Guidelines of the German Respiratory Society for Diagnosis and Treatment of Adults Suffering from Acute or Chronic Cough

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Abstract

The first set of German guidelines for diagnosis and treatment of patients suffering from acute or chronic cough was published in 2004. Scientific developments over the past five years necessitate an update.
The purpose of this document is to assist in ascertaining underlying causes and treating cough, in order to eliminate or minimize impairments of patients' health.
The guidelines aim to introduce scientifically founded, evidence-based steps for the diagnosis and treatment of cough and optimize cost-effectiveness. Recommendations are assessed through the GRADE system (The **G**rades of **R**ecommendation, **A**ssessment, **D**evelopment and **E**valuation).
Cough as a symptom is categorized as either acute (lasting up to 8 weeks) or chronic (lasting more than 8 weeks) and attributed to distinct diseases. For acute and chronic cough the diagnostic algorithms are updated; cost effectiveness is also taken into account. Additionally, the most frequent diagnostic errors are highlighted. Finally, available therapeutic options are discussed.

Introduction

The first set of German guidelines for diagnosis and treatment of patients suffering from acute or chronic cough was published in 2004. [1]. Scientific developments over the past five years necessitate an update.
The guidelines evaluate and establish required diagnostic and therapeutic measures. The purpose of this document is to assist in ascertaining underlying causes and treating cough, in order to eliminate or minimize impairments of patients' health.
The guidelines aim to introduce scientifically founded, evidence-based steps for diagnosis and treatment of cough and optimize cost-effectiveness. Recommendations are assessed through the GRADE system (The **G**rades of **R**ecommendation, **A**ssessment, **D**evelopment and **E**valuation) [2].
Nevertheless, each patient is entitled to individual diagnosis and treatment. A specific case can justify divergence from these guidelines.

Anatomy and physiology of cough

Cough is both an important physiological reflex protecting the airways, and a frequent complaint associated with virtually all pulmonary and several extra-pulmonary diseases. Cough is also a contributing factor in the spreading of infectious disease.
The reflex is triggered by physical and chemical stimuli. Irritant receptors and C-fibre receptors are activated in the airways, pleura, pericardium and esophagus. The impulse is then transmitted to the brainstem cough generator circuit via the vagus nerves. There is also a connection to the cortex, allowing voluntary control of both eliciting and - to a limited degree - inhibiting cough [3]. Thus, the reflex is characterized by complexity and plasticity. Diagnostic findings from animal testing are not unconditionally applicable to humans. Efferent innervations reach the effector muscles (diaphragm, abdominal, intercostals, back; as well as muscles of the larynx, and the upper airway) via the vagus.

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Mucociliary clearance is the primary means of clearing the bronchial system. Cough acts as a secondary mechanism when the primary is either impaired (e.g. by the effects of smoking) or overwhelmed (e.g. by aspiration). The clearing competence of the cough reflex depends on several conditions: obstruction of the airways, bronchial collapsibility, lung volumes, respiratory muscle- and laryngeal function, as well as the amount and viscosity of the mucus [4].

Cough is productive (wet) if the amount of the daily expectoration is at least 30 ml (two tablespoons worth). The phlegm can be mucous, serous, purulent or bloody. Bronchial casts can also be coughed up.

The cough reflex arc consists of five parts:

1. Cough receptors
2. Afferent nerves of the reflex arc
3. Brainstem cough generator circuit
4. Efferent nerves of the reflex arc
5. Effector organs (muscles).

Common causes and classification of cough

Table 1 Classification of clinical causes of cough.

Acute (< 8 weeks)	Chronic (> 8 weeks)
Diseases of the Airways:	*Diseases of the lower Airways/Lungs*:
– Infectious disease of the upper airways: mostly viral infection	– Chronic (non-obstructive) bronchitis, COPD
– Allergy	– Asthma and other eosinophile diseases
– Asthma	– Lung tumors
– Aspiration: commonly children between the ages of 1 – 3	– Infectious diseases
– Inhalation intoxication: accidents, fire	– Diffuse parenchymatous lung diseases (DPLD) – Systemic diseases with diffuse lung involvement
– Postinfectious cough	– Aspiration, RADS
Diseases of the Lungs/Pleura:	– Bronchiectasis, Bronchomalacia
– Pneumonia	– Rare, localized disease of the tracheobronchial tree
– Pleurisy	– Cystic fibrosis
– Pulmonary embolism	*Diseases of the upper Airways*
– Pneumothorax	*Gastroesophageal Reflux disease*
Extra Pulmonary Causes:	*Drug induced cough:*
– Cardiac disease with acute pulmonary congestion	– ACE inhibitors
	– others
	Cardiac Diseases:
	– Any including pulmonary congestion
	– Endocarditis

COPD: Chronic Obstructive Pulmonary Disease
RADS: Reactive Airways Dysfunction Syndrome
ACE: Angiotensin Converting Enzyme

Acute and chronic cough

Diagnosis and treatment of cough depend on whether the patient presents with acute (usual length up to three weeks, possible up to eight weeks) or chronic (more than eight weeks) cough. The natural history of an acute infection of the upper and/or lower airways – the most common cause of cough – is up to three (rarely up to eight) weeks. Medical history and physical examination are usually sufficient in the diagnosis of acute cough.

