

Management of Chronic Cough in Children

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ABSTRACT

Cough is a common reason for seeking medical advices for children. Cough is a natural defense mechanism and can frequently occur in healthy children and can be increased by urban living and polluted cities. Thus, previous history, cough exacerbations factors and quality of cough are very helpful in diagnosis of pathological cough. There are different definitions for chronic cough. In this article chronic cough in children is referred to as a cough over a three week period, which is divided into two categories specific and non-specific chronic coughs. In case of finding no specific cause for chronic cough, the elective management is follow up of the patient, insurance of parents and avoidance of unuseful antitussive drugs. Symptomatic treatment of cough has similar effects as the placebo. Thus, they are generally not recommended for children. Considering various aspects of diagnostic and therapeutic management of chronic cough in children and the right approach, are essential for different medical disciplines.

Keywords: Cough; Child; Antitussive Agents

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1. Introduction

Cough is a common symptom not only in patients but also in healthy children as a defensive reflex. It prevents entry of foreign bodies to airways and also clarifies them from normal secretions and suspended particles in inspiratory air. Every child gets respiratory infections 5 to 8 times on average per year and each time it lasts about 6-9 days. According to community-based surveys, parental reported cough as an isolated symptom has a high prevalence and reported cough without colds has a prevalence of 28% in boys and

30% in girls (1).

So, a healthy child has some degree of cough on average of about 50 days a year for respiratory infections (2), and 10 coughs per day without any infections, usually during day time and these may increase in frequency to 35 per day with air pollution and residence in crowded cities (expected cough) (3).

Cough receptors are both mechanical and chemical. Mechanical receptors are mainly on proximal upper airways like, larynx, carina and trachea despite of chemical recep-

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▶Implication for health policy/practice/research/medical education:

Chronic cough is an important and common problem in children. Many unnecessary anti tussive drugs are used for this problem and the burden of the laboratory investigations is considerable. Knowledge about how to approach to this symptom is necessary for all pediatricians and general physicians.

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tors which are predominantly on the lower airways like main bronchus and their distal branches. Terminal bronchioles and alveolus do not have receptors. They are also on the external auditory canal, pleural and pericardial membranes, diaphragm, esophagus and even gastric mucus membranes (3). Following stimulation of the cough reflex, afferent nerve messages are sent primarily by the vagus nerve to the cough centers in the medulla oblongata and pons and by two-way communications with the higher centers to the brain cortex. Thus, cough can be both voluntarily and involuntarily. Efferent nerves from the cough centers go to the following three areas:

A) Part of the spinal cord, especially motor part that also stimulates contraction of expiratory muscles and pelvic sphincters to prevent enuresis during coughing spells

B) Phrenic nerve which contracts the diaphragm muscle.

C) Efferent vagus nerve to the larynx, trachea and bronchi and allows them to contract

Generally cough cycle has three stages as follows:

Inspiration phase: A deep breath to produce volume of air required to produce a cough.

Pressure phase: Glottis is closure and contraction of the diaphragm and the muscles of the chest and abdomen resulting the chest pressure to rise.

Expiratory phase: begins with opening of the glottis and then exhalation occurs and the sound of the cough results (1).

2. Definition and Types of Chronic Cough

There is no consensus about the definition of chronic cough or prolonged cough, however, coughs lasting less than three-weeks in children is considered as an acute cough. These differences are due to duration of coughs followed by acute respiratory infections which last 10 days in 50%, and 25 days in 90% of cases (4). The coughs in adults can be divided into three categories based on their duration: acute cough lasts 3 weeks or less, prolonged cough lasts 3 to 8 weeks, and chronic cough can be considered as more than 8 weeks.

In school-age children, according to high incidence of upper respiratory tract infection, approximately 5 to 10% of children complain of prolonged coughs (5). Prolonged cough, especially and in early childhood at nights can lead to parental anxiety, as they think it may cause choking and eventually sudden death during sleep (6).

