Children with Persistent Cough

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Definition and General Concepts

Cough is a complex physiological reflex that protects the airway from chemical, mechanical, and thermal injury. It consists of violent expiration with the objective of freeing the airway of secretions and foreign material. Nevertheless, as a result of its chronic evolution or intensity, it can become an annoying symptom that seriously affects the quality of life of the child, interrupting sleep, studies, and sports, and creating anxiety in the family. It is of great clinical use to define cough according to its duration, its association with specific causes, and its response to rationally indicated therapy.

Cough is defined as acute when it lasts for at least 3 weeks and is defined as subacute when it continues for 3–8 weeks. Cough is recurrent when there are more than two episodes per year that are not associated with the common cold and that last for more than 1–2 weeks. Cough is defined as chronic in pediatric patients when it persists for more than 8 weeks. It is not a disease

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per se; rather, it is a cardinal symptom of numerous respiratory and nonrespiratory pathologies, and it is responsible for a large number of medical consultations. Cough is the reason for 10% of primary health care consultations for schoolchildren and 20% of consultations for preschool children.

Assessment and diagnosis of chronic cough in pediatrics require adequate knowledge of the possible causes. Consequently, correct identification of the cause is a priority for etiological treatment in order to avoid a symptomatic approach with antitussives or expectorants, which most often have disappointing results and pose risks of addiction and negative side effects.

Cough Reflex Anatomy

Key Concepts

1. Cough is an integral part of the defensive system of the respiratory tree, together with mucociliary clearance, alveolar macrophages, and the immune system.
2. The reflexive mechanism of cough is very complex and consists of five components (Fig. 18.1):
   (a) Cough receptors: These are distributed throughout the respiratory tract and extrarespiratory locations: the outer ear, stomach, pericardium, and diaphragm. There are rapid-adaptation irritant receptors (mainly concentrated in the higher-caliber airways on the luminal side of the basal membrane, close to the cilia of the pseudostratified epithelium), mechanical receptors (which are sensitive to changes in the caliber of the airway), and chemical receptors (which are sensitive to gases and smoke).
   (b) Afferent nerves: The afferent tracts reflect their origin in the different locations of the aforementioned receptors. Laryngeal impulses go through the homonymous nerve, while tracheobronchial impulses go through the vagus nerve—the high-velocity myelinated fibers being the most important in mediating centripetal stimulus. The phrenic nerve is responsible for passing a stimulus from the diaphragm and pericardium, and the trigeminal nerve passes a stimulus from the nose and paranasal sinuses to the cough center.
   (c) Medullary center: The integrating center is at the level of the medulla, although its existence is controversial.
   (d) Efferent nerves: The efferent–effector response is transmitted to the expiratory and diaphragmatic muscles by the spinal and phrenic motor nerves and to the larynx by the recurring branches of the vagus nerve. The ends of the parasympathetic nerve system supply the trachea and bronchi, and through their effect of contracting the smooth muscle, they contribute to the effort of cough by narrowing the airway and consequently increasing the velocity of airflow.
   (e) Effector muscles.

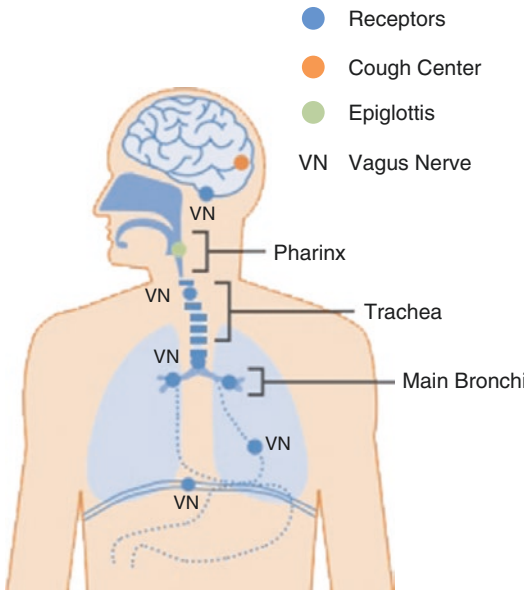

Fig. 18.1 Anatomy of cough

Etiology

Key Concepts

1. The causes of chronic cough in children and adults are different, and within pediatrics they can differ among infants, preschool children, and schoolchildren and adolescents.

