suggested to search for the cause of a chronic cough alongside the known anatomical locations of the cough receptors [16]. Based on an anatomical-diagnostic protocol, worldwide several studies were conducted in adults (43–329 patients) [18] [19] [15] [20] and children [21,22]. The most common causes of chronic cough, which could neither be explained by a chest x-ray nor by a pulmonary function test, were diseases of the upper respiratory tract, cough variant asthma (without obvious bronchial obstruction) and gastroesophageal reflux disease, sometimes also without classical heartburn. Since corresponding therapies do not always lead to an improvement of the cough [23,24] and on the other hand by far not every patient with rhinosinusitis, reflux disease or asthma suffers from cough a paradigm shift was carried out. In the latest literature, the diseases mentioned are no longer regarded as the cause but as triggers of a pathologically increased cough reflex sensitivity [25,26]. Indeed, the new hypothesis of the cough hypersensitivity syndrome explains why under ACE inhibitors gender-specific differences exist; why by far not all patients with proven reflux or rhinosinusitis do cough. Individual differences in cough frequency in well-known respiratory diseases such as COPD or idiopathic pulmonary fibrosis (IPF) can also be readily explained [27].

Chapter 3 Summary and practical recommendations:

- *Coughing can be elicited by almost all respiratory and some non-respiratory diseases.*
- *Diagnostic and therapeutic procedures differ for acute (usual duration up to three weeks), subacute (three to eight weeks) and chronic cough (over eight weeks).*

Practical recommendations:

- *If there are no alarm signs (e.g. hemoptysis, shortness of breath, thoracic pain, concomitant diseases, high fever, tbc contact etc.), the history and physical examination are usually sufficient for the diagnosis of acute and subacute cough.*
- *In the case of a chronic cough (i.e. already more than 8 weeks lasting), the diagnostic assessment must be initiated immediately with a chest X-ray and a lung function test.*

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Chapter 4

Acute cough

The most important clinical pictures:

4.1. Acute viral infections of the upper respiratory tract: the common cold

They are the most common cause of acute cough. Common cold can affect both the upper and lower respiratory tract, a distinction between a cold and acute bronchitis is hardly possible [1]. In addition to the symptoms of general discomfort, chills, increased temperature, sore throat, runny nose, blocked nasal breathing and sneezing, coughing is the most common disturbing and long-lasting symptom [2]. Adult patients often make their own diagnosis, or it is made by a doctor based on their medical history and physical examination. The acute viral infection of the respiratory tract with cough is a trivial disease that subsides spontaneously on an average after nine [3] (to twelve) days. (An acute, postviral rhinosinusitis can last up to 12 weeks after initial improvement and a biphasic course [4]). With a typical history for a common cold and without clinical evidence of pneumonia or other alarm signals requiring rapid action (Fig. 8.1 Algorithm for the diagnosis of acute cough and Table 3.2) "watch and wait strategy" (up to eight weeks) before initiating the full diagnostic assessment, is advisable because in most cases no further diagnostic measures are required. The possible anatomical localizations of the infection are rhinitis, rhinosinusitis, pharyngitis, laryngitis, bronchitis. The isolated occurrence of acute bronchitis is relatively rare [5]. The most frequent triggers of the common cold are rhinoviruses in 30–50% of cases, also corona-, parainfluenza-, respiratory syncytial-, influenza-, adeno-, entero-, and metapneumoviruses. Isolated acute bacterial bronchitis is most commonly caused by Mycoplasma pneumoniae, Chlamydia pneumoniae and Bordatella pertussis; acute bacterial sinusitis is caused by Streptococcus haemolyticus, Haemophilus influenzae, Streptococcus pneumoniae and *Staphylococcus aureus*. Compared to viral infections, bacterial infections are much less frequently responsible for the acute cough, which has important implications for antibiotic therapy (see Chapter 9).

4.2. Allergic diseases of the upper respiratory tract

Intermittent allergic rhinitis (hay fever), often associated with sinusitis, conjunctivitis, pharyngitis and laryngitis, can also lead to acute cough [6]. The differential diagnosis to the viral infections is based on the current allergen exposure in conjunction with the allergy test results and symptoms deviating from the viral infection i.e. itching of the conjunctiva, nose, pharynx and prolonged sneezing attacks, which are often most prominent. (Non-allergic - non-infectious or persistent allergic rhinitis usually causes chronic cough (see Chapter 6).

4.3. Asthma

The chronic disease asthma is often accompanied by chronic cough, while chronic dry cough as the main symptom masks often the diagnosis "asthma", or sometimes cough variant asthma [7]. But in 29.5% of asthma cases and in 19.6% of cases of cough variant asthma [8] acute cough is the main symptom. Infectious asthma and intermittent allergen exposure are common causes of acute dry cough with and without shortness of breath or wheezing. Asthmatic cough usually responds well to asthma therapy.

4.4. Aspiration

Cough protects against the consequences of aspiration. Aspiration of foreign bodies can lead to acute coughing, especially in 1-3-year-old children and elderly patients with a weak cough reflex, e.g. after stroke, but can also remain undetected for a long time. Foreign bodies of low radiation density are not directly recognizable on the chest X-ray. Indirect signs of an aspiration are one-sided hyperinflation, less frequently a reduction in lung volume or a reduced perfusion. A single aspiration with a retained foreign body or chronic recurrent aspirations can also cause chronic cough. In addition to a chest X-ray, a CT scan of the thorax and a bronchoscopy are helpful for diagnosis.

4.5. Acute inhalative intoxications (accidents at the workplace, fire, sniffing solvents)

They often cause bronchitis with acute cough, conjunctivitis and rhinitis simultaneously. Damage caused by heat and inhalable substances should be distinguished. Consequently, chronic damage can develop RADS (Reactive Airways Dysfunction Syndrome) [9]. Diagnosis is based on history, physical examination, lung function analysis including measurement of CO diffusion capacity and blood gas analysis

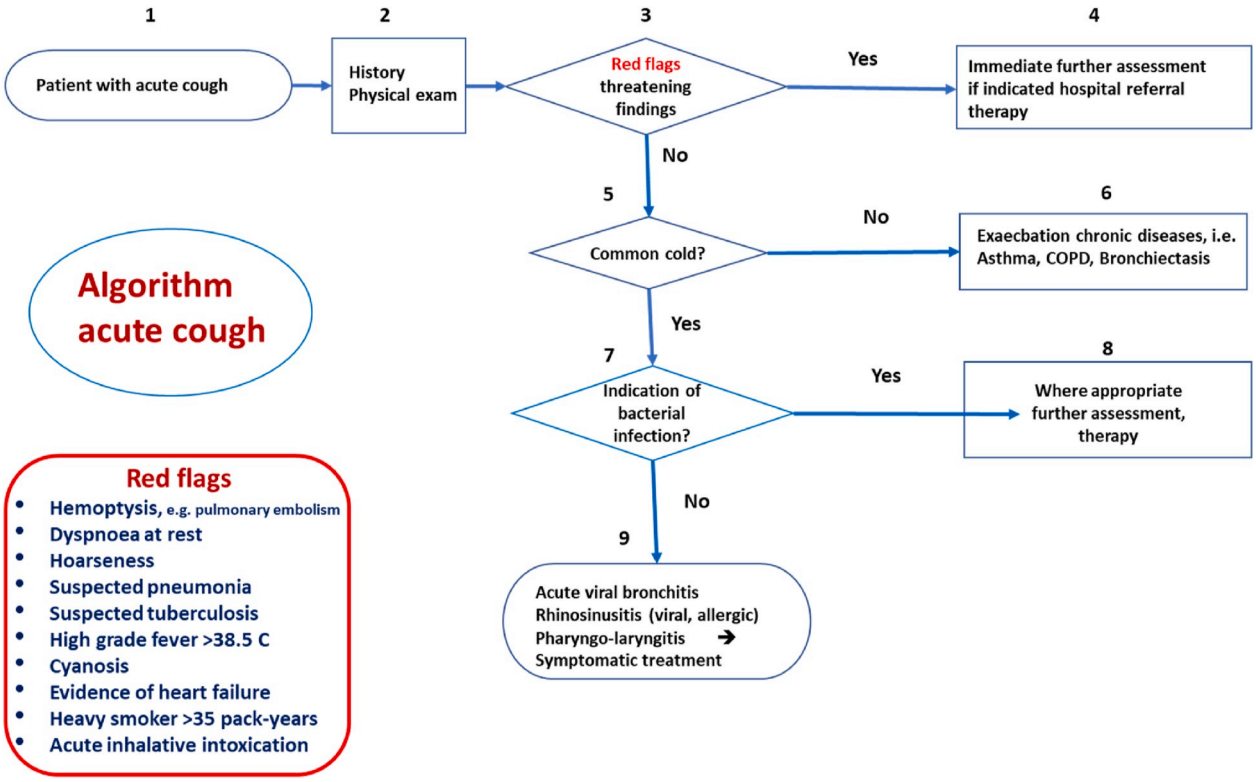

Fig. 8.1. Diagnostic algorithm for acute cough.

at rest and on exertion. Acute inhalative intoxications can also lead to toxic pulmonary edema, acute interstitial pneumonia and bronchiolitis with recurrence of cough after a symptom-free (and cough-free) interval of 6–48 h. Frequently, inpatient observation is necessary, often intensive care treatment. The German poison information centers - Internet address (www.medknowledge.de/patienten/notfaelle/vergiftungszentralen.htm) - can provide information on inhalative noxious agents and treatment options. High dose inhaled corticosteroids are primarily suitable. The anti-inflammatory therapy must be intensified depending on the clinical picture, but especially in case of clinical worsening.

4.6. Pneumonia

Acute cough is a classic symptom of pneumonia. Typical pneumococcal pneumonia may be accompanied by hemoptysis (rust-brown sputum).

On the other hand, a disturbed cough reflex often leads to recurrent pneumonia [10]. Regarding diagnostics and therapy of pneumonia, reference is made to the current guidelines of the Paul Ehrlich Society and the DGP [11]. Nosocomial pneumonia is associated with coughing, too.

4.7. Exacerbation of COPD

Acute cough may occur during exacerbation of chronic bronchitis or COPD. Symptoms of an exacerbation usually include an increase in shortness of breath, cough and sputum production [12]. For diagnostic assessment and therapy, see the current S2k guideline on the management of COPD [13].

4.8. Pleuritis

Acute pleuritis sicca can cause breath-dependent thoracic pain, usually associated with fever, dry cough, pleural friction and increased inflammatory parameters.

4.9. Pulmonary embolism

Acute cough with and without hemoptysis occurs in 7.6% and 22.9% of cases of confirmed pulmonary embolism. However, in suspected pulmonary embolism cough is not a specific symptom [14]. The recommended diagnostic procedure and the treatment algorithm can be found in the S2k guideline of the AWMF https://www.awmf.org/uploads/tx_szleitlinien/065-002l_S2k_VTE_2016-01.pdf.

4.10. Pneumothorax

All forms of pneumothorax can be accompanied by dry coughing.

4.11. Acute cardiac diseases

Acute left heart failure with pulmonary congestion can lead to bronchial hyperreactivity [15], bronchial obstruction (formerly called asthma cardiale) and cough. Bradycardia in high-grade AV block is associated with a reduction in minute volume, consecutive congestion and cough. Coughing itself - presumably via strong vagotonia - can trigger an AV block II or III degree [16]. The total AV block is discussed as a possible pathomechanism of cough syncope [17].