Recommendation: R1

- **Diagnostic tests for acute cough due to common cold:**
  History and physical examination only
- **Grade:** strong ⇧⇧
- **Evidence:** none

Special circumstances requiring immediate full diagnosis of acute cough are listed in **Table 2** below.

Table 2 Circumstances requiring an immediate investigation of acute cough.

Hemoptysis
Thorax pain
Dyspnea
High fever
Stay in countries with high prevalence of Tb, contact with a person, stricken with Tb, homeless
History of malignant tumor
Immune deficiency, HIV infection, immune suppressive therapy
Heavy smoker

Tb: tuberculosis, HIV: Human immunodeficiency virus

As opposed to acute cough, a chest x-ray and lung function test should be performed immediately in the case of chronic cough. If the chest x-ray proves inconclusive, the lung function test is unremarkable and cough is the only presenting symptom it will always be difficult to establish the diagnosis. Throughout English-language publications [5 – 9], these cases are called chronic cough or chronic persistent cough focusing the possible diagnosis on the three most common causes: upper airways cough syndrome, cough variant asthma and gastrooesophageal reflux disease [5, 10 – 15]. It is therefore imperative to note the distinction between the definitions of "chronic cough" in these guidelines vs. the use of the term in international publications. *In this document, chronic cough is defined just as lasting over eight weeks, while acute cough is defined as lasting up to eight weeks.*

Recommendation: R2

- **Likely causes of chronic cough without conclusive chest x-ray and lung function:**
  Upper airway cough syndrome
  Cough variant asthma
  Gastrooesophageal reflux
- **Grade:** strong ⇧⇧
- **Evidence:** moderate

Recommendation: R3

- **Distinction between acute and chronic cough:**
  Acute cough: lasting up to 8 weeks
  Chronic cough: lasting longer than 8 weeks
- **Grade:** strong ⇧⇧
- **Evidence:** none

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Acute cough

▼

Recommendation: R4

- **Appropriate diagnostic tests for acute cough:**
  In most cases history and physical examination suffice in absence of special circumstances (see ▶ **Table 2**)
- **Grade:** strong ⇧⇧
- **Evidence:** low

- **Acute viral infections** [16] **of the upper and lower airways (common cold)** are the most common cause of cough and usually subside spontaneously after three weeks.
- **Upper airways allergic disease** (Hay fever, intermittent or persistent allergic rhinitis), often in combination with sinusitis, conjunctivitis, pharyngitis and laryngitis, can also trigger acute cough. Itchy eyes and throat are usually characteristic [17].
- **Intermittent asthma: allergic or due to infection** can cause acute cough
- **Aspiration:** Aspiration of a foreign body, most commonly in 1–3 year-old children, as well as in elderly, fragile patients triggers acute cough with expectoration of the foreign body or permanent bronchial obstruction with consecutive chronic cough.
- **Acute inhalative intoxication** (workplace accidents, fires, solvent- or glue-sniffing) can lead to a toxic lung edema, acute interstitial pneumonia and bronchiolitis with re-emergence of cough, often after a discomfort- and cough-free interval of 6–48 hours. Information on treatment of inhaled substances is available in German at: www.medknowledge.de/patienten/notfaelle/vergiftungszentralen.htm

Recommendation: R5

- **Treatment of cough due to acute inhalative intoxication:**
  High dose inhalative corticosteroid
  Additional systemic corticosteroid, if necessary
- **Grade:** strong ⇧⇧
- **Evidence:** none

- **Postinfectious cough**: persists >3 weeks after an acute, often viral airway infection and resolves after <8 weeks. Epithelial damage after B. pertussis or M. pneumoniae infection or a transient increase in bronchial hyper-responsiveness (BHR) - later subsiding spontaneously - are responsible for post-infectious cough. In the latter case a short course of asthma treatment (inhaled corticosteroids [18] or beta$_2$-adrenergics [10]) is effective.
  (We describe persistent BHR with consequent chronic cough without airflow obstruction as cough type asthma, see below under chronic cough).

Recommendation: R6

- **Treatment of cough due to postinfectious BHR:**
  Inhalative corticosteroid or beta$_2$-adrenergic
- **Grade:** strong ⇧⇧
- **Evidence:** moderate

- **Pneumonia**
- **Pleurisy**
- **Pulmonary embolism:** 50% of patients with acute pulmonary embolism present with a cough [19].
- **Pneumothorax:** all forms can be accompanied by dry cough.
- **Acute heart failure with pulmonary congestion:** Acute left heart failure (up to lung edema) can trigger both cough and bronchial obstruction [20,21]. Bradycardia associated with acute emerging AV block II-III can greatly reduce stroke volume eliciting pulmonary congestion and cough [22].