2. The etiological spectrum can include one or more coexisting causes.

There are numerous causes of chronic cough as a consequence of the interaction of the mechanisms summarized in Fig. 18.2.

The cause of cough can vary according to age. In infants, cough in early life suggests the presence of congenital anomalies such as a tracheoesophageal fistula, vascular ring, innominate artery, neuromuscular disorders, or other abnormalities or malformations of the airways. Viral infections such as *Chlamydia*, *Bordetella pertussis*, mycobacteria (tuberculosis), and others should not be ignored, nor should the possibility of gastroesophageal reflux (GER), cough-equivalent asthma, or cystic fibrosis.

In preschool children, upper airway cough syndrome (UACS)—including rhinosinusitis, adenoiditis, infection, and inflammation of Waldeyer's lymphatic ring—and the effects of cigarette smoke (passive smoking) are added to the aforementioned range of causes. This is one of the periods of life when the possibility of asthma (cough-variant asthma) is particularly important. Cough caused by inhalation of a foreign body is typically paroxysmal but can be delayed and become chronic. Prolonged bacterial bronchitis, described above, is characterized by chronic productive cough caused by *Moraxella catarrhalis*, *Haemophilus influenzae*, or *Streptococcus pneumoniae*. It produces intense neutrophilic inflammation in the airways and characteristically resolves within 2 weeks of administration of amoxicillin and clavulanic acid or clarithromycin acid.

In schoolchildren and adolescents, postnasal discharge rhinosinusitis (UACS) is the main cause. Cough-equivalent asthma, exacerbated by smoking, and eventually a psychogenic cough, which characteristically calms during sleep, also acquire relevance and should be considered in the differential etiological diagnosis of this frequent symptom. The diagnosis of bronchiectasis should not be overlooked, especially in patients who have suffered severe pneumonia during childhood. Table 18.1 shows the main causes of chronic cough according to pediatric age.

Diagnosis

Key Concepts

1. The clinical history (interview and physical examination) is the fundamental diagnostic pillar.
2. Confirmation of a cause does not necessarily mean that it is responsible for the cough.

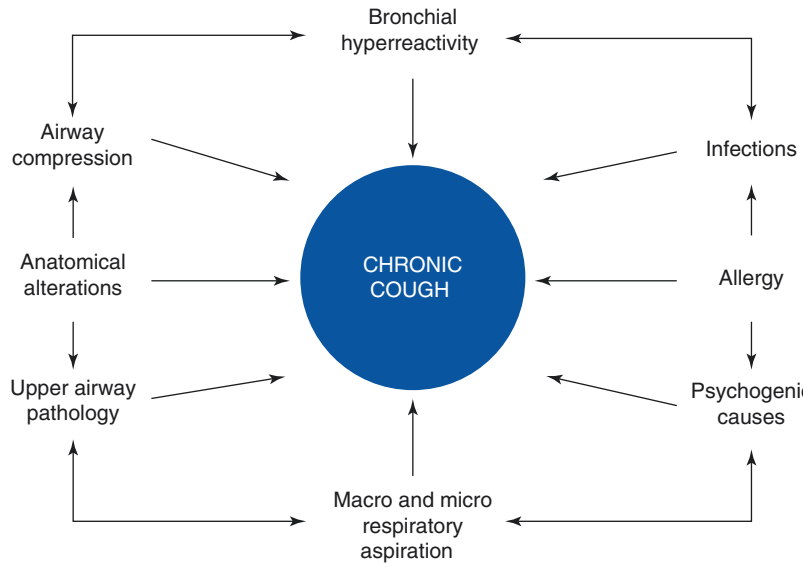

Fig. 18.2 Interaction of etiological factors in chronic cough

Table 18.1 Causes of chronic cough by age

Infant	Preschool	School and adolescence
Congenital anomalies	Infections	Asthma
Tracheoesophageal fistula	Bacterial	Rhinosinusitis
Vascular ring	Viral	Psychogenic
Airway malformation	*Mycoplasma*	Gastroesophageal reflux
Neuromuscular disorders	Tuberculosis	Infections
Infections	Rhinosinusitis	Tuberculosis
Viral	Asthma	*Mycoplasma*
Bacterial	Gastroesophageal reflux	Bronchiectasis
Tuberculosis	Foreign body	Irritative
Chlamydia	Irritative	Environmental pollution
Asthma	Passive smoking	Smoking
Gastroesophageal reflux	Cystic fibrosis	
Cystic fibrosis	Bronchiectasis	

3. The sensitivity, specificity, positive predictive value, and negative predictive value of the different diagnostic methods should be adequately considered.
4. A diagnostic test is accurate only if the cough is resolved with the specific therapy for that diagnosis.
5. Complementary studies should always be supported by the clinical history.