Cough is classified in these forms according to its characteristics:

- A dry cough or nonproductive cough and wet or productive cough. As children cannot spill out sputum, the term wet cough is more accurate than productive cough. Studies have shown that patient history provided by parents can be reliable regarding subject.

- Bark-like cough (barking or brassy cough) usually seen in the upper tract diseases, such as, croup and tracheomalacia

- Paroxysmal cough occurs when breathing stops between coughing, which is characteristic of pertussis or pertussis-like infection

- Staccato cough has short bursts and the patient breathes between two coughs and is characteristic of Chlamydia infection in infants.

- Habitual cough is a kind of nervous tic or tic cough.

- Chronic cough is generally divided into two categories, specific and non-specific chronic cough. Specific cough are caused by the known underlying disease, such as cystic fibrosis or bronchiectasis, but in the non-specific form, no known specific cause is defined. In the latter type usually no specific cause is found in history and physical examination and chest x-ray is normal.

The following positive findings on history and physical examination can help the clinicians to differentiate between specific and non-specific chronic cough:

- Daily wet cough or cough with sputum
- Growth and developmental delay (FTT children)
- Clubbing of fingers
- History of hemoptysis in children
- History of recurrent pneumonia in children
- Shortness of breath at rest (Rest dyspnea)
- Shortness of breath at work (Exertional dyspnea)
- Abnormal findings from lung examination (presence of wheezing, rales or crackles, stridor and decreased breath sounds)
- Abnormal findings from cardiac examination (such as heart murmurs)
- Diagnosis of immunodeficiency in children
- Chronic cough lasting more than 6 months
- Cough onset at neonatal or early infancy
- Swallowing disorders in children
- Family history of chronic lung disease
- History of sudden choking and cyanosis (choking) at the beginning of the chronic cough period
- Chest deformities and abnormalities such as a barrel chest
- History of recurrent vomiting in children
- Previous exposure to inhaled environmental allergens, especially smoking (passive smoker)

Other important factors provided by history and physical examination of children with chronic cough:

Previous respiratory problems in children, including history of hospitalization or lung damage (such as chest trauma, surgery or burns with smoke) should be considered. Previous history of recurrent pneumonia may suggest immune deficiency, CF, anatomical anomalies, swallowing problems, or bronchiectasis in children, for example, a child with a history of tracheoesophageal fistula (TEF) and repair can be prone to tracheomalacia and gastroesophageal reflux and chronic cough resulting from them, or in a child with a history of respiratory distress syndrome (RDS) or neonatal severe Hualine membrane disease, restrictive lung disease and obstructive airways disease can be developed.

History of recurrent infections, previous blood transfusions, parental intravenous drug addiction, and growth delay in children may be the key for diagnosis of AIDS in children with chronic cough. History of atopy, such as eczema, atopic dermatitis, hay fever or allergies may be suggestive of asthma in children with chronic cough. Headache, particularly in the early morning and tenderness of the sinus area and possibly tooth pain without lesions of the teeth can be suggestive of sinusitis as a cause of chronic cough.

Poor weight gain, edema without a known cause and shortness of breath, especially during exercise may represent a hidden and progressive heart disease in children. Presence of neurological symptoms such as seizures or neurodevelopmental delays can suggest aspiration syndrome as a frequent cause of chronic cough in children. Fatty stools, bloating and intolerance to fatty foods could be the key for the diagnosis of CF.

2.1. Examination of the Ear, Nose and Mouth

Examination of ears for foreign bodies or signs of infection or rupture of the tympanic membrane and middle ear anomalies as determinants of chronic cough are very important. Transverse lines near nasal wrinkles may present repeated rubbing due to itching and nasal discharge and could represent that child has a history of allergy. Also, dark halo and swelling around the eyes (allergic shiner) or transverse lines below the lower eyelid (Dennie line) could represent a child with atopic cough from an allergic origin. Deviated nasal septum, especially following trauma or congenital anomalies could represent a predisposing factor for sinusitis. Polyps in the nose can represent CF or immotile cilia syndrome. Nasal malodorous discharge, especially one-sided, can represent nasal foreign bodies as the cause of chronic cough in children. Color of nasal mucosa also helps as congested mucosa, identifies infectious rhinitis and sinusitis and pale mucosa implies allergic rhinitis. A stained smear of nasal secretions is helpful too, as increase of polymorph nuclear cells indicate infectious causes and eosinophils indicates allergies.