Recommendation: R7

- **Acute cough and heart failure:**
  Breathlessness, palpitation and acute cough is indicative of left heart failure and/or AV block
- **Grade:** strong ⇧⇧
- **Evidence:** low

Chronic cough

▼

- **Chronic Bronchitis and COPD:**
  The WHO defines chronic (non-obstructive) bronchitis as presence of cough and phlegm on most days over a period of at least three months during two consecutive years without other causes. Many patients suffering from chronic cough meet these criteria. For patients complaining chronic cough this diagnosis is only therapeutically useful, if the cause of their chronic bronchitis (i.e. smoking, work-related exposures) can be identified, cessation is possible and other causes of chronic cough have been excluded. Because smokers rarely complain of cough and phlegm, chronic bronchitis is seldom a reason to attend a cough clinic. Consequently they can rarely be included in diagnostic and therapeutic trials (5 to 14%) [11,13,14,23,24].
  - COPD: by definition patients with the chronic obstructive bronchitis phenotype of COPD are suffering from cough and phlegm. Chronic cough is a common symptom of COPD.
- **Asthma and other eosinophilic respiratory disease:**
  - Asthma: often responsible for chronic cough [25]. Dry cough can elicit or worsen an asthma attack.

Recommendation: R8

- **Persistent cough despite controlled asthma:**
  Additional antitussive up to 4 weeks duration indicated
- **Grade:** weak ⇧
- **Evidence:** none

  - Cough type (variant) Asthma is characterized by dry cough and bronchial hyperresponsiveness (BHR). Wheezing, dyspnea and bronchial obstruction are absent. Chronic cough with proven BHR can only be confirmed as variant asthma if asthma treatment (inhaled corticosteroids or beta$_2$ adrenergics) eliminates the cough [10,13–15,26–30].

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Recommendation: R9

- **Chronic cough due to BHR:**
  If responsive to inhaled corticosteroid, montelukast or beta$_2$-adrenergics: ⇨ cough variant asthma
- **Grade:** strong ⇧⇧
- **Evidence:** moderate

Recommendation: R10

- **Prevention of progression from variant asthma to asthma:**
  Early treatment with inhaled corticosteroid
- **Grade:** strong ⇧⇧
- **Evidence:** low

  – Eosinophilic bronchitis: characterized by chronic cough and sputum eosinophilia in absence of BHR. Eosinophilic bronchitis is invariably responsive to inhaled corticosteroid treatment [31].

Recommendation: R11

- **Chronic cough with sputum eosinophilia w/o BHR:**
  Eosinophilic bronchitis, responsive to inhaled corticosteroid
- **Grade:** strong ⇧⇧
- **Evidence:** moderate

- **Lung tumors:** Cough is the most common initial symptom of lung tumors [32]. If a patient presenting with chronic cough is not taking an ACE inhibitor, a chest x-ray should be done at the first consultation. Furthermore, in order to exclude a lung tumor each patient with unexplained chronic cough should have a bronchoscopy at the end of the diagnostic algorithm (**Fig. 2**).

Recommendation: R12

- **Primary work-up of chronic cough:**
  Perform chest x-ray at first consultation
- **Grade:** strong ⇧⇧
- **Evidence:** none

Recommendation: R13

- **Stepwise work-up of chronic cough w/o conclusive chest x-ray:**
  Before performing HR-CT or bronchoscopy consider asthma, COPD, upper airway cough syndrome and gastrooesophageal reflux
- **Grade:** strong ⇧⇧
- **Evidence:** moderate

Recommendation: R14

- **Bronchoscopy for chronic cough:**
  Indicated for every patient at the end of the diagnostic algorithm, if cough remains unexplained
- **Grade:** strong ⇧⇧
- **Evidence:** none

- **Upper airway cough syndrome includes:**
  – Chronic rhinitis and sinusitis, often with postnasal drip [33]
  – Chronic pharyngitis and laryngitis [34]
  – Chronic affections of the external auditory canal [7]
  – Vocal cord dysfunction: recurrent voluntary inspiratory (sometimes also expiratory) adduction of the vocal cords eliciting throat clearing, dry cough, wheezing and dyspnea. VCD can mimic asthma and often affects younger women [35].
- **Gastrooesophageal reflux disease:** Cough is triggered either by reflex or through reflux to pharynx and larynx (laryngopharyngeal reflux) and micro-aspirations [36]. Cough due to reflux can occur with or without heartburn [6], and not necessarily coincides with reflux oesophagitis (non-erosive reflux disease). Thus the gold standard of the reflux diagnosis is a triple sensor 24-hour pH probe and impedance pH-probe. The latter allows diagnosing both acid and weakly acid reflux. Since pH-probes are frequently not available and poorly tolerated, high dose (2 × 40 mg) proton pump inhibitor treatment over the course of up to three months can alternatively be carried out, thereby confirming or excluding the diagnosis of reflux cough [37]. In distinct cases surgical treatment (fundoplicatio) can be performed [38, 39], yet no evidence-based selection criteria for surgery are available.