The anamnesis should detect and characterize the time of onset and evolution, type of cough, hourly rhythm, aggravating and triggering factors, production and quality of sputum, and presence of associated symptoms. Orienting signs and the growth and development of the child should be assessed in a detailed physical examination (Table 18.2).

In particular, consideration should be given to infants' neonatal and feeding history, any habits relating to putting foreign objects in the mouth, and the personal and family background in relation to allergies. The pediatrician should review the history of vaccinations, irritants, and allergies at home and the prescribed medications: the dosages, durations of treatment, adherence, and responses to medication. The use of angiotensin-converting enzyme (ACE) inhibitors should be investigated.

Asthma-associated cough is typically nocturnal and exacerbated by cold air, irritants, allergens, and exercise. Cough can be the only manifestation for a long period and can delay a definitive diagnosis. Knowledge of the personal and family history of atopy can be orienting.

A chronic cough associated with purulent expectoration indicates bronchiectasis, suppurative pulmonary, or cystic fibrosis. An associa-

Table 18.2 Symptoms and signs associated with specific causes of chronic cough in childhood

Symptom/sign	Possible etiology
Pulmonary auscultatory findings	Asthma, bronchitis, foreign body, aspiration, congenital anomalies, cystic fibrosis
Heart murmur	Heart disease
Chest pain	Asthma, pleurisy
Thoracic deformity	Severe chronic obstructive pulmonary disease
Productive cough	Chronic bronchitis, suppurative lung disease, cystic fibrosis
Nail clubbing	Suppurative lung disease, cystic fibrosis
Dyspnea on exertion/ at rest	Airway or lung parenchymal disease, heart disease
Growth retardation	Severe lung or heart disease, cystic fibrosis
Deglutition disorders	Gastroesophageal reflux, primary aspiration
Immunodeficiency	Suppurative lung disease, atypical infections
Recurrent pneumonia	Immunodeficiency, congenital anomalies of the lung, tracheoesophageal fistula
Fever	Tuberculosis, suppurative lung disease, bacterial bronchitis, other infections
Hemoptysis	Suppurative lung disease, vascular anomalies, bronchitis

This is only a partial list of associated symptoms and signs

tion with chronic diarrhea, slow growth, nasal polyposis, and/or nail clubbing provides strong evidence of cystic fibrosis.

Postnasal discharge in children often indicates nasal obstruction and mucopurulent rhinorrhea. Persistent headaches and eventually facial pain and pain around the eyes are symptoms suggestive of sinusitis, while a history of recurrent febrile syndrome, with general malaise and generally productive cough, indicates the need to inquire about contacts and raises suspicion of tuberculosis.

Cough can be linked in aspiration syndromes to regurgitation and choking, and can be exacerbated during or after eating. Occasionally, wheezing and basal crackling can be heard. Finally, psychogenic cough is unproductive, relaxes while the subject is sleeping, and does not improve with antitussive drugs. It is usually diagnosed by a process of elimination.

The pediatrician should carefully consider complementary studies, which will depend on the initial clinical assessment. A chest x-ray is the first indicated study and should be done in almost all cases. It can confirm the existence of an organic pulmonary cause of cough, and it is the guide for an algorithm of subsequent complementary studies. If the chest x-ray is abnormal—for example, if it shows the presence of localized shadows or diffuse infiltrates—more complex imaging techniques, cultures, sputum cytology, and/or diagnostic bronchoscopy should be employed.

In children under 3 years of age, spirometry can contribute to detection of reversible bronchial obstruction, which is compatible with a diagnosis of asthma. If the results are normal, with a strong suspicion of asthma, a bronchial provocation test with either exercise or methacholine, and an airway inflammation study measuring exhaled nitric oxide or induced sputum, are indicated if they are available. The sensitivity and specificity of the method that is employed should be considered in order to optimize the diagnostic utility.