Poor oral hygiene and dental caries raise the possibility of chronic aspiration syndrome. Examination of palate, for cleft palate and bifid uvula (sub mucous cleft palate) can suggest the cause of cough. Abnormal movement of uvula especially in children with developmental delay can present disturbances in swallowing and raise the possibility of chronic aspiration. Examination of the pharyngeal tonsils and throat to detect cobble stoning patterns can represent large adenoids, which can be seen in allergic children.

2.2. Chest Examination

Increase in the anteroposterior diameter of the chest is important and indicates a barrel chest which is seen in chronic obstructive lung diseases and uncontrolled asthma. The normal diameter is equal to head circumference in

infants, but is larger than that in older children.

Presence of a transverse groove at the bottom of the chest known as the Harrison's groove may be seen in patients with increased work of respiration such as patients with CF or not well controlled asthma, as seen in advance cases of Rickets. In these cases retraction of respiratory muscles, supra clavicular, intercostal and subcostal can be seen. In infants and young toddlers, subcostal retraction is more prominent, as the chest wall is compliant, while at an older age suprasternal and intercostal muscles are more involved.

Accordingly, chronic cough should firstly be classified to one of these categories: expected chronic cough, chronic cough with specific causes and chronic cough with nonspecific causes. The etiologies for the two latter categories are going to be discussed more.

3. Specific Causes of Chronic Cough in Children

3.1. Respiratory Infections

Viral upper respiratory tract infection (URI) can cause a prominent cough named post viral cough and as previously mentioned, they are usually recovered within three weeks, so are not classified as a chronic cough. However, atypical lower respiratory infections sometimes result in chronic coughs. These include viruses such as CMV, RSV, adenovirus, or other micro-organisms such as *Mycoplasma*, *Chlamydia* or *Bordetella* which can cause pertussis-like syndromes (7, 8). Accordingly, in case of suspected infectious causes, antibodies against mycoplasma infection (Cold agglutination) and serology, culture, or PCR of nasopharyngeal secretions for *Bordetella pertussis* can help. Pertussis-like infections are common causes of chronic cough in Iranian children (9). Occasionally, fungal infection such as, histoplasmosis, blastomycosis and coccidiomycosis can cause a chronic cough in children in endemic areas (9).

Nonspecific bacterial bronchitis is an important cause of chronic cough in children and usually manifests as a chronic cough with sputum. Unlike the case of viral bronchitis they usually last more than three weeks, and respond to beta-lactam antibiotic therapy within two weeks (10).

Mycobacterium tuberculosis is among the most important causes of chronic cough in children, especially in developing countries. Presence of chronic cough accompanied by other symptoms such as fever, weight loss, growth failure, history of contact with a person with suspected tuberculosis and a positive PPD skin test for tuberculosis can be strongly in favor. Cough can be caused by; enlarged hilar lymph nodes that put pressure on the main bronchi; bronchial involvement in bronchial tuberculosis; or presence of pulmonary cavities (11). Overall, cough profile in TB can vary from dry cough to cough with excessive sputum (due to bronchiectasis) or cough associated with blood and hemoptysis (12).

3.2. Asthma (Hyperactive Airway Disease)

Asthma is one of the most common causes of chronic cough in children. Although cough is a common symptom in children with asthma, but asthmatic patients are less often presented with coughs alone (13). The characteristic of cough in these patients is a dry cough without sputum that is often worse at nights (14). Allergic cough has a broader range of cough etiologies than asthma alone which include non-asthmatic eosinophilic bronchitis, allergic rhinitis and adenoid hypertrophy with allergic background (15).