Recommendation: R15

- **Treatment of chronic cough due to multiple underlying causes:**
  Treat all conditions appropriately, if present (e.g. asthma, rhinitis, reflux)
- **Grade:** strong ⇧⇧
- **Evidence:** moderate

Recommendation: R16

- **Pharmacologic treatment of chronic cough due to reflux:**
  Use double standard dose proton pump inhibitor
  Duration of treatment: 2 – 3 months
- **Grade:** strong ⇧⇧
- **Evidence:** moderate

Recommendation: R17

- **Surgical treatment of chronic cough due to reflux:**
  Should only be performed if preoperative pharmacological reflux treatment for cough is successful
- **Grade:** weak ⇧
- **Evidence:** moderate

Recommendation: R18

Surgical treatment of chronic cough due to weak acid reflux:
Initiate surgical treatment if proton pump inhibitor fails:
no general recommendation
Grade: none ⇦⇨
Evidence: none

- **Drug induced cough:** Approximately 10 % of women and 5 % of men cough while taking ACE-inhibitor medication [40]. The therapeutic (antihypertensive, cardiac or nephroprotective) effects of an ACE treatment can be replaced by angiotensin II receptor antagonists, which do not cause cough more frequently than placebo. For further drugs inducing cough updated information is available on www.pneumotox.com.

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Recommendation: R19

- **Therapeutic implications for patients suffering of chronic cough taking an ACE inhibitor:**
  Stop/replace ACE inhibitor first even if cough has other possible causes
- **Grade:** strong ⇧⇧
- **Evidence:** high

- **Infections:**
  - Pertussis in adults is a rare cause of chronic cough, but has been described even without a preceding phase of acute infection. Particularly patients with recent contact to persons suffering from acute pertussis infection should be checked for antibodies. However, interpretation of the results is difficult. After the acute exudative phase of infection (taking up to ten days) a direct culture of Bordatella is no longer possible and antibiotics will have no effect on cough or on the natural history of the infection.

Recommendation: R20

- **Treatment of cough due to pertussis:**
  Use central cough suppressants
- **Grade:** weak ⇧
- **Evidence:** none

  - Tuberculosis: chronic cough is a typical symptom, and was one of its key diagnostic criteria in the pre-x-ray era.

Recommendation: R21

- **Treatment of chronic cough due to active Tb:**
  Use additional central cough suppressants
- **Grade:** weak ⇧
- **Evidence:** none

- **Chronic cough due to heart diseases:** Aside from chronic left heart failure (cough generally occurs upon physical exertion or prone position), cardiac drugs including ACE inhibitors, beta-blockers (only in patients with BHR), Amiodarone (eliciting Alveolitis), AV – block II – III, endocarditis [41] and cardiac arrhythmia [42, 43] can cause chronic cough.
- **Diffuse parenchymatous lung diseases (DPLD) – Systemic diseases with diffuse lung involvement:**
  - DPLD: In addition to dyspnea, dry cough is the most common symptom. Some forms of diffuse parenchymatous lung disease (▶ **Table 3**) cause cough at such an early stage that the DPLD can be missed by conventional chest x-ray. Thus, an apparently "normal" chest x-ray and spirometry do not rule out early lung disease with cough. A high resolution CT scan can establish the diagnosis.
  - Most systemic autoimmune disease can develop lung involvement and cause cough (e.g. Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis and vasculitides).
- **Cough due to inhalative events:**
  - Aspiration: Chronic cough is caused if the foreign body becomes trapped in the bronchial system (usually in children between 1 – 3 years old), or due to chronic recurrent aspiration of food (liquids) resulting from dysphagia in underlying neurological conditions (e.g. bulbar paralysis, Parkinson disease [44], myasthenia gravis). Other causes: tracheooesophageal fistula, malformations, neck dissection (head and neck cancer), regurgitation in heavy gastrooesophageal reflux disease.
  - RADS (reactive airways dysfunction syndrome) occurs following short-term, intense inhalation of vapors, smoke or gases [45] (usually due to accidents in the workplace) and often develops into difficult asthma.

Table 3 Diffuse parenchymatous lung diseases with cough as an early symptom.

DPLD	Comments
Amiodarone induced DPLD	Cough can be the sole early manifestation
Methotrexat induced DPLD	The autoimmune disease itself or the methotrexat treatment can cause the cough.
Sjögren's syndrome	9 % pulmonary involvement, cough is rarely the presenting symptom.
Giant cell arteritis Horton's disease	Cough indicates lung involvement
Wegener's disease	Airway involvement can cause cough even when chest x-ray is negative
Inflammatory bowel disease	Bronchiectasis, bronchial narrowing, COP* or even treatment (sulfasalazine) can trigger cough
Sarcoidosis	Airway involvement can cause cough

* COP: Cryptogenic organizing pneumonia

- **Bronchiectasis and tracheobronchomalacia**
  - Bronchiectasis can be missed on chest x-ray. Gold standard of the diagnosis is a high resolution CT scan. Usually causes productive cough with voluminous secretion, often hemoptysis.