On the other hand, arbitrary coughing at the beginning of cardiac arrest can maintain circulation and consciousness [18].

Chapter 4 (Acute Cough): Summary and practical recommendations:

- The most common cause of acute bronchitis is viral common cold.

Practical recommendations.

- -In otherwise healthy individuals, diagnosis should be based on history and physical examination.
- In patients suffering from common cold, in absence of alarm symptoms, beyond history and physical exam no further diagnostic assessment is required
- In the case of fever >38.5° C, shortness of breath, hemoptysis, suspected pneumonia, heart failure, immunodeficiency, inhalative intoxication, further diagnosis/therapy must be initiated immediately.

- Antibiotics are usually not indicated for acute cough due to common cold.
- Several herbal remedies, dextromethorphan and ambroxol have acceptable randomized controlled trials demonstrating a reduction in duration and/or intensity of cough in acute bronchitis.

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Chapter 5

Subacute cough

Cough of 3–8 weeks duration is considered as subacute cough and it was newly introduced into the classification in the current guideline.

International guidelines [1-3] refer to the grey area of the cough classification: Acute cough is usually the result of a self-limiting, mostly viral infection and was defined as lasting for up to three weeks. However, after an acute infection of the airways not all cases of cough will subside after three weeks. Self-limiting cough lasting three to eight weeks is called subacute. This definition implies that full diagnostic assessment should be initiated only after eight weeks (algorithm Fig. 8.3). In the case of subacute cough - in absence of alarm signals (Fig. 8.2 Algorithm for diagnosing subacute cough and Table 3.2) - it is sufficient to exclude chronic diseases such as COPD that have not yet been diagnosed.

Patients present themselves frequently with postviral subacute cough if an innocuous infection in an otherwise healthy person slowly subsides. Weinberger et al. investigated the most frequent pathogens for a longer-lasting infection [4] in Germany and found according to the frequency of isolates adenovirus, respiratory syncytial virus, Bordetella pertussis and influenza virus. The average duration of cough was six weeks (4-11 weeks). Other pathogens may also play a role [5].

5.1. Pertussis

Pertussis is increasingly being found as the cause of a post-infectious, protracted cough. An acute infection with b. pertussis usually causes an acute febrile disease with an acute and characteristic “pertussiform” long-lasting staccato cough, mainly in (non-vaccinated) children. The protective effect of the vaccination can be lost until adolescence and adulthood [6]. Therefore, appropriate contact provided, even repeated pertussis in adulthood is conceivable. The time of the first disease shifts worldwide in the direction of adulthood. Pertussis should be considered in adult patients who vomit when coughing [7]. Recently, pertussis as a cause of chronic cough in adulthood without a previous acute infection phase has been described more frequently [8]. Mixed respiratory infections also should be considered. The gold standard of the diagnosis, the direct detection of B. pertussis on the agar plate after coughing up, at the time of the initial presentation of adults is rarely successful. PCR from nasopharyngeal swab specimens may be more sensitive. Serological diagnosis is often method-dependent and difficult to interpret (threshold value of positivity, old or fresh infection, increase in titer) [9]. Therefore, pertussis as a cause of subacute (or chronic) cough is often overdiagnosed [10].

Macrolide antibiotics are the therapy of choice. If the acute exudative phase of the infection has subsided (up to ten days), however, they no longer have any effect on coughing and cure. A Cochrane Review found no effective drugs for pertussis [11]. Antitussives can provide relief.

Other subacute cough pathogens.

Adenoviruses, mycoplasma pneumoniae and chlamydia pneumophila can also cause delayed bronchitis with 2–8 weeks of coughing.

5.2. Postviral rhinosinusitis

Regardless of the causative agent, postviral rhinosinusitis with a biphasic course (after initial improvement recurrence after 3-4 weeks) can last up to twelve weeks but subsides without intervention (in particular without antibiotics) [12].

5.3. Postinfectious cough

If the cough persists after an acute infection of the upper/lower respiratory tract for longer than two to three weeks, a post-infectious cough may be present, which usually does not last longer than 8 weeks and is usually self-limiting [13]. Although in one study 97.2% of patients with H1N1 influenza infection complained of acute cough, only 8.5% developed subacute post-infectious cough. A minority of 2.4% of

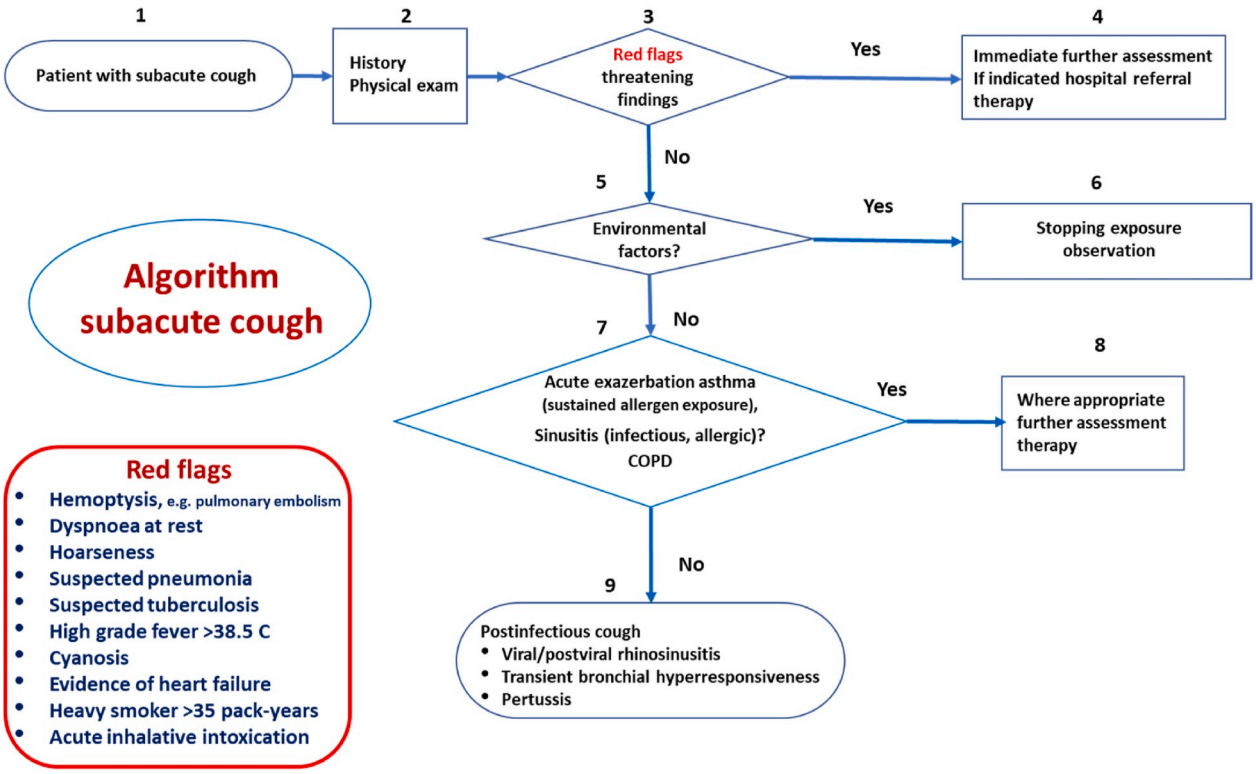

Fig. 8.2. Diagnostic algorithm for subacute cough.

patients developed chronic cough over 8 weeks. The patients who developed postinfectious cough had a higher sensitivity of the cough reflex, but no increased bronchial hyperreactivity [14].

Post-infectious cough is diagnosed by taking a careful history and exclusion of other causes.

The pathomechanism of the postinfectious cough is not clearly clarified. In some cases, it is assumed that epithelial damage of the upper/lower respiratory tract leads to intensive exposition of the "irritant" receptors in the bronchial mucosa, e.g. in infection by B. pertussis. In the case of extensive epithelial damage, the cough can persist even for longer than 8 weeks, as also can in infections with mycoplasma pneumoniae. Persistent inflammation can also cause "postinfectious" cough. Patients with persistent inflammation respond well to inhaled corticosteroids in contrast to those with a pertussis infection with damaged epithelium [15].

Within the framework of a respiratory infection, a temporary increase in bronchial responsiveness can also trigger the cough reflex - independent of the causative pathogen - often with eosinophilia but without the occurrence of other asthma symptoms beyond the cough [16]. This cough responds well to beta-2 sympathomimetics or inhaled corticosteroids (ICS) [17]. Both can shorten the course of the subacute cough. Montelukast, however, had no effect in a study in unselected patients with postinfectious cough from general practice, probably because the bronchial hyperresponsiveness was not tested and therefore not an inclusion criterion [18].

High FeNO (Fraction of exhaled nitric oxide) values are indicators for a good response to ICS. They also serve the differential diagnostic distinction between both the "cough variant asthma" with chronic cough (see chapter 7) and a temporary self-limiting increase in bronchial hyperresponsiveness with subacute cough on the one hand (high values) and postinfectious cough by other causes without bronchial hyperreactivity (lower values) on the other.

Chapter 5 (Subacute Cough): Summary and Practical Recommendations:

- The subacute cough is caused by slowly subsiding viral and postviral sinusitis, infections by Bordetella pertussis or Mycoplasma pneumoniae, or temporary post infectious bronchial hyperresponsiveness.
- If there are no alarm symptoms, a watchful waiting up to eight weeks without further diagnostic assessment is acceptable.
- In subacute cough due to Bordatella pertussis, antibiotics are only effective during the first 10 days of the infection.
- ICS therapy is only effective in the presence of temporally increased bronchial responsiveness caused by infection (usually with increased FeNO values).

Practical recommendation.

- Some herbal remedies, dextromethorphan and ambroxol show positive results in randomized controlled trials in acute cough - can also be prescribed for subacute cough. However, there is no evidence for their efficacy in subacute cough.

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Chapter 6

Chronic cough

Chronic cough affects more women than men, has a negative impact on quality of life and generates a psychological burden. Successful therapy can reverse these negative effects [1]. The duration of the cough and its severity do not allow conclusions to be drawn about the underlying cause or disease.

Even if a cough persists after an acute respiratory infection, this is not equivalent to the persistence of the virus. An initially viral triggered acute bronchitis can increase the sensitivity of the cough reflex and/or the bronchial responsiveness over a period of more than eight weeks or unmask a reflux disease and thus lead to persistent coughing.

Chronic cough can be accompanied by severe attacks triggering a syncope, limiting attention (e.g. in traffic) or it can provoke stress incontinence.

The carefully taken history often provides information for the cause or trigger, e.g. coughing immediately after eating or drinking can indicate a swallowing disorder with aspirations or a reflux disease. Coughing with sputum is mostly due to chronic bronchitis in smokers, or - rarely - chronic dust exposure (e.g. at the workplace, passive smoke exposure). Based on the patient's history, various chronic diseases (see Table 6.1 below) or a combination of several factors can be suspected.

If the sensitivity of the cough reflex is increased and thus the threshold of the stimulus triggering the cough is lowered, a chronic cough can also occur after laughing, talking, singing, at cold temperature, dry air, perfume smell [2]. ACE inhibitors and some other drugs (Table 6.2) also increase the sensitivity of the cough reflex in healthy people [3] and can be the sole cause of the chronic cough. In chronic idiopathic or refractory cough (CIC, CRC) [3,4,5] the cause or trigger remains unknown (Chapter 7)

The most common diseases with chronic cough are described below. Other factors, and rare diseases that can cause chronic cough, are listed in Table 6.3.