According to the GINA definition, asthma is a chronic inflammatory disorder of the airway with hyper-responsiveness that leads to recurrent wheezing, breathlessness, chest tightness and coughing, particularly at night or in the early morning (16).

Clinical diagnosis of asthma is based on its clinical pattern and associated signs and symptoms. Cough associated with wheezing, family history of asthma, eczema or allergic rhinitis, and good response to treatment with bronchodilators especially in younger children, in whom there is no facilities to do spirometry, are strongly in favor of the diagnosis of asthma. Repeated attacks of wheezing, especially after viral infections of the upper respiratory tract, suggest the diagnosis of asthma. Spirometry in children over 6 years and in trained children over 3 years old can be used for accurate diagnosis of asthma (17). Spirometry is used to confirm diagnosis in older children and peak flow measurement is used for evaluating response to treatment in these children (18). Although, normal spirometry does not always rule out the diagnosis of asthma, as it may be normal between attacks or in well controlled patients (19). Rodriguez claimed that there are the following two important, applied criteria for recognition of asthma in children with recurrent wheezing (20).

1) Presence of 3 or more wheezing attacks in a child until the age of 3

2) Presence of a major criterion or two minor criteria in children

Major criteria: Family history of asthma in parents - previous history of eczema in children.

Minor criteria: the presence of allergic rhinitis, wheezing without viral infection of the upper respiratory and eosinophilia in peripheral blood ($4\% \leq$ eosinophils).

There is another condition which is called "cough variant asthma" that presents in some asthmatic children with cough alone without wheezing and usually responds well to bronchodilators and high-dose inhaled corticosteroids for at least 6 to 8 weeks, and often has a better prognosis than patients with asthma (21, 22). Some experts believe that these patients will recover spontaneously without any treatment and so recommend that in patients with dry cough without other symptoms of asthma the best intervention is assurance of parents (23, 24).

3.3. Gastro Esophageal Reflux Disease (GERD)

Gastro esophageal reflux is a common phenomenon in the neonatal period and early infancy (about 50-30%) which is considered as a disease if it is symptomatic. This disease is one of the three common causes of chronic cough in adults with the three common causes being: asthma, GERD, postnasal drip or upper airway cough syndrome. In fact, it is not clear whether gastro esophageal reflux in children can cause a chronic cough or it is a chronic cough that exaggerates to a gastro esophageal reflux. Nocturnal cough in children can imply the possibility of GERD, which results not only the aspiration of gastric contents into the esophagus, but also instability and abnormality of the epithelium of the large airways. In micro aspiration due to reflux, stimulation of vagal receptors in the esophagus can cause a cough. In the case of macroaspiration, presence of lipid laden macrophages in bronchoalveolar lavage (BAL) secretions indicate this disease, although it can be seen in other conditions as well (25).

In gastro esophageal reflux, esophageal PH monitoring is the method of choice for diagnosis, and if at least in 4% of test duration, PH content is less than 4, it is considered to be a positive test (26). As PH monitoring is not feasible, other methods including ultrasound and Barium swallow are alternative procedures with less sensitivity.

In bottle feeding infants who feed in the supine position, bottle propping cause chronic cough and wheezing (27).

3.4. Foreign Body Aspiration

One of the important and potentially serious causes of chronic cough, especially in young children, is foreign body aspiration and is usually seen before the age of 4 and is more common in boys. Although, history of choking and sudden beginning of cough, are very important, yet they are present only in 1/3 of patients. Detailed history may reveal these points in 50% of cases (28). Thus, this has to be considered in all patients with chronic cough.

Comparison of inspiration and expiration chest X-ray and also right and left lateral decubitus in uncooperative children may help identify fixed hyperaeration in favor of foreign body aspiration. Rigid bronchoscopy is the method of choice for diagnosis, but flexible bronchoscopy is sometimes required for the following conditions: evaluation of more terminal airways, airway anomalies, broncho alveolar lavage (BAL).