X-rays of the paranasal sinuses offer low diagnostic specificity, but it improves significantly when combined with clinical findings for etiological determination of cough syndromes associated with upper airway pathologies (UACS). Computerized tomography is not generally recommended to assess sinusitis, although it can provide more diagnostic precision.

Rhinopharyngeal assessment can contribute to detection of organic pathologies of the upper airway and provide indirect signs of a laryngopharyngeal reflux that is responsible for cough. An esophagogastroduodenal transit study allows us to study GER, foreign bodies in the esophagus, tracheoesophageal fistulas, and exogenous compressions of the esophagus. GER and/or laryngopharyngeal reflux should be suspected in all cases of cough with an undetermined cause. In this respect, 24-hour esophageal pH monitoring may be useful, although a normal study does not rule out nonacid reflux as a cause of associated cough, which can be detected by impedance measurement.

Allergological assessment (skin tests for immediate detection of allergens, immunoglobulin dosages, etc.) should be reserved for specialist use for proper interpretation.

A study of tuberculin sensitivity is absolutely necessary if epidemiological evidence of tubercular contacts is found, including the entire family if necessary.

Figure 18.3 shows a diagnostic algorithm for chronic cough in pediatrics.

Treatment

Key Concepts

1. The treatment of chronic cough has a greater possibility of success when the precise cause has been identified and is specifically addressed.
2. Before prescribing any symptomatic medication, the pediatrician should perform an exhaustive causal investigation of the symptoms.
3. Analysis of the evidence according to the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system supports more precise therapeutic recommendations.