Recommendation: R22

- **Surgical treatment of chronic cough due to bronchiectasis:**
  Complete surgical resection of localized bronchiectasis is also effective for cough
- **Grade:** weak ⇧
- **Evidence:** low

Recommendation: R23

- **Antitussive treatment of chronic cough due to bronchiectasis:**
  Central active cough suppressants contraindicated
- **Grade:** weak ⇧
- **Evidence:** none

  - Tracheobronchomalacia elicits chronic cough due to contact between the anterior and posterior wall of the bronchus intermedius or the trachea [46, 47].

Recommendation: R24

- **Physiotherapy for tracheobronchomalacia:**
  Use cough - preventing physiotherapy techniques
- **Grade:** weak ⇧
- **Evidence:** none

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Table 4 Rare isolated disease of the tracheobronchial tree.

Rare isolated diseases of the tracheobronchial tree	Comments
Tracheobronchomegaly (Mounier-Kuhn syndrome)	Commonly in male patients
Tracheobronchial amyloid infiltration	Local infiltration of the central airways (possibly the larynx) by AL amyloid
Relapsing Polychondritis	Autoimmune inflammatory disease
Tracheobronchopathia osteo-chondroplastica	Heterotopic ossification
Juvenile recurrent respiratory papillomatosis	Adolescents, young adults, ca-sued by human papilloma virus

- **Isolated orphan airways disease:** usually emerges in patients over 40 years old. Can lead to expiratory bronchial collapse, irreversible central obstruction of the airways. Coughing is frequently the main symptom. (**Table 4**)
- **Cystic fibrosis:** CF is an autosomal recessive inherited disease. Abortive forms can manifest in adulthood for the first time through cough, bronchial infections and bronchiectasis [48].
- **Chronic cough and sleep apnea:** Sleep apnea patients often complain of chronic cough.
- **Psychogenic (habit or tic) cough:** By definition the sensitivity of the cough reflex is not increased in patients with psychogenic cough, but difficult to measure reliably. There is always a risk of misdiagnosis of multicausal or idiopathic cough as being psychogenic cough.
- **Chronic idiopathic cough:** Despite extensive diagnostic procedures, underlying causes of cough cannot be determined in up to 18 % of patients with chronic persistent cough (ratio female/male = 2 : 1). Capsaicin or citric acid sensitivity of the cough reflex is increased in these patients [49].

Recommendation: R25

- **Chronic idiopathic cough:**
  Do not perform diagnostic cough provocation test with capsaicin according to standardized provocation protocol
- **Grade:** weak ⇧
- **Evidence:** low

Recommendation: R26

- **Chronic idiopathic cough:**
  Treatment with inhaled off label local anaesthetics
- **Grade:** weak ⇧
- **Evidence:** very low

Diagnosis of cough

Applying the algorithms frequently allows for a provisional diagnosis, which must be confirmed by successful treatment. Failure can therefore require continued investigation based on the algorithm. Multicausal cough requiring combination treatment also has to be considered.

Recommendation: R27

- **Stepwise diagnostic workup of cough:**
  Use algorithms for acute and chronic cough, respectively
- **Grade:** strong ⇧⇧
- **Evidence:** none

Cough can persist up to eight weeks after subsiding of an acute infection (postinfectious cough). Except for special circumstances (**Table 2**), further examination according to the algorithm for chronic cough is only necessary after eight weeks (box 12).

Recommendation: R28

- **Diagnostic work-up of acute cough:**
  Usually taking history and physical exam are sufficient
- **Grade:** strong ⇧⇧
- **Evidence:** low

Recommendation: R29

- **Antibiotic treatment in otherwise healthy patients suffering of acute cough:**
  Not necessary
- **Grade:** strong ⇧⇧
- **Evidence:** moderate

Every patient with unexplained chronic cough must have a bronchoscopy performed by the end of the diagnostic algorithm. If a patient complains of cough lasting over eight weeks, diagnostic workup should be initiated immediately. The first steps consist of collecting the patients' medical history and a physical exam (box 1). If a (primarily) cardiac or neurological cause of cough is suspected, appropriate diagnostic workup must be initiated (box 3).

Establishing the cause of chronic cough is challenging if neither the chest x-ray nor the lung function test prove conclusive. If BHR can be established by nonspecific inhalative provocation test (box 11) the cough can be treated as probable variant asthma.