Principally, foreign body aspiration in children presents as one of the following forms:

1 - Choking and sudden cough, and wheezing after aspiration

2 - Insidious from presents as chronic cough with wheezing

3 - Recurrent pneumonia and constant infiltration indicated by chest x-rays even after treatment

4 - Chronic lung disease due to long-term damage to lung tissue and bronchiectasis.

3.5. Sinusitis

Sinusitis is not common in infants and younger children. Patients with sinusitis, usually have a cough with sputum that is worse early in the mornings. Chronic coughs are usually caused by subacute sinusitis (duration lasts three weeks to three months after onset of symptoms) or chronic sinusitis (more than three months from the onset of symptoms). Therefore, symptoms usually include purulent secretions from the nose and pharynx and nasal congestion rather than fever, lethargy and acute intense headaches which are characteristic of acute sinusitis. Evidences of chronic sinusitis in a child indicate underlying problems, including adenoid hypertrophy, allergic disease, CF, immunodeficiency syndrome and immotile cilia syndrome.

Graphy from sinuses is useful after age of 6 as it reveals, opacification, or mucosal thickening of more than 4 mm and air-fluid levels. However, only 57 to 81% of abnormal sinus x-rays are in favor of sinusitis (29). But still normal sinus x-ray children nearly refuse sinusitis. CT scan of the sinuses, despite its high sensitivity and specificity is only recommended in complicated sinusitis or when sinus surgery is required.

3.6. Bronchiectasis

Bronchiectasis in children can be primary (idiopathic) or secondary. Important causes of secondary bronchiectasis are foreign bodies, CF, immunocompromisation especially humeral immune deficiency and immotile cilia syndrome. When chronic sinusitis is associated with bronchiectasis, the underlying diseases are most common. Purulent abundant sputum is a characteristic of cough in children with bronchiectasis, which aggravates at the beginning of the day and responds just temporary to antibiotic treatment. Persistent cough more than 3 months, recurrent cough (A recurrent coughs without a cold are taken as repeated (> 2/year) cough episodes—apart from those associated with head colds—where each lasts more than 7-14 days) (30) or clubbing in children may suggest underlying pulmonary disorders such as bronchiectasis (31). Lung scan particularly high resolution CT scan (HRCT) is a precise and selective tool for evaluation of airways, especially diagnosis of bronchiectasis, however 87% of patients have abnormalities in chest x-rays as well (32).

3.7. Congenital Anomalies

Congenital anomalies that can cause chronic cough in children include the following:

Laryngotracheomalacia, tracheoesophageal fistula (TEF) and the H-type form, laryngeal cleft, cleft palate (especially the membranous type), the presence of ectopic thoracic artery (aberrant vessels), bronchogenic cyst, pulmonary sequestration, discoordination of swallowing muscles and congenital anomalies of the heart. The characteristics of coughing in congenital anomalies begin at the neonatal pe-

riod or early infancy with typically dry coughs. Sometimes the cough can be wet with sputum such as alveolar proteinosis (33). In some cases, such as muscle discoordination or TEF, coughing is stimulated by feeding.

3.8. Inhaled Allergens

Environmental factors and inhaled allergens are important causes of chronic cough in children. Accordingly, the most important cause is being a passive smoker, which can increase the rate of respiratory infections, including sinusitis in children (that can also cause chronic coughs) (34). The effects of maternal smoking are far greater than paternal habits. Other effects of smoking are increased rates of asthma and reactive disease in them.

In dealing with chronic coughs in children and possibility of inhaled allergens as the cause, removing the child from exposure to potential allergens for at least two weeks and observing improvements is the diagnostic (35, 36).