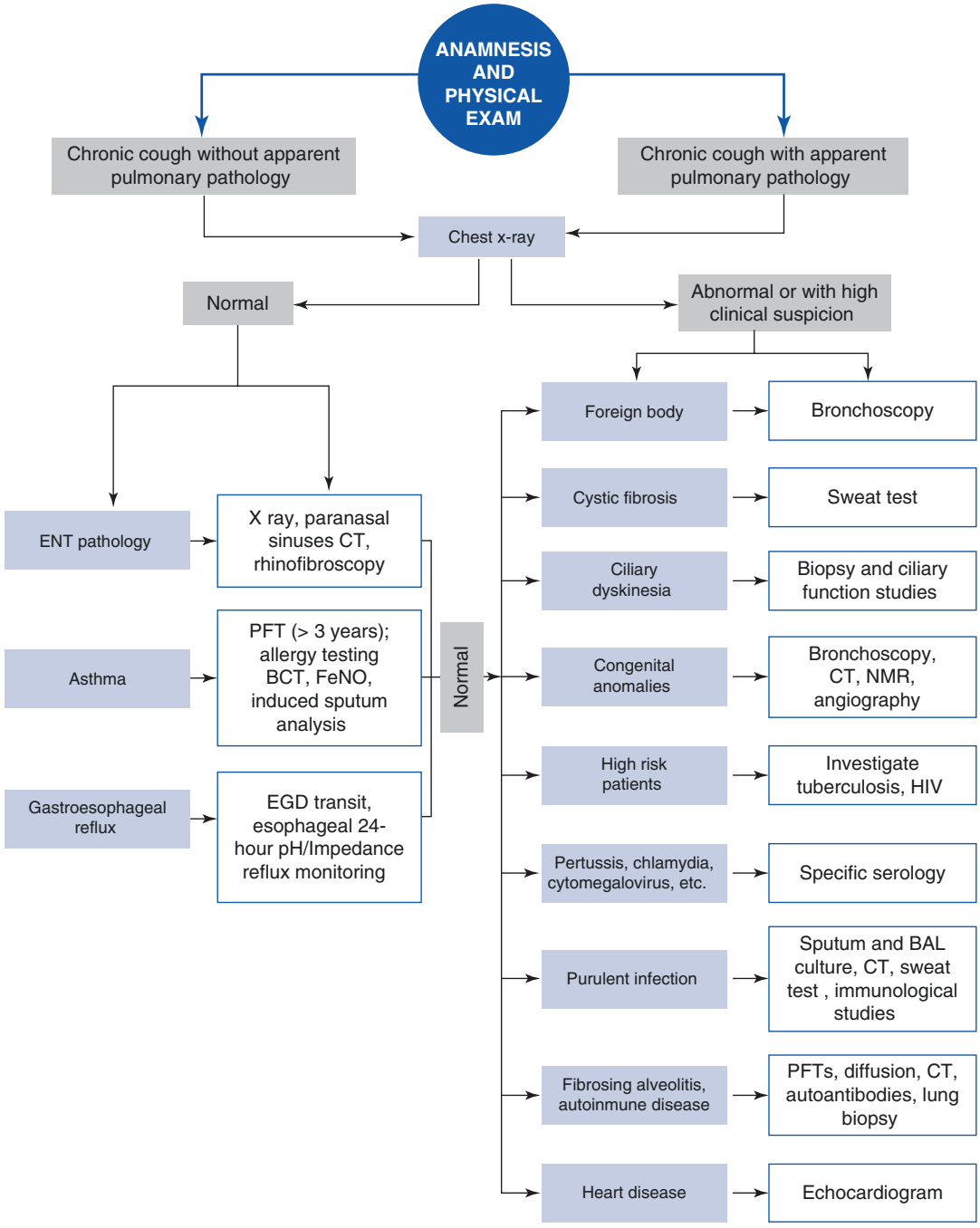

Fig. 18.3 Algorithm suggested for diagnosis of chronic cough in pediatrics. *BAL* bronchoalveolar lavage, *BCT* bronchial challenge test, *CT* computerized tomography, *EGD* esophagogastroduodenal transit, *ENT* ear, nose, and throat, *FeNO* fraction of exhaled nitic oxide, *PFT* pulmonary function test

At the beginning of the twentieth century, Chevalier Jackson said, "The cough is the guard dog of the lungs that protects them from external damage and internal enemies. However, doctors often give us drugs that put the guard dog to sleep just when we need it most." This author considered that cough was a physiological defense mechanism and that doctors of that time were,

wrongly, more concerned with treating symptoms than identifying the origins of them; the same occurs today.

The objectives of treating chronic cough can be summarized as follows:

1. Remove the causal agent or irritant.
2. Mobilize and facilitate expectoration.
3. Suppress stimulation of peripheral receptors.
4. Depress the cough center.

Treatment of Chronic Cough with an Identified Cause

1. Chronic cough due to asthma requires treatment with a bronchodilator, antileukotrienes, and/or steroids via inhalers. These treatments should be accompanied by measures to avoid allergens and irritants, such as avoiding cigarette smoke (GRADE recommendation strength: strong).
2. For cough associated with allergic rhinitis, allergens should be avoided, and nasal antihistamines and steroids should be applied (GRADE recommendation strength: weak). If there is bacterial sinusitis, antibiotic therapy is imperative.
3. There is no specific GRADE recommendation for use of a proton pump inhibitor assay in children for 8–12 weeks. Laparoscopic fundoplication is not advised for relief from cough caused by GER.
4. For cough produced by prolonged bacterial bronchitis, antibiotic therapy with amoxicillin and clavulanic acid or clarithromycin is useful for 2–6 weeks (GRADE recommendation strength: strong). Antituberculosis therapy should be given in response to a confirmed diagnosis of tuberculosis. The most common viral causes of respiratory infection are generally not self-limited.
5. Psychogenic cough requires detailed exploration of the family situation and dynamics, and of stressful aspects of the family and school environments. This can require the involvement of a psychologist.
6. For any type of cough, smoking cessation by the parents (where applicable) carries the strongest GRADE recommendation.

Chronic Cough Without an Identified Cause: Is Symptomatic Treatment Useful?

Key Concepts

1. The cause of cough can sometimes not be determined, or it can present prejudicial effects such as chest pains, fatigue, vomiting, headaches, or disturbed sleep, making symptomatic treatment necessary.
2. Nonspecific therapy tends to provide relief from symptoms when the cough does not serve any physiological reason (such as irritative, dry, and prolonged postviral cough) or to avoid these complications or pernicious effects.
3. Productive cough should not be suppressed, given that retention of secretions can prolong the base disease and the consequent symptoms.
4. Many therapeutic combinations used in symptomatic treatment of cough (antitussives and mucolytics) do not make sense, given that their components have contradictory effects, as well as toxic and addictive side effects.

The practice of "observe, wait, and review" is strongly recommended to avoid unnecessary medication, given that the benefit of such medication generally does not exceed that of a placebo, and because in a high percentage of cases, nonspecific cough resolves spontaneously.

1. Antitussive drugs: There is a wide variety of commercial antitussive drugs, which are classified according to their site of action. Narcotic and non-narcotic centrally acting agents depress the integrating medullar reflex center, while peripherally acting agents depress or anesthetize the receptors where the cough reflex originates.