In smokers with inconclusive chest x-ray and normal lung function, smoking related chronic, non-obstructive bronchitis is the most likely cause of cough. Therefore a period of smoking cessation is recommended before further diagnostic workup is initiated (Box 14). If smoking cessation fails, or abstention remains unsuccessful after four weeks, diagnostic workup according to the algorithm should be continued.

Provided their chest x-ray proves negative, patients with cough and heartburn can be provisionally diagnosed with suspected gastrooesophageal reflux and PPI treatment can commence. In case of remarkable gastroenterological history, one should proceed according to current gastroenterological recommendations. If after three months at the latest high-dose PPI treatment proves unsuccessful, and the cause of cough is not determined at the end of the algorithm (including CT and bronchoscopy), extensive and targeted gastroenterological diagnosis should be performed. This includes endoscopy, esophageal manometry, triple sensor pH-probe (or impedance for both acid and weakly acid reflux). At this point the indication for surgery (fundoplicatio) can be assessed as well.

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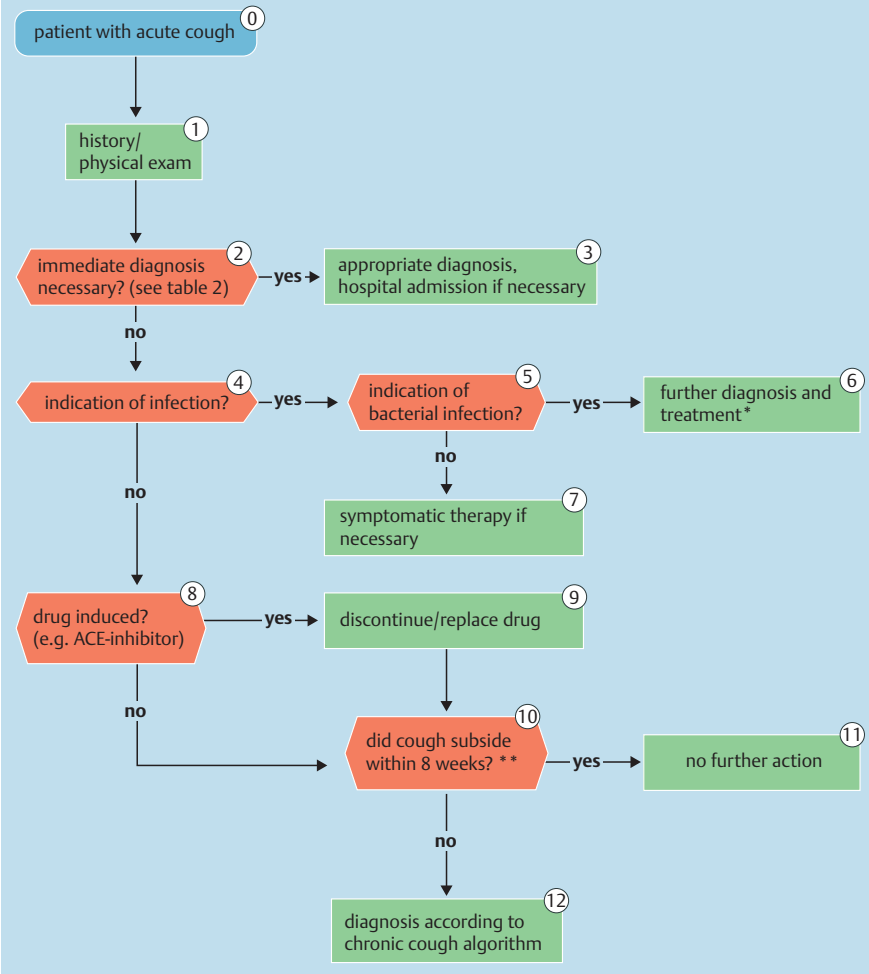

Fig. 1 Clinical algorithm for the diagnosis of acute cough.
* In otherwise healthy patients, antibiotics are not beneficial even in cases of purulent (green or yellow) sputum [50]. They are only recommended in comorbid or elderly patients with sputum purulence.
** Caveat remittent small pulmonary emboli with episodes of remittent cough, palpitations, breathlessness; slight hemoptysis may also occur.

Also the most common diagnostic and therapeutic shortcomings should be considered: early-stage, diffuse parenchymatous lung disease not yet evident on chest x-ray, eosinophilic bronchitis (eosinophile cell count in the sputum > 3 %) and a psychogenic cough (rare in adults) all should be taken account of. In some patients, the cause of chronic cough will remain unclear despite exhausting available diagnostic tools. In this case the patient suffers from chronic idiopathic cough where the source of an increased sensitivity of the cough reflex cannot be established (Box 26).

Recommendation: R30

- **Cost-effective diagnostic work-up of cough:** Follow algorithms
- **Grade:** strong ⇧⇧
- **Evidence:** none

The most frequent shortcomings in diagnosis of cough

- Trivialization of cough in smokers without diagnostic workup.
- Change of the established sequence of examinations without reason.
- Extrapulmonary causes (ENT, gastric, neurological, cardiac) are disregarded.
- No bronchoscopy though cause of cough was not determined.
- Multiple causes overlooked.