4. Rarer Causes of Chronic Cough in Children

4.1. Drugs

Cough can be induced by consumption of angiotension converting enzyme drugs such as captopril or enalapril. This side effect occurs in 5 to 10 percent of consumers where patients present dry coughs within a few weeks to a few months after initial consumption of the drugs and this is not related to the dose of the drug and will resolve after drug discontinuation (37). Use of beta-receptor antagonists such as propranolol may cause bronchoconstriction and increased asthma symptoms in children and can result in chronic cough.

4.2. Irritation of Auditory Cough Receptors

This irritation can result from excessive cerumen or cholesteatoma in the external auditory duct. Therefore, it is necessary to examine the ear in children with chronic cough.

4.3. Chronic Cough After Surgery

Thoracic surgery, especially open heart surgery due to stimulation of the vagus nerve can be the cause of chronic cough in children.

6. Evaluation of Children With Chronic Cough

Assessment of the prevalence of chronic cough in children due to various factors is somewhat different from its evaluation in adults. On the other hand, the age of the child has a major role in determining etiologies of chronic cough, so management in children is different for those under and over 6 months old. Causes of chronic cough, in

the age group under 6 months are congenital abnormalities, gastro esophageal reflux, CF and pertussis-like syndrome and asthma, tuberculosis, sinusitis, bronchiectasis, foreign body aspiration, humeral immunodeficiency syndrome and immobile cilia, that usually present after 6 months (Figure 1).

6.1. Evaluation of Chronic Cough in Children Under 6 Months

In this age group, after taking a detailed history, onset of chronic cough is determined. After rule out of the causes of pertussis-like syndrome and a possible encounter with al-

lergens, it is recommended to do chest x-rays.

If the cough starts early after birth, and the chest x-ray is normal, barium swallow is recommended for the diagnosis of gastro esophageal reflux, TEF, aberrant vessels, and un-coordination of the swallowing muscles. A normal barium swallow indicate sweat test for CF screening which is one of the common causes of chronic cough in the first few months after birth. In case of an abnormal chest x-ray or any clinically suspected congenital anomalies, pediatric surgical consultation is recommended. In the case of cardiac abnormalities, pediatric cardiology consultation and echocardiography should be performed (41).