Table 6.1
Most common symptoms and clinical signs of upper respiratory tract disease with chronic cough.

Postnasal drip
Compulsory throat clearing
Chronic or intermittent nasal stuffiness
Inspection: cobblestone appearance of the pharyngeal mucosa (=lymphofollicular hyperplasia of Waldeyer's ring),
Globus feeling
Headache/facial pain
Loss of smell and taste
Recurrent hoarseness

6.1. Diseases of the upper respiratory tract

Chronic diseases of the upper respiratory tract can trigger chronic cough in many patients. Since the nose and sinuses do not have vagal sensory innervation, it has been assumed that the cough is caused by postnasal drip. The hypothesis favored today, however, states that the inflammatory mediators released in rhinosinusitis transmit the stimulus via afferent fibers of the trigeminal nerve and sensitize the cough reflex centrally [6]. In pharynx and larynx glossopharyngeal and vagal receptors, respectively are responsible. Diseases of the upper respiratory tract only lead to chronic cough if the cough reflex is hypersensitive [7]. Diseases of the upper respiratory tract are therefore not regarded as a cause but rather as a trigger for cough. In case of a sinubronchial syndrome both the upper airways and a cough variant asthma (paragraph 6.3) are involved. A gastroesophageal reflux disease (paragraph 6.8) can also trigger laryngo-pharyngitis. If multiple causes are present all of them must be treated accordingly to relieve the cough and thus, to

Table 6.2
Drugs which frequently induce cough.

Drugs	Comments
ACE Inhibitors (class effect)	See above
Amiodaron	Can induce alveolitis
Beta-blocker	Can induce cough variant asthma
Methotrexat, Bleomycin, Mitomycin C, Busulfan, Checkpoint Inhibitors	Chemo- and immunotherapies with pulmonary toxicity [93] and infect susceptibility
Gliptine	According to a single case study, [94] no subsequent cases of gliptin induced cough were published
inhalative corticosteroid (ICS) delivered in: -Metered dose aerosol -Dry powder inhaler -Jet nebulizer	After onset of the ICS effect in asthma, the cough caused by inhalation may improve. Some patients respond only to systemic steroid therapy because of the protussive effect of ICS, which also prevents deposition [95].
Other inhalative drugs: β2 - adrenergics, ipratropium, tiotropium, nedocromil, DSCG, pentamidine, secretolytics, zanamivir	Indacaterol induce a short bout of cough just after inhalation
systemically administered secretolytics	
Interferon alpha-2b and alpha-2a	
Fentanyl	iv application at start of general anesthesia [96]
Mycophenolate mofetil	[97]

Table 6.3
Rare diseases causing chronic cough.

•Tumors of the lung and pleura
•Recurrent small pulmonary emboli
•Cardiovascular diseases and other cardiac causes of chronic cough
•Systemic diseases with lung involvement
•Repeated microaspirations
•RADS (reactive airway's dysfunction syndrome)
•Tracheobronchomalacia
•Rare isolated diseases of the tracheobronchial system
•Tracheobronchomegaly (M. Mounier - Kuhn)
•Tracheobronchial amyloidosis
•Relapsing polychondritis
•Tracheobronchopathia osteoplastica
•Juvenile laryngotracheal papillomatosis
•Cystic fibrosis (also in adults)
•Cough in obstructive sleep apnea syndrome

confirm the diagnosis [8].

6.1.1. Chronic diseases of the nose and sinuses. Most frequently, persistent allergic rhinitis, non-allergic chronic rhinosinusitis with or without nasal polyps (e.g. Samter trias with aspirin intolerance), *Staphylococcus aureus* enterotoxin-positive rhinosinusitis, eosinophilic fungal sinusitis trigger chronic cough. Chronic sinusitis is also a frequent trigger of chronic cough in children. The diagnosis of a disease of the upper respiratory tract poses a challenge to general practitioners, pediatricians, specialists in internal medicine or pneumologists, as the appropriate examination techniques are usually not available for them. The following symptoms/clinical signs suggest a disease of the upper respiratory tract that can trigger chronic cough (Table 6.1).

Minutes on diagnostic assessment: In most cases, referral to an ear, nose and throat specialist.

Minutes on therapy: In chronic rhinosinusitis, the focus is on nasal glucocorticosteroids and, if necessary, surgical measures.

6.1.2. Chronic diseases of the pharynx and larynx. Usually pharyngitis sicca and malignancies are associated with chronic cough. Postoperative defect states at the base of the tongue, pharynx and hypopharynx and constrictive processes in the hypopharynx and upper esophagus should also be considered. A rare cause is an acquired esophago-tracheal fistula.

In the laryngeal area, all inflammatory diseases and tumors must be considered for differential diagnosis. Often the laryngitis sicca (laryngitis atrophica) and the laryngitis hyperplastica lead to chronic cough, which is mostly accompanied with changes of the voice (hoarseness, in part aphonia). If polyps of the vocal cord, contact granulomas and ulcers, vocal cord cysts, vallecula cysts and papillomas achieve a certain size they cause chronic irritative cough. Functional voice disorders, especially muscle tension dysphonia [9-11], are also frequent causes of chronic cough.

Recent research attributed some of the above findings to gastro-esophageal or laryngo-pharyngeal reflux (paragraph 6.8) or as a consequence of a chronic rhinosinusitis. [12] [13] [14,15]

In addition, sensory and motor neuropathy of the larynx was also attributed to chronic cough [16] [17].

Tonsillar hyperplasia: Case histories show that hypertrophic tonsils can cause chronic cough that discontinues after tonsillectomy [18,19].

Minutes on diagnostic assessment: Diagnosis is usually made by laryngeal endoscopy, possibly in combination with stroboscopy and electromyography of the larynx.

Minutes on therapy: Depending on the findings, topical corticosteroids, physical measures (inhalations), microsurgical and laser surgical measures and/or speech therapy may be considered.

6.1.3. Chronic ear infections. Irritations of the auricular nerve in the area of the auditory canal (Arnold's nerve, branch of the vagus nerve) can cause cough [20]. Firm cerumen, foreign bodies, manipulations, e.g. with ear canal eczema, tumors, etc. must be evaluated and removed otoscopically.

6.1.4. VCD ("vocal cord dysfunction"), (pseudoasthma). The VCD is characterized by an intermittent inspiratory, possibly also expiratory adduction of the vocal cords. VCD can be the sole cause of (inspiratory) shortness of breath and can be confused with refractory asthma. VCD is accompanied by throat clearing and dry coughing. On the other hand, (arbitrary) cough can trigger VCD in stress and anxiety, as can gastro-esophageal reflux, pharyngitis and laryngitis. Laryngeal sensory and motor hypersensitivity is discussed as a prerequisite for VCD [21,22].

Minutes on therapy: Information, speech therapy, respiratory and behavioral intervention [9,23]. Asthma therapy may be required for comorbid asthma.

6.2. Asthma

Coughing is a cardinal symptom of asthma. Asthma can cause acute cough (Chapter 4) but is often responsible for chronic cough [24]. A persistent dry cough can lead to an acute worsening of the asthma. Chronic cough with bronchial hyperresponsiveness but without other asthma symptoms i.e. bronchial obstruction according to normal lung function and physical exam is discussed in the following chapter 6.3 (Cough variant asthma).

6.3. Cough variant asthma

If patients with a dry cough exhibit non-specific bronchial hyperresponsiveness, the latter may be responsible for the cough [26] [27] [28] [29] [30] [31] [32] [33]. Other cardinal symptoms of asthma, i.e. shortness of breath and wheezing are absent. Therefore, this cough variant asthma (or cough type asthma) cannot be diagnosed by spirometry or body plethysmography according to the characteristic reversible bronchial obstruction. For diagnosis a non-specific inhalative provocation test is required.

Cough variant asthma is the most frequent [28,29] or second most frequent [26,34] cause of cough without further chest x-ray and lung function findings. If bronchial hyperresponsiveness is detected the final diagnosis "cough variant asthma" can be only established if it is confirmed by response to asthma therapy, since asymptomatic bronchial hyperresponsiveness is very common in the general population (25% [35] to 30% [36]). A negative inhalative provocation test with methacholine, on the other hand, is very likely to rule out cough variant asthma as the cause of cough.

If bronchial hyperresponsiveness develops after viral infection cough can persist for years, but usually subsides spontaneously within six weeks (subacute postinfectious cough, chapter 5.3).

Minutes on diagnostics: Refer to the guidelines of the German Airway League and the DGP [25] and http://www.ginasthma.com/respectively. Chronic asthmatic cough usually improves on asthma therapy when asthma control has been achieved. If asthma patients continue to cough despite otherwise good asthma control, they suffer from chronic refractory cough due to hypersensitivity of the cough reflex (provided that other causes of cough have been excluded) (Chapter 7).

Minutes on therapy: Patients with cough variant asthma respond very well to classical asthma therapy, usually to inhaled corticosteroids, but also to β2-agonists or leukotriene antagonists [37]. Some patients develop classical asthma [30,32].

Therapy of refractory asthmatic cough: In addition to the appropriate asthma therapy in otherwise controlled asthma, additional antitussives can be prescribed temporarily for up to 4 weeks, after which an omission attempt is indicated.

6.4. Eosinophilic bronchitis

Eosinophilic bronchitis is diagnosed by sputum eosinophilia (>3%) in spontaneous or induced sputum (or in a bronchial mucosal biopsy), with normal lung function and without bronchial hyperresponsiveness.

FeNO is often elevated. [38,39] In the United Kingdom about 13% of cases of chronic cough are attributed to eosinophilic bronchitis [40]. Eosinophilic bronchitis responds very well to inhaled corticosteroids.

6.5. Chronic bronchitis and COPD

6.5.1. Chronic (non-obstructive) bronchitis. The clinical diagnosis of chronic bronchitis is based on the WHO definition: cough and sputum on most days of the year, that lasts for three months or more per year for at least two consecutive years, if further diseases that may cause cough had been excluded. Chronic bronchitis due to smoking is probably the most common cause of chronic cough. However, patients with chronic bronchitis rarely seek medical advice because they feel the cough is "normal", i.e. it is not a complaint. Therefore, the proportion of smokers - if not excluded a priori [29] - was low in all studies conducted in patients with chronic cough without radiological or lung function-abnormalities [28] [34,41], mostly by 5%.

Diagnostic minutes: If chronic bronchitis is not associated with bronchial obstruction (i.e. not included in the spectrum of COPD, (section 6.5.2), the diagnosis is based only on the exposure history and symptoms. No conventional x-ray or CT findings are to be expected. Therefore, chronic (non-obstructive) bronchitis remains a diagnosis of exclusion. An identifiable cause (smoking, passive smoking [42], strong workplace-related pollution, e.g. underground work) helps to make the diagnosis of chronic bronchitis probable. There is always a risk of overlooking other causes of chronic cough (e.g. bronchial carcinoma, reflux, asthma, tuberculosis) as the symptoms overlap. The cough in chronic bronchitis is caused both by inflammation of the bronchial mucosa [43] and by an increased amount of mucus (hypercrinia) [44], which is a physical stimulus of the cough receptor.