Symptomatic treatment of cough

Causal treatment should always be sought. However, if this approach is impossible (e.g. acute viral respiratory infection) or would only prove effective in a delayed manner (e.g. tuberculosis), symptomatic treatment can be considered instead or in addition to causal treatment of cough. Symptomatic treatment targets one or several of the five parts of the cough reflex arc. Effects can be protussive (increasing cough and expectoration) or antitussive.

- **Physiotherapy of cough:** Despite being clinical routine in both hospital and outpatient care [51] as well as in rehabilitation, evidence for the physiotherapy of cough is very low. Physiotherapy aims to:
  - increase expectoration using effective coughing techniques for patients with productive but ineffective cough
  - suppress voluntarily non-productive cough
  - instruct patient in the use of physiotherapeutic equipment improving expectoration such as Acapella®, Flutter® and RC Cornet®.

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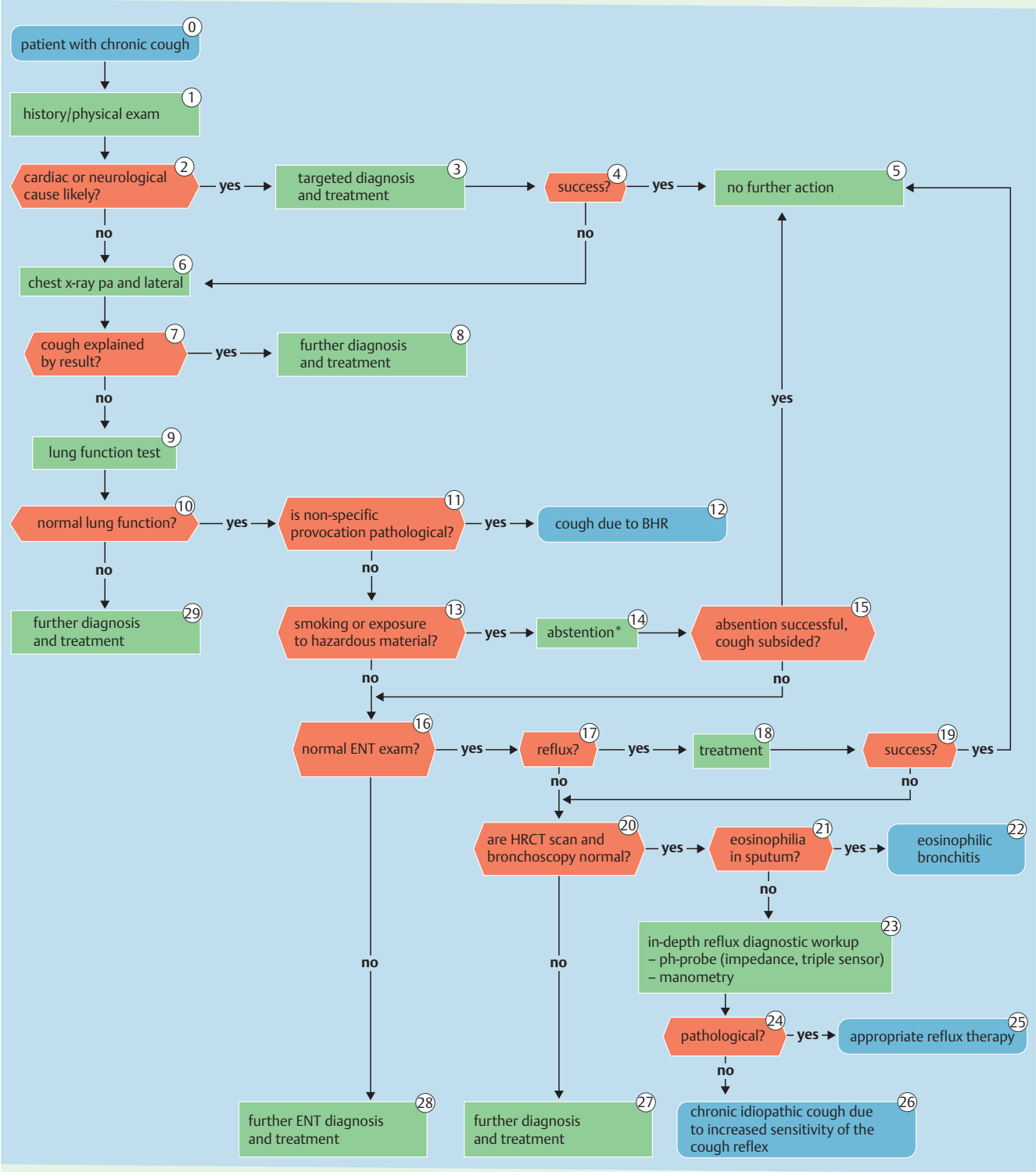

Fig. 2 Clinical algorithm for the diagnosis of chronic cough.
pa: postero-anterior.
* based on clinical suspicion, changes in severity and/or characteristics of cough may require immediate bronchoscopy therefore ignoring the steps of the algorithm.