2. Centrally acting antitussives are most widely used. Codeine, a narcotic antitussive par excellence, is one of the most potent cough suppressants and has addictive effects. It is usually well tolerated but can provoke drowsiness, dizziness, symptoms of digestive intolerance, and a dry mouth. It is contraindicated in all guidelines.
3. Synthetic derivatives of codeine and morphine, such as oxycodone and hydrocodone, can be found in many preparations. They are highly effective but can have the same side effects as their parent drugs. There are strong GRADE recommendations against their use in all cases.
4. Dextromethorphan is one of the most important non-narcotic antitussive agents. Acting at the central level, it appears to be as potent as codeine. It is better tolerated but can sometimes have unwanted gastrointestinal effects, although the recommended dose does not produce the types of sedative and respiratory depressant effects that often accompany codeine. Dextromethorphan is rarely addictive. Noscapine, chlophedianol (clofedanol), clofedianol, clobutinol, oxeladin, and butamirate complete the list of non-narcotic antitussives recommended for children over 6 years of age.
5. Mucolytic and expectorant drugs: These liquefy mucus, reduce retention of secretions, and increase mucociliary clearance, because of which they are used in patients who have difficulties in expectorating abnormally viscous secretions.

Guaifenesin and iodine compounds are present in several commercial preparations, but as iodine-containing drugs they carry the risk of causing hypothyroidism, skin rashes, and mouth infections. More modern drugs such as bromhexine and ambroxol are available in our pharmacopoeia, but their effectiveness does not exceed the mean range of the other drugs mentioned above. As a mucolytic agent, N-acetylcysteine interferes with disulfide bonds in the mucus, reducing its viscosity. However, these drugs can increase bronchial hyperresponsiveness. GRADE strongly recommends minimizing the use of mucolytics and demulcents.

Despite these warnings—and although symptomatic cough medicines are not recommended by the American Academy of Pediatrics and the US Food and Drug Administration (FDA) did not approve their use in children under 4 years of age in 2008—they continue to be the drugs most commonly prescribed by doctors and consumed by patients.

Advantages of Managing Chronic Cough with Diagnostic–Therapeutic Algorithms

The clinical performance of chronic cough management is improved by incorporation of a standardized diagnostic–therapeutic sequence. The more rapidly an algorithm is applied, the sooner the problem is resolved and the sooner the quality of life of the patient is improved. Chang et al. (2013) conducted a multicenter study to test the hypothesis that management of chronic cough in children according to an evidence-based algorithm is feasible and improves clinical outcomes (Fig. 18.4). Two groups, with early use and late use, were compared with the aid of the algorithm shown in the figure. The percentage of cough-free children at 6 weeks (the primary outcome) was significantly higher ($p < 0.0001$) in the early use group (54.3%) than in the late use group (29.5%). The absolute reduction in risk among the intention-to-treat groups was 24.7% (95% confidence interval (CI) 13–35), with an NNT of 4 during a 6 week period (95% CI 3–8). In effect, 85% of the diagnoses were made following this protocol, without the need for specialized investigation, showing that standardized management of chronic cough leads to improved results in practice.