Minutes on therapy: Smoker's cough may worsen immediately after giving up smoking because cigarette smoke (and e-cigarette vapor) reduces the sensitivity of the cough receptors [45]. The cough, however, improves after four to eight weeks under nicotine abstinence [46,47], but in advanced cases it does not disappear completely.

6.5.2. COPD. The term COPD stands for the clinically coincident chronic obstructive bronchitis and emphysema. By definition, chronic bronchitis is associated with cough. COPD can be accompanied by both a productive cough, usually in the morning, and a dry cough (often intensified in the course of exacerbations). The hypercrinia is mainly responsible for the cough in combination with the deterioration of the mucociliary clearance due to inhalative noxae (in Germany mostly smoking). COPD patients with the phenotype of pronounced cough and sputum production (chronic obstructive bronchitis) have a worse quality of life [48] suffer more frequently from exacerbations, have worse lung function compared to COPD patients without cough complaint [49,50].

Diagnostics and therapy: Refer to the current guidelines of the German Airway League and the DGP [51].

6.6. Bronchiectasis

Bronchiectasis comprises of irreversibly dilated bronchi with inflammatory wall thickening. The dilatation can be cylindrical, varicose or cystic. It usually produces cough with voluminous sputum (at least >30 ml, corresponding to two full tablespoons in 24 h), often mucopurulent or purulent. A predominantly dry irritable cough may also occur. Bronchiectasis is a frequent cause of hemoptysis. Usually, during an exacerbation intensive productive cough occurs.

Diagnostic assessment. The diagnosis is made by a multislice CT examination with 1 mm reconstructions. Bronchiectasis may remain undetected on the chest X-ray. Newly diagnosed bronchiectasis patients should be routinely examined at least for common variable immunodeficiency (CVID), allergic bronchopulmonary aspergillosis (ABPA), non-tuberculous mycobacteria (NTM), tuberculosis, inflammatory bowel disease (IBD) and pulmonary fibrosis.

Minutes on therapy: Refer to the new European Bronchiectasis Guideline [52]. Patients benefit from both physiotherapy (Chapter 9.1) while learning mucus clearence techniques and from rehabilitation. Pharmacotherapy also target the elimination of phlegm (chapter 9.2.1). Individual patients are eligible for surgical resection (if the bronchiectasis is limited to a few segments).

The antibiotic therapy of acute exacerbation should, if possible, be targeted by current antibiotic resistance testing, have a standard duration of approximately 14 days, i.e. longer than the recommended antibiotic therapy of pneumonia or COPD exacerbation. For patients with frequent exacerbations (≥3 exacerbations per year) different antibiotic long-term therapy regimes are available.

In case of colonization with Hemophilus influenzae, *Staphylococcus aureus*, antibiotic treatment is only recommended for exacerbations [52]. In contrast, patients with newly detected *Pseudomonas aeruginosa* colonization should have a targeted antibiotic therapy with the aim of eradication.

Antitussives are contraindicated in productive cough due to bronchiectasis, except for bronchiectasis sicca with severe dry cough, in this case the temporary prescription (e.g. 14 days) of an antitussive is acceptable.

6.7. Diffuse parenchymal lung diseases (DPLD)

Clinical symptoms of interstitial pneumonias (ILD) including idiopathic pulmonary fibrosis (IPF) comprise chronic cough and dyspnea on exertion. On physical examination "velcro" rales are an early finding. The incidence increases with age (6th - 7th decade of life) [53]. Many factors (dust exposure, allergens, infections, medication, autoimmune diseases) can induce interstitial lung disease both in children [54] and in adults [55]. Sometimes the trigger remains idiopathic. A successful, disease-specific therapy is often, but not always, recognizable by the reduction of cough symptoms [53]. In the case of refractory cough in the context of an ILD, a recently published metanalysis did not find any specific drug treatment; symptomatic therapy measures were recommended (Chapter 9) [56]. Furthermore, there was no evidence for the efficacy of the previously recommended ICS (inhaled corticosteroid) therapy in sarcoidosis [56].

Diagnostic assessment: The most important diagnostic step is the multislice CT thorax scan with 1 mm reconstructions. in children and adolescents in the case of chronic cough (>3 months) and/or sputum production and/or wheezing and/or clubbing, cystic fibrosis (CF) should be considered.

Therapy of cough in diffuse parenchymal lung diseases includes causal treatment of the DPLD if possible and symptomatic pharmacological (secretolytics, antibiotics) and non-pharmacological (respiratory physiotherapy) measures.

6.8. Gastroesophageal reflux (GER)

Gastroesophageal reflux was previously considered as one of the frequent causes of chronic cough. However, the pharmacological treatment of GER - although highly effective against the typical reflux symptoms i.e. heartburn and regurgitation - remains only weakly – if at all - effective against the cough associated with reflux. Today, reflux is regarded as one out of many trigger factors for chronic cough, which only occurs with reflux if the sensitivity of the cough reflex is pathologically increased. Therefore, only a small proportion of reflux patients suffer from cough.

J. Smith et al. [57] investigated cough-reflux associations in patients with chronic cough with objective registration of both cough (acoustic cough monitor) and reflux (impedance pH-probe). They found that patients with reflux cough suffered from hypersensitivity of the cough reflex. They generally coughed more than comparable patients but did not have necessarily an above-average number of reflux episodes or acid exposure time in the esophagus. These results were confirmed in a recent multicenter study [58]. On the other hand, when cough-induced

transesophageal pressure fluctuations trigger reflux, the reflux barrier (the lower esophageal sphincter) is damaged, acid exposure is prolonged, but the characteristics of the cough do not change.

The prevalence of gastroesophageal reflux disease is particularly high in western industrial countries. In a German general practice 51% of a non-selected population had reflux symptoms [59]. In the industrialized countries, a prevalence of 20–40% is expected [60]. Both the prevalence of cough in reflux patients and the prevalence of reflux in patients with chronic cough is higher if compared with normal populations [61].

The limits between physiological and pathological reflux are vague. The definition of gastroesophageal reflux disease requires pathological reflux time as well as reflux symptoms that impair the patient's quality of life. Cough is defined as an extraesophageal symptom of reflux disease [62].

Two mechanisms are discussed for cough caused by reflux: [63]

a. Reflex theory: The cough is triggered by a gastroesophageal reflux into the distal esophagus irritating esophageal cough receptors.
b. Aspiration theory: The pathological gastroesophageal reflux leads to microaspiration. Regurgitation of fluid and stomach contents in the proximal esophagus and further into the pharynx leads to irritation of cough receptors in the upper respiratory tract and/or leads to fluid aspiration in the lower respiratory tract causing cough.

Diagnostic assessment:

- To assess the patients reflux – cough history in a structured way a German Version of the Hull Cough Hypersensitivity Questionnaire containing specific questions for cough-reflux associations.is available under http://www.issc.info/HullCoughHypersensitivityQuestionnaire.html
- In epidemiological studies and clinical practice, gastroesophageal reflux disease is defined by typical reflux symptoms heartburn and regurgitation. This procedure is neither specific nor sensitive for reflux disease if confirmed by impedance pH-probe [64]. The clinical diagnosis of reflux cough due to reflux symptoms is even more difficult because reflux cough can occur without heartburn [65] [66]. On the other hand, most gastroesophageal reflux patients do not suffer from chronic cough.
- Therefore, an ex juvantibus diagnosis of reflux-related cough with a proton pump inhibitor (PPI) therapy with or without motility drugs is not recommended [61], unless there is an indication for PPI therapy anyway due to typical reflux symptoms [62]. PPI can also reduce the total volume of reflux of pepsin-containing stomach contents, but coughing is unlikely to respond to PPI. Also, alkaline (slightly acidic) reflux can be responsible for the cough.
- Gastroduodenoscopy only provides a possible positive result about gastroesophageal reflux related cough if esophagitis was seen. Hence, the negative predictive value is low [67,68]. In addition, esophagitis may have causes other than reflux. Pathological reflux can also occur without esophagitis. Therefore, evidence of reflux esophagitis on endoscopy is not adequate to ensure causality between reflux and cough.
- 24 h multichannel intraluminal impedance measurement (MII) with pH-probe (impedance pH-probe):

If no other cause for the cough was found at the end of the diagnostic algorithm of chronic cough (Fig. 8.3), after endoscopy and esophagus motility measurement impedance pH probe should be done. A causality of the cough with confirmed reflux can be assumed if there is a high symptom association probability (SAP) of >95% with cough episodes [69]. However, not all patients performing pH-probe are able to fully record their cough episodes by manual signal input at the device [70,71]. The lower the number of reflux episodes, the more likely an overinterpretation of an apparently high SAP [72].

- The pharyngeal pH measurement with a short and therefore less invasive oropharyngeally placed probe allows the assessment of aerosolized (gaseous) acid from the esophagus with rapid response to changes in acidity. Normal values were established [73]. Laryngopharyngeal reflux (LPR) with or without typical reflux symptoms is considered responsible for laryngeal hypersensitivity. Symptoms of laryngeal hypersensitivity are non-specific such as hoarseness, functional dysphonia, vocal cord dysfunction, globus sensation, coughing and throat clearing. Vocal cord polyps, laryngeal carcinoma, posterior laryngitis might be also associated with laryngeal hypersensitivity. The classical examination methods (inspection, laryngoscopy IIP) have poor sensitivity and specificity in the diagnosis of LPR. Therefore, pharyngeal pH probe is promising. A study in patients with both typical and extraesophageal reflux symptoms shows that oropharyngeal pH probe provides additional information to classical IIP and may be helpful in deciding on surgical treatment of reflux [14]. However, only a few patients with chronic cough were tested [69], a correlation of cough with pharyngeal pH metrics was not demonstrated. The role of pharyngeal pH-probe in cough diagnostics is not yet established.

Therapy.

1. Pharmaceutical therapy: A 2016 meta-analysis of the available therapy studies for the reflux cough by the Chest Guideline Panel [61] showed that in the 14 identified randomized placebo-controlled studies the drug treatment of the reflux cough (predominantly with PPI) showed no significant effect compared to placebo. The negative result could be due to the inclusion criteria of these trials. They were purely symptomatic (heartburn and regurgitation) and thus many patients with hypersensitive esophagus without reflux or with weakly acid reflux may have been included [63]. Therefore, possible positive results were masked by a "dilution" of a potentially suitable population. In addition, there is a strong placebo effect. In this meta-analysis. The best effect on cough was achieved by lifestyle changes and weight loss diets. Raising the head end of the bed is also recommended in the American guidelines. If there are also typical reflux symptoms (i.e. heartburn, regurgitation, retrosternal pain), PPI's, H2 antagonists, alginates and antacids are recommended.

In the presence of both, a typical reflux symptomatology and chronic cough, drug therapy should be initiated. In contrast to the typical reflux symptoms with rapid response, it takes up to three months to improve the cough under PPI therapy. In most cases, long-term therapy with high doses may be necessary [74]. After one year, a let-out trial is recommended. If the cough recurs, the therapy should be reintroduced, and after detailed gastroenterological diagnostic assessment (see below) the possibility of surgical options should be examined.

For exclusively extraesophageal reflux symptoms, such as cough, PPI therapy is only recommended after detailed reflux assessment (questionnaires, endoscopy, manometry and impedance pH measurement), if the results provide a verifiable indication of reflux-related cough with high reflux-cough symptom association probability (95%). In cases with positive diagnostic assessment but refractory cough, additional medication for motility, i.e. metoclopramide, baclofen, domperidone can be considered. However, neither is approved for this indication; black box warning must be also considered. A further therapeutic principle is azithromycin: long-term therapy reduces the duration of the refluxate in the esophagus, but it is not approved for this indication (off label treatment). Both the empirical therapy of motility and the azithromycin therapy may have important side effects.