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Recommendation: R31

Physiotherapy for chronic productive cough with and w/o bronchiectasis:
Prescribe physiotherapy
Grade: weak ⇧
Evidence: very low

Recommendation: R32

Physiotherapy for chronic dry cough:
Prescribe physiotherapy for voluntary cough suppression
Grade: None ⇦⇨
Evidence: none

Recommendation: R33

Use of physiotherapeutic equipment for chronic productive cough with and w/o bronchiectasis:
Prescribe physiotherapeutic equipment
Grade: Weak ⇧
Evidence: low

▶ **Pharmacotherapy**

Expectorants reduce irritation of the cough receptors by accumulated mucus through "coughing up", and represent the most common medication used for respiratory diseases in Germany (e.g. ambroxol and N-acetylcysteine, in the USA guaifenesin and iodinated glycerol.). Because of the lack of appropriate methods effectiveness is difficult to assess. Regarding relative effectiveness of different expectorants, conflicting or inconsistent evidence exists throughout the published literature [52, 53]. Symptomatic use of expectorants is recommended to ease cough in cases with production of viscous secretions (COPD, bronchiectasis). Many patients also report positive subjective effectiveness using self-medication for acute bronchitis.

Recommendation: R34

Prescription of expectorants to ease cough:
In symptomatic COPD and bronchiectasis patients
Grade: weak ⇧
Evidence: very low

Combination phytotherapeutics can reduce the duration of acute cough of the common cold [54, 55]

Recommendation: R35

Use of fixed combination phytopharmaca (ivy, thyme, primerose) for acute cough due to common cold:
Prescribe fixed combination
Grade: strong ⇧⇧
Evidence: moderate

In cystic fibrosis bronchiectasis inhaled dornase alfa eases cough [56].

Recommendation: R36

Cystic fibrosis bronchiectasis:
Use dornase alfa
Grade: strong ⇧⇧
Evidence: moderate

Recommendation: R37

Bronchiectasis with persistent cough:
Use inhaled antibiotics (i.e. tobramycine, colistine)
Grade: weak ⇧
Evidence: high

Drugs that reduce mucus production

Inhalative anticholinergics (i.e. ipratropium and tiotropium) are thought to reduce mucus production; however their antitussive effect is not consistent [57].

Drugs that increase mucociliary clearence

Theophylline and beta$_2$-adrenergics do increase mucociliary clearence but are not effective reliving cough [58].

Drugs for the reduction of irritation of cough receptors

By "coating" cough receptors in the throat, demulgents are thought to have an antitussive effect. Cough syrups, lozenges, cough drops and honey, share sugar as the common ingredient. Effectiveness, if any, is limited in time to the contact of the sugar with the receptor, usually 20–30 minutes.

Drugs that affect mucosal oedema

Systemic alpha-adrenergics for nasal decongestion are popular in the US but virtually not in use in Germany. Fixed combinations with anticholinergic and central effective antihistamines clorpheniramine or dexbrompheniramine are not available.

Antibiotics are only effective against cough caused by a bacterial infection characterized by purulent phlegm (i.e. suppurative bronchitis, bronchiectasis, exacerbation of COPD, purulent rhinitis and sinusitis). Antibiotics are not indicated in acute bronchitis.

Anti-inflammatory therapy: inhalative und nasal corticosteroids (oral leukotriene antagonists and probably topical nedocromil) alleviate cough in asthma, eosinophilic bronchitis, postinfectious cough due to BHR and rhinitis.

Local anesthetics: Local anesthetics disable electrophysiological activity in the receptors and afferent nerves [59] (e.g. during bronchoscopy). They are increasingly used off label for idiopathic cough and in palliative medicine [60].

Drugs affecting central mechanism for cough (antitussives) are systemically applied morphine or codeine as well as natural and synthetic derivatives (i.e. dextromethorphan, dihydrocodeine, noscapine and pentoxyverin). Some non-addictive herbal remedies (thyme, ribwort, sundew) claim central antitussive properties, though this is not proven by clinical studies. Opiates are recommended for symptomatic treatment of dry cough [61]. They have limited efficacy in the treatment of cough resulting from common cold [62].

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Complications of cough

Case reports are available for most complications of cough, listed below.

Table 5 Complications of cough.

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

Conflict of interest

According to the rules of the Association of the Scientific Medical Societies in Germany, http://www.uni-duesseldorf.de/AWMF/ the conflict of interest statements were reported on the appropriate AWMF form and assessed by all authors. According to the subject of the guideline no conflict of interest was detected.[1]

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[1] The evidence tables were published in German on the AWMF website http://leitlinien.net/

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