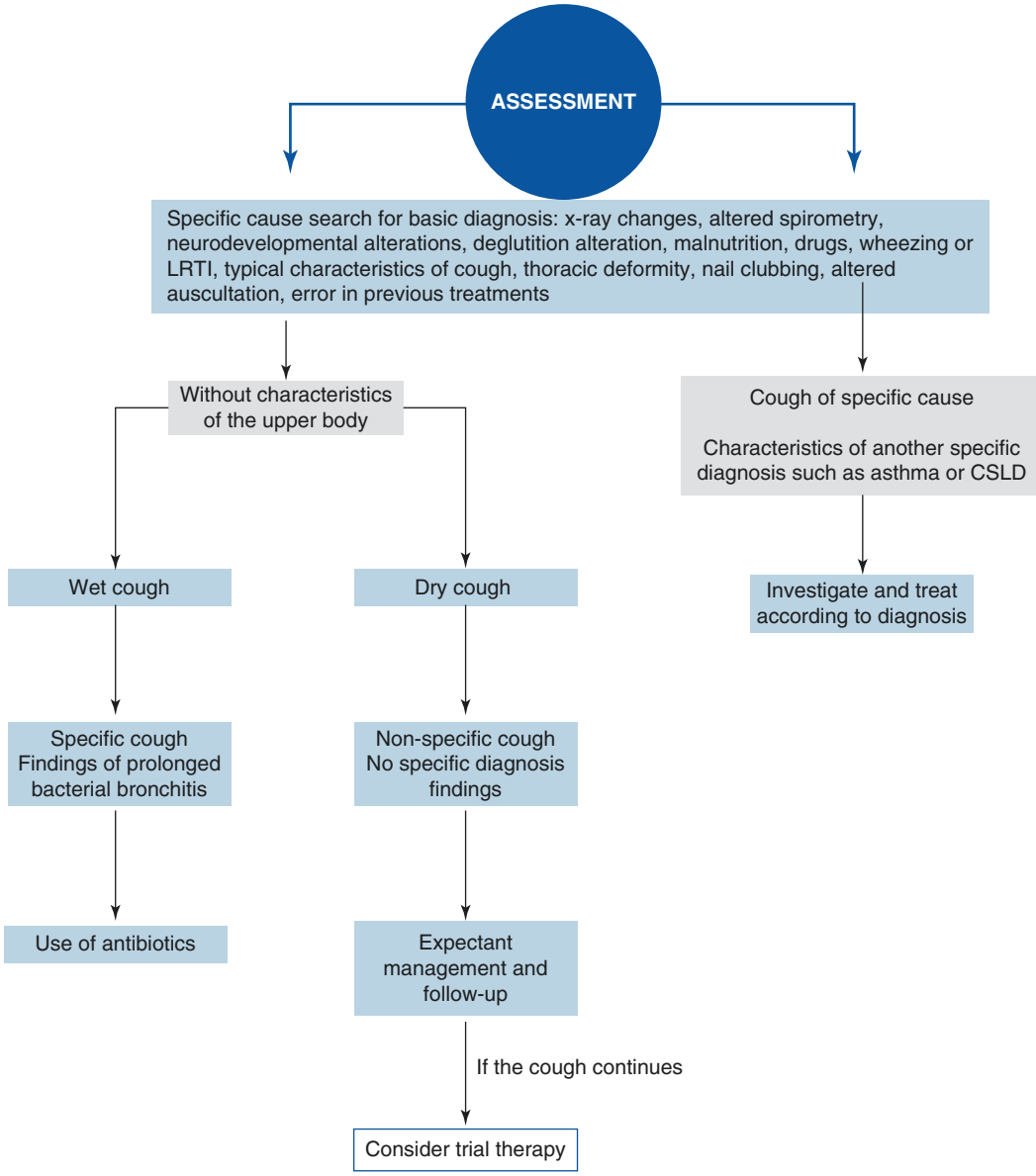

Fig. 18.4 Algorithm for diagnostic and therapeutic management of chronic cough. *CSLD* chronic suppurative lung disease. (Adapted from Chang et al. 2013)

Conclusion

1. Cough is a cardinal symptom of numerous respiratory and nonrespiratory diseases. In pediatrics, cough is defined as chronic when it persists for more than 8 weeks, and chronic cough requires an ordered and precise diagnosis.
2. A careful and exhaustive anamnesis and physical examination are fundamental pillars of the diagnosis.
3. The etiological spectrum is different in children and adults, with consequent therapeutic implications.
4. The causes of chronic cough in childhood vary with age. The most common causes are cough syndrome related to upper airway

pathologies, cough-variant asthma, and prolonged bacterial bronchitis.

5. The exact etiological identification should be followed by specific treatment. If this does not prove effective, the following should be considered:
   (a) The cause is partially identified and undertreated.
   (b) The diagnosis is incorrect.
   (c) The treatment is not appropriate.
   (d) The patient is not compliant with the treatment.
6. Symptomatic therapy is necessary in rare instances if the cause is properly determined. Treatment with antitussives, mucolytics, and expectorants is often disappointing. It has undesirable side effects and should be considered for use only as an adjuvant in the case of an "irritating" cough that does not respond to a demonstrable cause, or used as a complement to a specific therapy.
7. New symptomatic therapies are being developed with specific effects on peripheral receptors and channels involved in the cough reflex and in the modulation of the sensorial peptides of the respiratory tract. These therapies are opening promising new fields of treatment for cough.

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