2. Surgical therapy:

In patients with chronic cough and reflux there are several studies from the last 15 years on antireflux surgery (laparoscopic fundoplicatio) [75-82]. Unfortunately, these studies often have a low number of cases, are retrospective in nature with the known weaknesses of retrospective

trials. The patient's selection is often problematic due to unclear definitions, the follow-up time is relatively short. Therefore, the conclusions from these studies are limited, as are for endoscopical antireflux procedures, e.g. the Stretta radiofrequency energy treatment of the lower esophagus sphincter or the LINX® magnetic device.

The indication for a surgical therapy to eliminate the cough should only be made after flawless detection of the pathological reflux by impedance-pH-probe and/or three-channel-pH-probe including pharyngeal derivation in order to justify the operation. A strong correlation between detected reflux episodes and cough episodes (SAP > 95%) should have been demonstrated.

The current guidelines of the various professional societies point to a judicious examination of the indication for surgery [61] [83]. Symptoms alone are not a reliable parameter for ensuring reflux triggered cough and they must be combined with objective examination methods [84]. A comprehensive preoperative diagnosis is required, especially if extra-esophageal symptoms (i.e. cough) prevail and different examination results contradict each other [83] [84].

The results of laparoscopic antireflux surgery in patients with chronic reflux and classical symptoms (i.e. heartburn and regurgitation) were promising in some studies. [79] [80] [81] [85] [86,87] [88].

In well selected patients with extraesophageal symptomatology (cough) the corresponding study results show good postoperative results if simultaneous detection of chronic reflux, cough and other criteria are fulfilled [85-88]. It is important to follow the established indication criteria (see above, and in the guidelines [83] for laparoscopic antireflux surgery).

There is currently no evidence that laparoscopic antireflux surgery should be performed for cough in the absence of pathological acid reflux, defective sphincter, hiatal hernia, typical reflux symptoms and effective PPI therapy. The more of these criteria are met, the more is surgery justified. (Most of the criteria should be met). The sole detection of non-acidic fluid regurgitation with cough in the history but without further criteria (i.e. SAP >95% etc.) is not a valid indication for surgery. Close interdisciplinary cooperation is therefore particularly important, as antireflux surgery for "reflux cough" is an individual decision. In patients with proven gastroesophageal reflux disease in the classical sense and chronic cough, adequate preoperative PPI therapy is justified. A preoperative PPI therapy time of at least 6–12 months applied to classic reflux patients should also be adhered in patients with reflux-cough to before surgery is performed. If the criteria are met - laparoscopic antireflux surgery can be considered.

There are only a few studies on antireflux surgery for non-acidic reflux [89,90]. The same arguments as described above apply here. Especially in these cases, a strong cough-reflux correlation (SAP) should be demonstrated.

6.9. Drugs induced cough

ACE ("Angiotensin converting enzyme") inhibitors are the most common cause of chronic cough. They block the degradation of bradykinin and substance P as well as prostaglandins in the bronchial mucosa. This increases the sensitivity of the cough reflex in healthy individuals and patients [3]. About 10% of all women and 5% of men complain from cough under ACE inhibitors. The dry cough can appear already a few days or many months after beginning the ACE - inhibitor therapy and disappears within 4–21 days after its discontinuation. It is a class effect of all ACE inhibitors [91]. If a patient with ACE inhibitor coughs chronically [92], the therapy should be discontinued or changed without further diagnostic assessment. If the chronic cough does not stop at the latest three weeks after discontinuation, full diagnostic assessment should be initiated.

Other drugs can also trigger cough (Table 6.2). The same procedure therefore applies to them as to ACE inhibitors.

6.10. Tuberculosis

Germany is a low prevalence country for tuberculosis. Tuberculosis in Germany is almost exclusively restricted to risk groups (TB contact persons, immunosuppressed including HIV patients, patients born in countries with high prevalence, drug addicts, homeless or geriatric patients). Thus, in Germany, chronic cough is seldom due to tuberculosis. Even in countries with high prevalence of tuberculosis, it is not a common cause of chronic cough [98]. Nevertheless, in at-risk patients it is very important to consider tuberculosis as a possible cause of chronic cough, as the cough promotes the spread of tuberculosis bacteria. Patients at risk who cough should be explicitly examined for tuberculosis infection. (see alarm signals when coughing, Chapter 4).

Diagnostic assessment: The mandatory chest X-ray for the initial diagnosis of both the chronic cough and in the case of presence of an alarm signal for acute cough, will provide the first indication of suspicion of tuberculosis. Regarding further diagnostics, refer to the ERS standards [99].

6.11. Somatic cough - syndrome (formerly psychogenic or habitual cough) and cough tic

According to recommendations of psychiatrists, the term psychogenic cough should be replaced by the term somatic cough syndrome, i.e. psychologic distress is transferred ("somatization") as a physical symptom, cough. A somatic cough syndrome is present if the cough considerably affects the life of the patient, he or she attaches excessive importance to the cough, is anxious and deals with the cough disproportionately. The 2014 established American Chest Expert Panel for the renewal of the 2006 Cough Guideline [100] found no validated definition of psychogenic (habit) cough [101] and suggested replacing the term with somatic cough syndrome, too.

Tic is a repetitive involuntary motor or vocalization phenomenon in children (e.g. blinking, clearing of the throat, coughing, screaming). Tic cough can occur in children in isolation, or as part of Tourette syndrome.

Diagnosis of somatic cough syndrome: If no cause for chronic cough is found after exhaustion of the diagnostic algorithm (Fig. 8.3), a chronic idiopathic or refractory cough (CIC) must be distinguished from somatic cough syndrome. Neither characteristics of the cough (barking, honking, nightly etc.) nor the diagnosis of depression and/or anxiety disorder are helpful, since chronic annoying cough of any cause can lead per se to depression. A psychiatric co-evaluation may be necessary.

Therapy: Psychiatric interventions.

6.12. Chronic cough: associated conditions

Several case reports are available showing conditions, which may be associated with cough. (see Table 6.4)

Chapter 6 (Chronic Cough): Summary and Practical Recommendations

- Chronic (smoker's) bronchitis is an exclusion diagnosis. Other causes of chronic cough must be excluded before making the diagnosis

Table 6.4
Conditions associated with (chronic) cough.

Urinary incontinence (in women) (102)
Hoarseness
Pungent thorax pain
Triggering of asthma attacks in patients with bronchial asthma
Conjunctival ecchymosis
Epistaxis
Gastroesophageal reflux
Petechial hemorrhage
Rib fracture (103,104)
Mediastinal emphysema (104)
Cough Syncope (105)
Seizure initiated by cough
Headaches
Inguinal herniation
Rupture of the rectus abdomini muscle

"chronic bronchitis". For non-smokers, the diagnosis should only be made if exposure to harmful substances (e.g. at the workplace) is present.

- The most common diseases that present with chronic, at least eight weeks lasting cough can be best assessed by a chest X-ray and a pulmonary function test, which should always be carried out during the initial examination of these patients. Diagnostic results may include COPD, asthma, lung tumors, tuberculosis, aspiration, parenchymal lung diseases and others.
- Before initiating further diagnostic assessment, an ACE inhibitor therapy should always be terminated or replaced, and the patient observed whether the cough wanes.
- If x-ray and pulmonary function assessments are not indicative, chronic cough triggered by upper airway's disease, gastroesophageal reflux and cough variant asthma should be considered.
- Further diagnostic procedures should consider rare diseases of the tracheobronchial system (including bronchiectasis), drugs that can cause cough, heart disease with pulmonary congestion, pertussis, tuberculosis and early stages of a diffuse lung parenchymal disease.
- Further diagnostic assessment usually includes multislice computed tomography of the chest including 1 mm reconstructions; and bronchoscopy if necessary.
- If the chronic cough in patients with reflux, asthma or sinusitis does not respond to the appropriate therapy, a chronic refractory cough (CRC) is present. Middle-aged women are often affected. The increased sensitivity of the cough reflex explains, why these patients are coughing.
- In some patients with chronic cough there is no cause and no obvious trigger. These patients suffer from chronic idiopathic cough (CIC).

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Chapter 7

7.1. Cough as a disease on his own: chronic idiopathic cough (CIC) and chronic refractory cough (CRC)

In clinical trials performed in patients with chronic cough in 0%–46% the cause of the cough remained unclear [1], regardless of accomplishing all diagnostic measures. Older guidelines, including the precursor of this guideline [2], have attributed the cough without evident (chest x-ray and lung function) cause essentially to one of the following diseases:

- Cough as a result of upper respiratory tract disease (rhinosinusitis, pharyngo-laryngitis), also called upper airway cough syndrome
- Asthma with bronchial hyperreactivity, but without apparent obstruction (“cough variant asthma")
- Gastroesophageal reflux with or without reflux esophagitis or reflux disease with typical (intraesophageal) symptoms
- Taking ACE inhibitors (rarely also other drugs)

This causal assignment rather than an association presumes however, that the patient responds to the appropriate therapy. For example, the response of presumably reflux triggered cough, was tested in a meta-analysis of randomized controlled trials [3]. The reflux treatment (in most studies proton pump inhibitors, PPI) was not more effective than placebo. However, the diagnosis of reflux in these studies was based only on history of heartburn and/or regurgitation without objective tests (endoscopy, impedance pH-probe, manometry, see chapter 6.8). The sensitivity and specificity of “heartburn” for pH-probe detected pathological reflux is low [4].

Due to response to targeted therapy in some patients a causal assignment rather than an association of cough to reflux, asthma, diseases of the upper airways or the intake of ACE inhibitors is possible. However, even this assignment does not answer the question of why only a small proportion of patients with reflux, asthma, sinusitis suffers from chronic cough [5]. An attractive hypothesis for the explanation is that the peripheral and/or central sensitivity of the cough reflex (see chapters 2 and 3) is increased in these patients. Then, cough is already triggered by low-threshold thermal, chemical or mechanical stimuli. For example, these patients do cough due to physiological reflux episodes or slight air pollution. In the capsaicin provocation test for hypersensitive

cough reflex, coughing will be triggered by inhalation of a concentration as low as 1 - 10 μmol/ml, whereas normal persons tolerate a concentration of up to 500 μmol/ml.

Patients with high sensitivity of the cough reflex frequently report coughing if exposed to low concentrations of smoke, cold air, dry air, perfume smell or telephoning and prolonged speaking (i.e. as a teacher) [6].

Most respiratory and some non-respiratory conditions - when accompanied by cough - temporarily or chronically increase the sensitivity of the cough reflex. It can subside spontaneously after 14 days in the event of a common cold, after discontinuation of ACE inhibitor medication, or when asthma control has been reached, upper respiratory tract inflammation has subsided, or reflux has normalized.

Cough with permanently increased cough reflex sensitivity is called chronic refractory or chronic idiopathic cough (CRC, CIC).

7.2. Chronic refractory cough (CRC)

If targeted therapy improves the underlying condition (upper airway's disease, asthma, gastroesophageal reflux disease with heartburn and regurgitation) but the cough persists, it called *chronic refractory cough*. Multiple trigger chronic refractory cough - based on two or more conditions (e.g. chronic sinusitis and reflux) - can persist despite all conditions were diagnosed and treated accordingly.

7.3. Chronic idiopathic cough (CIC)

If no trigger was found despite completing the diagnostic algorithm for chronic cough (Fig. 8.3), these patients suffer from CIC due to an idiopathic increase in the sensitivity of the cough reflex. The ERS cough guidelines use only the term chronic refractory cough and do not differentiate between chronic refractory and idiopathic cough. This distinction is only possible after careful diagnostic workup and exclusion of all potential triggers.

Most patients with CRC and CIC are women (with onset of the chough around menopause) – with a ratio women: men 2:1. Often, patients report a common cold occurred years ago as the starting point of their complaints. Compared to patients with an established cause of chronic cough who respond to appropriate therapy, the duration of symptoms in CIC patients is significantly longer, the fraction of exhaled nitric oxide (FeNO) lower and capsaicin sensitivity higher [7]. Histologically, one study found a basement membrane thickening but no increased mucus production or inflammation [8] (Table 7.1).

The CIC and CRC caused by afferent hypersensitivity of the cough reflex can be considered as neuropathy of the cough reflex, comparable to the neuropathy of the pain reflex [9,10]. Neuropathy can be caused by inflammation, infection or allergy. Afferences from the upper respiratory tract, especially from the larynx, are often affected [11].

Minutes on diagnostics: CIC is an exclusion diagnosis. The diagnostic algorithm "Chronic cough" (Fig. 8.3) should be processed before the diagnosis CIC is made. In the case of CRC, a therapeutic trial, corresponding to the diagnoses received (e.g. reflux) which remains ineffective should also have been carried out. Increased sensitivity of the cough reflex in CIC and CRC is an entirely clinical diagnosis. Testing e.g. with capsaicin or citric acid is reserved for scientific investigations. [12]

Minutes on therapy: Only symptomatic therapy can be considered. In some patients, low-dose retarded morphine or the inhalation of local anesthetics, both as an off-label treatment, can help. (Chapter 9). Also, off-label treatment with gabapentin, pregabalin or amitriptyline can be successful [13-15]. Experienced speech therapists may achieve cough relief with their treatment methods [16,17]. Several drugs are under development in Phase 3 trials, such as P2X3 receptor blockers. (see Chapter 2).

Table 7.1
Chronic idiopathic or refractory cough).

Characteristic	Clinical findings	Comments
Age	>40 years	Women after menopause
Ratio of women to men	2:1	Non-smoker
Duration of complaints	Several years at presentation	
Symptoms	Dry irritative cough Sensation of phlegm Larnygo-pharyngeal symptoms	No expectoration Throat clearing, Globus Urge to cough
Temporal assignment of symptoms	Typically coughing during daytime	If caught a cold also during night
Lung function	normal	Bronchial hyperresponsiveness possible No response of cough to asthma treatments
Heartburn	no	(or <2 times/week)
Nasal breathing	free	
Cough triggers [6]	- temperature change (from cold to hot) - telephoning, longer speaking - Laughing - perfume smell - food intake - laying down	common inhalative stimuli e.g. dust, smoke, vapors can also trigger cough

Chapter 7 CIC and CRC: Summary and Practical Recommendations

- If chest X-ray and lung function assessment are not indicative, cough triggering by upper airway's disease, gastroesophageal reflux, or cough variant asthma should be considered. Before performing further diagnosis, any therapy with an ACE inhibitor must be stopped or replaced and after three weeks the patient re-assessed.
- The cause for the CIC and the CRC is an increase in the sensitivity of the cough reflex, thus even week stimuli elicit cough.

Practical recommendations

1 With the exception of patients who take an ACE inhibitor (which should be replaced), at the first presentation of the patient with chronic cough a chest x-ray and a lung function test should be performed
2. if these tests are not diagnostic, cough triggered by asthma (cough variant asthma), eosinophilic bronchitis or upper airway's affection and gastroesophageal reflux should be considered and appropriate diagnostic assessment (chapter 8) may be performed.
3. the sequence of the assessment should be carried out according to the algorithm chronic cough (Fig. 8.3).
4. bronchoscopy is recommended for each patient with an ultimately unexplained cough

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Chapter 8

Diagnostic assessment of cough

Cough is a common symptom of a variety of diseases with different diagnostic assessment needs and therapies. This chapter will discuss the general principles of step-by-step diagnosis, which are summarized in flow charts. Additional existing diagnostic measures are listed for individual clinical presentations. The purpose of the step-by-step diagnosis is rapid and rational elucidation of the cause, if possible and initiation of an adequate therapy.

A classification into acute, subacute and chronic cough (definitions see chapter 4) can be made in a first step of assessment based on the duration of cough, a characteristic which can be easily determined by history. However, a clear distinction between acute and subacute or chronic cough is not always feasible.

Accordingly, 3 diagnostic algorithms were developed for acute (Fig. 8.1.), subacute (Fig. 8.2.) and chronic (Fig. 8.3.) cough. The algorithms based mainly on expert opinion, there is only a low level of evidence [1].

The algorithms serve for assessing systematically the underlying causes of the cough. If, a priori a history-based diagnosis can be suspected, a deviation from the algorithm may be useful. However, frequent and often costly errors occur in diagnostic assessment if there is no reason to deviate from the sequence of diagnostic measures specified in the algorithms.

If after applying the algorithm a diagnosis with some certainty could be established, we recommend an appropriate therapeutic trial. In these cases, the success of the therapy can contribute to the final diagnosis. If the therapy attempt is unsuccessful, verifying possible errors in diagnosis and therapy, the patient's adherence and the continuation of the assessment on the next step of the algorithm, frequently a second therapeutic trial is necessary. These algorithms can also be applied to immunosuppressed outpatients [2].

8.1. Acute cough

If at examination in the patient's history there is evidence for alarm signals (as given in Fig. 8.1), immediate further assessment, - often in an emergency or inpatient setting -is necessary.

The most frequent causes of acute cough are primarily viral respiratory infections, followed by exacerbations in asthma and COPD and pneumonia. The cough as a result of an acute viral infection can persist for up to 8 weeks (called then as subacute cough) or longer (chronic cough). Even after the infection has subsided bronchial hyperreactivity or inflammatory changes of the bronchial mucosa may persist.

The diagnosis acute cough by viral infection requires usually the patient's history including the occupational anamnesis and possible environmental pollution [3], inhalative intoxications as well as a physical examination to exclude other causes such as pneumonia, or acute left heart failure.

In otherwise healthy patients with acute cough a chest X-ray, laboratory examinations including microbiological and serological examinations are usually not necessary.

A yellow/green colored sputum indicates a possible bacterial infection. In most cases, however, differentiation between a viral and a bacterial infection based on clinical characteristics is not certain. An acute respiratory infection in an otherwise healthy patient is not an indication for antibiotic therapy, even in the case of a suspected bacterial infection [4] [5].

Only patients with purulent (yellowish-green) colored sputum and a chronic primary disease (COPD, coronary heart disease, diabetes mellitus, renal failure, immunodeficiency, malignancies etc.) and/or at an advanced age may benefit from antibiotic therapy. Symptoms lasting longer than two weeks with increased inflammatory biomarkers and yellow or green sputum may also indicate a secondary bacterial infection which could benefit from antibiotics.

Validated questionnaires can be used to estimate cough intensity [6]. In acute cough due to upper respiratory infection, objective cough frequency as measured by the Leicester Cough Monitor could be correlated with a visual analogue scale and the Leicester Questionnaire for Acute Cough [7]. Currently, such measurement techniques appear unnecessary for the routine management of acute cough in everyday clinical practice.

8.2. Subacute cough

The subacute cough diagnostic algorithm (Fig. 8.2) is the appropriate diagnostic tool for patients who cough for 3-8 weeks. At the consultation, the alarm signals for a threatening situation, similar those for acute cough, must be excluded [1]. The main causes of subacute cough are post-infectious cough and exacerbations of asthma, COPD or upper airways cough syndrome with rhinosinusitis, pharyngitis and laryngitis. After initial assessment by history and physical exam, a follow-up after 4-6 weeks is recommended to ensure that the cough has subsided.

8.3. Chronic cough

The diagnosis of chronic cough should be carried out according to the algorithm shown in Fig. 8.3. A chest X-ray often provides clues to further diagnostic assessment (e.g. for pneumonia, diffuse parenchymal lung diseases). If, due to history and physical examination, there is indication for cardiac or neurological cause of the cough, further specialist neurologic or cardiologic assessment must be initiated (e.g. Holter monitoring, see Box 3 Fig. 8.3).

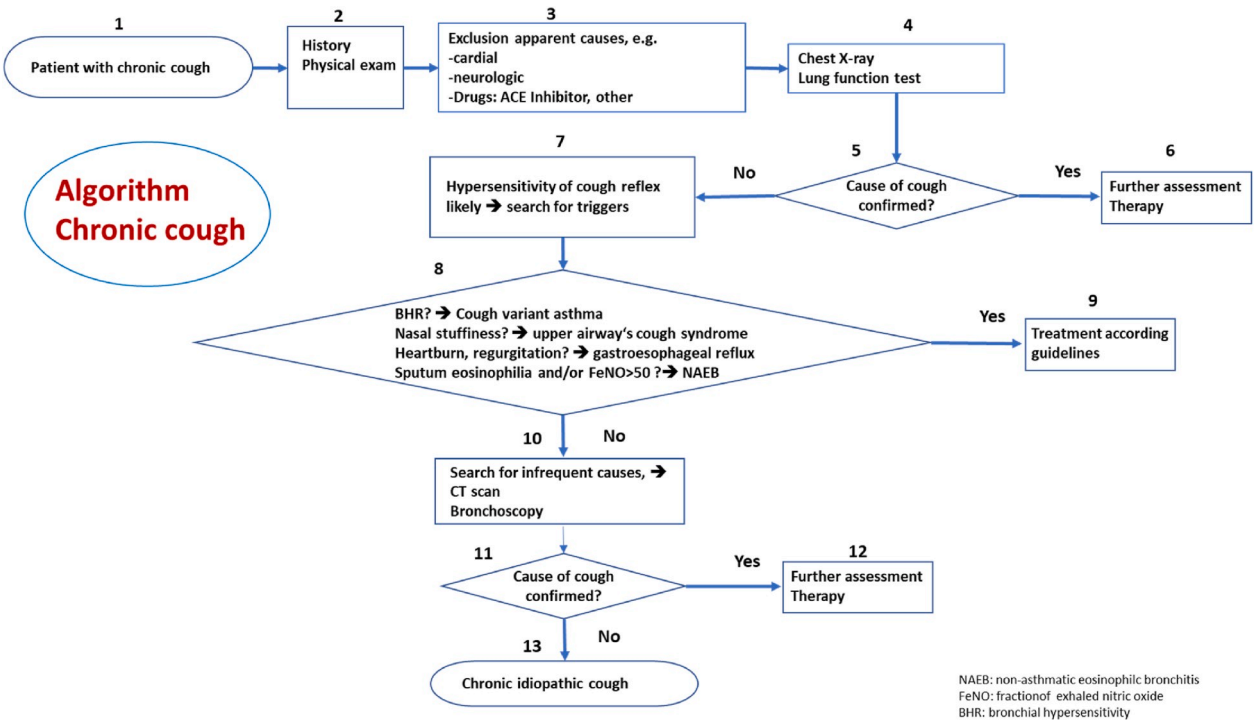

Fig. 8.3. Diagnostic algorithm for chronic cough.

After completing the algorithm patients with chronic cough of ultimately unexplained cause should undergo bronchoscopy.

- If the clinical picture is otherwise inconspicuous, prior to further diagnostic assessment cough-fostering drugs such as ACE inhibitors should be discontinued for 3 weeks and re-assessment thereafter is recommended.
- After a chest X-ray was performed patients with symptoms of rhinosinusitis should be evaluated by otolaryngological examination. For the diagnosis of rhinosinusitis, a nasal endoscopy should be performed, in individual cases supplemented by computer tomography or digital volume tomography. The diagnosis of pharyngitis or laryngitis includes a pharyngo-laryngoscopy, which in individual cases should be supplemented by a videostroboscopic examination.
- Cough can occur in the context of gastroesophageal reflux disease with symptoms such as heartburn and regurgitation. The latter should be adequately treated e.g. with proton pump inhibitors and lifestyle changes. A trial therapy of a gastroesophageal reflux disease with exclusively extraesophageal symptoms (cough without regurgitation and/or heartburn) with proton pump inhibitors should not be performed [8]. If the cause of the cough is unclear and reflux-triggered cough is suspected, a targeted, detailed gastroenterological assessment (endoscopy, impedance pH measurement, esophageal manometry (see Chapter 6.8 Chronic cough) should be performed before reflux therapy is initiated.
- Patients with clinical or radiological signs of pulmonary congestion, cardiac arrhythmia, conspicuous heart murmurs must be subjected to specialist cardiological assessment in addition to a chest X-ray.
- Patients with neurological disorders (e.g. bulbar speech, paresis, Parkinson's symptoms) can cough as a result of recurrent aspirations and should be examined neurologically in addition to a chest X-ray.
- For the diagnosis of suspected bronchiectasis as the cause of chronic cough, multislice computed tomography of the thorax should be used (no contrast enhancement necessary) with 1 mm reconstructions.

The lung function test enables the differentiation of cough caused by diseases that are associated with a restrictive or obstructive ventilation pattern. The most common are asthma and COPD. Eosinophilic bronchitis without bronchial hyperreactivity as the cause of cough cannot be diagnosed by lung function analysis. Eosinophilia in the sputum is indicative (but available only in scientific settings). An increased FeNO level and negative lung function test may be of diagnostic value.

In the case of a restrictive ventilation pattern, diseases of the rib cage or neuromuscular diseases should be considered. If CO transfer is additionally restricted, diffuse lung parenchymal disease may be considered.

If neither X-ray nor lung function findings are indicative, non-specific bronchial hyperreactivity, e.g. by methacholine provocation can be considered for cough variant asthma and treated with ICS (Fig. 8.3 Box 8). Increased FeNO values support this diagnosis.

In smokers and patients with chronic cough who are exposed to noxious substances, the cause may be chronic bronchitis as defined by the WHO. It should be noted that smokers complain less frequently of chronic cough than non-smokers [9]. However, smoking is the most likely cause of cough in smokers with a non-diagnostic chest X-ray and normal lung function. Therefore, after stopping smoking, reassessment of the patient should be performed after four to eight weeks before further diagnostic steps are recommended. If there is no improvement within, further diagnostic assessment according to the algorithm is indicated (Fig. 8.3).

In the case of persistent cough after completing the algorithm (including the above mentioned detailed gastroenterological assessment), one should consider the following:

- An early diffuse interstitial lung disease with increased markings only on HR-CT
- A CIC or CRC (chronic idiopathic cough or chronic refractory cough) due to hypersensitivity of the cough reflex, especially in women (Fig. 8.3 Box 13),
- The rarely occurring somatic cough syndrome or
- Errors in diagnosis and/or therapy.

Frequent errors include inadequate diagnostic assessment of disorders in the upper respiratory tract, incomplete reflux assessment,

overlooking left heart failure, refraining from bronchial provocation with metacholine or bronchoscopy. In addition, lack of treatment for the frequently multiple diseases underlying the cough or too short duration of the assigned treatment (rhinitis, nasal polyps) can be the cause of diagnostic or therapeutic failure.

8.4. Outpatient and inpatient diagnostic assessment

As a rule, all listed diagnostic tests can be performed in outpatient setting. The need for inpatient examination depends on the condition of the patient (e.g. emergency situations), co-morbidities and the disease underlying the cough. Especially with the alarm signals mentioned in Figs. 8.1 and 8.2, a quick clarification under inpatient conditions often makes sense.

8.5. Side effects and complications of diagnostic assessment of the cough

In general, the examination methods used in the diagnosis of cough are at low-risk. In non-specific inhalative provocation a severe obstruction can occur, in 24h-pH-probe nausea, vomiting and aspiration, in bronchoscopy in rare cases hypoxia, bleeding, infection or pneumothorax, the latter only after a transbronchial biopsy.

The greatest risk of diagnosis lies in overlooking serious diseases such as pulmonary embolism, lung carcinoma and tuberculosis. The step-by-step diagnosis recommended in the guideline enables the timely (not too early and not too late) use of invasive examination methods and thus optimizes the risk/benefit ratio. Adherence to the algorithms also contributes to cost reduction.

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Chapter 9

Symptomatic therapy of cough

Before initiating therapy for (chronic) cough, the cause of the cough shall be first determined in order to be able to treat it causally. The merely symptomatic therapy of a chronic cough that has not been diagnosed is a common error that occurs frequently in practice during the treatment of cough. Serious diseases, e.g. COPD, pulmonary fibrosis, lung tumors, can thus be overlooked.

After diagnosis, causal therapy should be carried out in accordance with the relevant guidelines.

In addition to the causal treatment of the underlying disease, a temporary symptomatic therapy of the cough with antitussives and/or mucoactive drugs may also be indicated for:

- Chronic idiopathic cough (CIC), chronic refractory cough (CRC) (Chapter 7)
- Self-limiting infections of the upper and/or lower respiratory tract (i. e. common cold) to relieve and shorten the duration of the cough (chapters 4 and 5).
- If causal therapy does not effectively relieve the cough (e.g. pulmonary fibrosis, pulmonary tumors)
- In palliative medicine
- the effect of causal therapy is delayed (tuberculosis, Chapter 6).

9.1. Physiotherapy

Physiotherapy is applicable for both unproductive and productive cough with and without use of special devices.

The available evidence usually refers rather to the secret elimination than to the cough itself. However, in two Cochrane analyses an unambiguous evidence for individual techniques of protussive physiotherapy and their effects on cough could not be shown [1,2]. Despite lacking or weak evidence, addition of physiotherapy to standard treatment for expectoration is recommended in otherwise evidence-based guidelines [5] for many lung diseases (e.g. cystic fibrosis, COPD [3] or bronchiectasis [4]) and in patients with neuromuscular diseases.

For an individual case, after learning the suitable physiotherapy techniques by the physiotherapist, the affected patient himself must it apply daily to relieve the cough.

From a therapeutic point of view, a distinction must be made:

- Physiotherapy for productive cough to promote cough clearence
- Physiotherapy for dry cough to relieve cough
- Physiotherapy with PEP (positive endexpiratory pressure) devices, vibration vest; Cough Assist for weak or absent cough reflex

A detailed overview of physiotherapeutic measures for cough can be found in [5,6] and http://www.atemwegsliga.de/download/empfehlungen_physiotherapeutischen_atemtherapie.pdf.)

9.2. Pharmacotherapy for cough

Cough relief is based on two principles:

- protussive (promotes coughing and expectoration) or
- antitussive (cough suppressant)

Which of the principles should be applied depends on the underlying disease:

- Protussive therapy:

The elimination of secretions relieves the irritation of the cough receptors.

Fostering the expectoration is the central principle in the therapy of all diseases with hypersecretion, e.g. chronic hypersecretory bronchitis, COPD with grade 3 and 4 obstruction and retention of viscous mucus, [3], CF and non-CF bronchiectasis [4]. In these cases, antitussives are only indicated for exceptional cases, e.g. at night for cough attenuation in combination with expectorants during the day [7].

- Antitussive therapy:

The overwhelming majority of patients who consult a doctor due to

cough suffer from an unproductive "irritable cough" (e.g. in asthma or lung parenchymal diseases) or from coughing with small amounts of secretion (in acute respiratory infections). If there is no (e.g. common cold, acute viral bronchitis) or no fast onset causal therapy avalaible, temporary cough suppressants can be prescribed. A simplified classification of cough suppressants focuses on their site of action, but the distinction is fuzzy (Table 9.1)

9.2.1. Protussive (mucoactive) therapy)

9.2.1.1. Chemically defined expectorants mucolytic and mucoactive drugs. By increasing the secret volume (expectorants) and reducing the viscosity (mucolytics) and mucoactive drugs hypothetically facilitating the bronchial clearence, to remove viscous mucus and inhaled foreign particles. Consequently, the irritation of the cough receptors is diminished. In Germany these drugs are frequently used in acute viral bronchitis, although there is little evidence of hypersecretion [8]. In preclinical studies, most mucoactive drugs show further properties (anti-inflammatory, antioxidative, local anesthetic, antiviral) which could be responsible for their efficacy. The substances most commonly used in Germany are ambroxol and N-acetylcysteine, in English-speaking countries guaifenesine and potassium iodide. The increase in fluid intake in normal hydration state does not lead to an increase in secret volume [9].

Concerning the efficacy of synthetic mucoactive drugs on cough in acute bronchitis, there are only two methodologically acceptable randomized placebo-controlled studies:

- one for a diphenhydramine, ammonium chloride and levomenthol-containing cough syrup from the United Kingdom [10] and
- another for ambroxol [11].

Many patients report a favorable subjective effect on cough relief by self-medication, for example with ambroxol in acute bronchitis [12], although reviews show unclear evidence [13,14].

9.2.1.2. Herbal medicine. Herbal remedies contain several potential active ingredients extracted from plants. The active ingredient content and thus the effect depends on many factors, including the origin of the plants used, the extraction method, standardization and manufacturing process. Therefore, different extracts, for example from ivy, are not interchangeable. Results of research with herbal remedies do not apply to the investigated plant(s) but only to the tested formulation. Herbal remedies have complex ingredients and effects (e.g. anti-inflammatory, antitussive, antiviral in addition to mucolytic and expectorant). Many herbal remedies with these effects have been tested in preclinical studies. Moreover, there are several herbal remedies with proven efficacy in randomized controlled trials in common cold patients showing a reduction of the duration and relieving the intensity of acute cough if compared to placebo. These include a formulation of ivy [15], cineol [16], myrtol [11,17], pelargonium sidoides [18,19], the combination formulations ivy and thyme [20] as well as primroses and thyme [21]. Thus, the current evidence for the above herbal remedies for the indication acute bronchitis and common cold is better than for synthetic mucoactive drugs.

For other, centrally acting herbal remedies containing alkaloids from the poppy plant (papaver somniferum) or from the Chinese herb ephedra sinica, Ma huang), there are no methodically acceptable controlled trials, although they are in regular use not only in the Chinese medicine, in India (Ayurveda medicine) or Japan but also in western countries.

Table 9.1
Classification of cough therapeutics according to their site of action.

Antitussives with predominant effect on the cough receptor
Antitussives with predominant effect on the reflex arch
Centrally acting antitussives
Antitussives acting on effector organ (muscle relaxants)

Table 9.2
Herbal mucoactive extracts.

Herbal pharmacon	Plant (examples)	Side effects
Essential oils: as *capsule tablet, lotion, bath additive, tea infusion, inhalation*	Anise Eucalyptus Myrtle Peppermint Plantain Thyme	Hypersensitivity Rash Gastrointestinal complaints Many contain alcohol
Saponine	e.g. ivy leaves	
Glycoside	Primerose root	

Note: In the case of active herbal ingredients, there is not always a clear separation of the mode of action as an antitussive or mucoactive drug. Thus, plantain is listed under different trade names as both an antitussive and mucoactive, probably because of the claimed clinical effect depends on the type of extraction.

Tables 9.2 and 9.3 list the most common herbal and synthetic mucoactive drugs.

Many herbal supplements contain combinations of herbal drugs.

9.2.1.3. Drugs to increase mucociliary clearence. Mucoactive drugs, theophylline [22] and β2 – adrenergic drugs [23] increase in vitro the mucociliary clearence. They could have a cough-relieving effect in patients with bronchial obstruction, but not in non-obstructive patients [24].

9.2.2. Antitussive therapy

9.2.2.1. Drugs to reduce mucus production.

- Inhalative anticholinergics (ipratropium, aclidinium, glycopyrrhonium, umeclidinium, tiotropium) reduce the often pathologically increased secret production (due to inflammation), they also affect the efferent part of the reflex arc, an additional effect by reducing bronchial muscle tone and relieving the slowly adapting receptors has to be assumed. Inhalative anticholinergics are not approved for merely antitussive indication.

Table 9.3
Synthetic (chemically defined) mucoactive drugs.

Active substance	Side effects
Bromhexin	Nausea, Type IVc hypersensitivity
Ambroxol	Nausea, Type IVc hypersensitivity
N-Acetylcystein	Nausea, vomiting, Type IVc Hypersensitivity
Guaifenesin	Nausea, rash
Dornase alfa (only for cystic fibrosis)	Hoarseness, bronchospasm
Potassium iodide	Hyperthyroidism
isotonic or hypertonic (3-7%) Saline for inhalation Emser Salt (potassium chloride)	Bronchospasm

- Nasal ipratropium in high doses (up to 360 μg/die), not approved in Germany, relieves the cough caused by vasomotor rhinitis.
- The first generation H1 antihistamines with anticholinergic effect (chlorpheniramine, recommended in the US guideline [25]) and triprolidine in Germany, commercially available as combination preparation with pseudoephedrine only. They also have a central antitussive effect [26].

9.2.2.2. Drugs to reduce the irritation of the cough receptors in the pharynx. Demulcents work by "encasing" the cough receptors in the throat. Antitussive syrups, cough juices, gargle solutions, lozenges, honey, cough sweets contain as the common ingredient sugar syrup or other mucus. The duration of action is limited to the length of stay of the sugar at the receptor, usually to 20–30 min. Antitussive drugs in the formulation of syrup or as lozenges are therefore more effective and have a faster onset of action than capsules or tablets [8]. Table 9.4 lists a small selection of herbal cough syrups. Additionally, many other herbal remedies (see 9.2.1.2) in liquid formulation ("German: Saft") contain high sugar concentrations.

9.2.2.3. Mucosal decongestants. Mucosal swelling (hyperemia, edema) can irritate cough receptors in the upper airway. Decongestant substances such as topical or systemic α-adrenergics - possibly in combination with H1 anticholinergic antihistamines [27] - have a decongestant effect and thus, relieve upper airway's cough (rhinitis, sinusitis, pharyngitis). In Germany, pseudoephedrine is available only in combination with antihistamine: the H1 antihistamine triprolidine or H2 class cetirizine. The patient should be aware of the sedative side effect (ability to drive!) of the antihistamine and the adrenergic side effects of pseudoephedrine.

9.2.2.4. Antibiotics.

- The antibiotic therapy of rare acute bacterial infections of the upper and lower respiratory tract is a causal treatment of the cough caused by the production of bacterial inflammatory mediators and secretions.
- Acute bronchitis, which occurs in isolation or in the context of common cold is a primarily viral infection. In otherwise healthy individuals in most cases, antibiotic therapy is not indicated [28]. A Cochrane review [29] showed an advantage of antibiotic therapy in terms of a faster improvement of the cough of only 0.46 days compared to placebo. This minimal advantage is largely outweighed by individual and societal (e.g. promoting bacterial resistance) side effects.

9.2.2.5. Anti-inflammatory substances. Inhaled corticosteroids act on the cough only in eosinophilic bronchitis and in allergic and non-allergic asthma (including cough variant asthma). Nasal corticosteroids help with rhinosinusitis.

9.2.2.6. Cough therapeutics with predominant effect on the reflex arch (local anesthetics). Local anesthetics block the electrophysiological activity of receptors and afferent nerve fibers and thus act as potent antitussives. The use of local anesthetics in bronchoscopy is daily routine [30]. They can be used off label silencing uncontrollable cough [31-33]. They have a short duration of action (up to 30 min), and there is no suitable form of inhalative application; except their use with a jet nebulizer. As an off-label therapy, 2-4 ml 2% prilocaine, xylocaine or lidocaine can be nebulized 2-3x daily. The nebulizer should have a large droplet spectrum for central deposition in pharynx, larynx and large bronchi. Nebulized local anesthetics can be used in palliative care, too [34]. The most important side effect is aspiration after inhalation; food and drinks should be withheld for 2 h.

Local anesthetics in lozenges and gargle solutions work in the pharynx and could miss the intended antitussive effect if the cough is originated by irritation of receptors in the larynx or deeper.

9.2.2.7. Predominantly central-active antitussives.

- Opiates

Opiates exert their main effect by binding to the opioid – receptors in the cough center in the brain stem. Dextrometorphan has an additional peripheral mechanism of action. For antitussive therapy they are available in oral, but not parenteral formulation only. Codeine and dihydrocodeine represent the gold standard of antitussive action. However, they are metabolized to morphine at an unpredictable rate. Morphine is therefore better and safer, but it is not approved as an antitussive. Also, depression of breathing and addictive effects and constipation must be considered if opiates are prescribed. With productive coughing, opiates are relatively contraindicated. In common cold and in the postinfectious cough, codeine in standard doses up to 120 mg is no more effective than placebo [35]. However, placebo has a strong antitussive effect if compared to "non-treatment" which is attributed to central cough regulation on endogenous opioids [36].

Table 9.5 shows synthetic opiates.

- Non-opiate synthetic and herbal cough inhibitors with central and peripheral effects: Some synthetic and herbal drugs without addictive potency claim a central antitussive effect. Their efficacy, however, was not shown in methodologically acceptable clinical trials. Table 9.6 lists these antitussives.

The references [8, 37] give a contemporary overview of the - sometimes contradictory - results regarding the clinical efficacy of these antitussives.

9.2.2.8. Cough therapeutics with effect on the effector organ (muscle relaxants). Antitussive therapeutic trials of the central muscle relaxant baclofen are only available from one working group [38.39]. Baclofen is effective in low doses of 3 × 10 mg/die., several side effects are to be considered. Baclofen is not approved for this indication (off label).

Chapter 9 summary

- *A causal therapy of the cough if possible is always preferable –.*
- *The symptomatic pharmacotherapy of cough comprises either a protussive (mucoactive agents) or an antitussive (prototype: opiate) therapeutic intention.*
- *Currently, symptomatic treatment of cough is very limited both in terms of the evidence base and its efficacy or side effects.*
- *Physiotherapy is applicable to both chronic productive but ineffective and dry irritant cough. Personal respiratory physiotherapy devices are also frequently used. In the outpatient sector, patients can learn appropriate therapy measures under the guidance of the respiratory physiotherapist*

Practical recommendations:

Table 9.4
Herbal Cough syrups.

Herbal pharmacon	Side effects, contraindication
Plantain	Hypersensitivity
Icelandic moss	Gastrointestinal complaints
Jebian root	Alcohol content
Sugar in syrups and candies	Diabetes

Table 9.5
Synthetic opiates.

Active substance	Side effects
Morphinsulfat up to 2 × 10 mg/die (for cough, doses as low as 2 × 5 mg/die may be effective).	Addiction, respiratory depression, constipation, sedation. Not approved for antitussive therapy
Codeine (In the body metabolized to morphine). Dihydrocodeine	Addiction, depression of breathing, constipation, nausea
Dextromethorphan	Constipation, nausea, less addictive potency
Noscapin	Headache, nausea, but little addictive potency

Table 9.6
Non-opioid herbal and synthetic antitussives.

Active substance	Side effects
Thyme	Hypersensitivity
Ivy	Gastrointestinal complaints
Primrose	contains alcohol
Eucalyptus	
Plantain	
Drosera	
Wool flowers	
Pentoxyverin	Constipation, nausea, fatigue
Levodropropizin	Urticaria, rash, gastrointestinal complaints
Benproperin	Drowsiness, nausea, dry mouth.

1. If physiotherapy is considered for a chronically productive ineffective cough, it should be performed by physiotherapists specializing in this therapy. The patient should learn the exercises under supervision and perform them regularly at home. If prescribing physiotherapy availability and adherence must be considered.
2. Under supervision of a specialized therapist physiotherapy can help patients with therapy-resistant chronic irritant cough.
3. In some cases expectorants can lead to subjective improvement in cough.
4. Opiates are the gold standard of antitussive therapy, but for the indication of cough in common cold no more effective than placebo.
5. The acute cough in common cold is of predominantly viral origin. It is the domain of self-medication.
6. In common cold/acute bronchitis certain herbal remedies have proven evidence from randomized controlled trials for relieving cough intensity and reducing cough duration against placebo.
7. Antibiotic therapy is indicated only in few exceptional cases (in elderly and comorbid patients).

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Chapter 10

Future research directions

In Germany many patients with chronic cough will be referred from primary to secondary respiratory care. However, for complex cases of (chronic) cough multidisciplinary cooperation with ear-nose-throat (ENT), gastroenterology and other specialists with experience in cough is essential but specialist cough clinics are lacking. Establishing an appropriate infrastructure is urgently needed.

Now chronic (refractory or idiopathic) cough is recognized as a disease entity and not only a symptom of many respiratory and non-respiratory diseases. Yet, only an ICD code for the symptom cough exists. Recently, the German Respiratory Society applied for a respiratory disease ICD code for chronic cough. This would allow to perform epidemiological research for desperately needed data on prevalence, incidence and natural history. Moreover, clinical trials with upcoming new medications for the disease chronic cough and the symptom cough (in different respiratory diseases) are needed for safe and effective use of these new medications according to different phenotypes of chronic cough and symptomatic cough.

Development, validation and cost effectiveness evaluation of the minimum necessary diagnostic procedure to ensure the diagnosis “chronic refractory or idiopathic cough” should be implemented.

Patient related outcome tools for outpatient care must be developed.

Declaration of competing interestCOI

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: PK received honoraria for presentations from following pharmaceutical companies (producers of herbal drugs for acute cough): Bionorica Engelhard, Klosterfrau and Schwabe. Moreover, he also received honoraria for advisory board meetings and presentations from Bayer and MSD.All other authors declare they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

This Guideline was founded by the German Respiratory Society. Travel meeting costs were reimbursed, no honoraria were paid except to the consensus managing methodologist (HS).