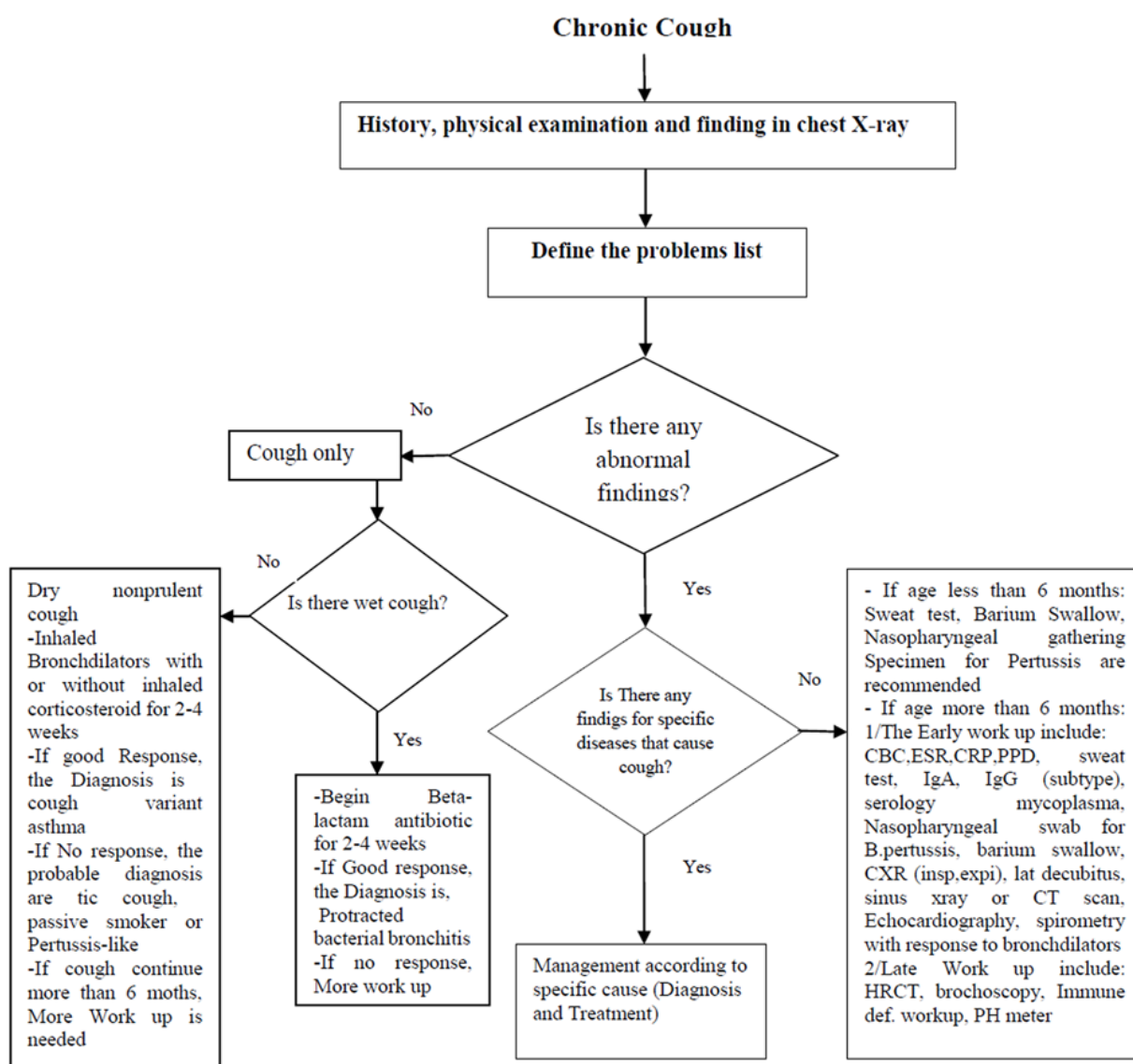


Figure 1. Approach to Child With Chronic Cough

6.2. Evaluation of Chronic Cough in Children Over 6 Months

In this age group, also obtaining the history and physical examination after confirmation of chronic cough is recommended (42). In case of abnormal examination or suspected history of underlying disease or abnormal x-ray, the term "chronic cough with specific disease" is used in which any early work up for the particular suspected disease should be performed which include the following:

CBC, Diff, ESE, CRP, PPD skin test, sweat test, PH monitoring test or barium swallow, measuring immunoglobulin, including IgM, IgG, IgA, IgE, graphy of sinuses, chest x-rays in inspiration and expiration or bilateral decubitus chest x-rays. Late work up and additional tests should be done for cases with the most likely causes of a chronic cough.

In a lack of specific clinical suspicion diagnosis and normal initial tests but continuing chronic cough, high resonance tumography (HRCT) with or without bronchoscopy is recommended. These tests are requested based on the patient's condition and the possibility of specific etiologies for chronic cough and not for all children, as CT scans have a risk of high radiation for children (10 times more than adults) and bronchoscopy has the risk of general anesthesia, so both should be undertaken with caution (43, 44).

In cases where the patient's history, physical examination and chest are normal, chronic cough is considered as non-specific and the evaluation is done according to the type of cough in children. If there is dry cough without sputum, asthma is probable and patients are treated with bronchodilators with or without inhaled corticosteroids at high doses (400 mg daily) for 2 weeks. If the response is partial, cough variant asthma is considered and treatment can be continued for an additional 4-6 weeks (11).

And, if cough is wet or with sputum, by considering probable bacterial bronchitis treatment with co-amoxiclav (40 mg/kg/day amoxicillin content) with or without a macrolide is monitored for two weeks and if partial response or relapse are seen, antibiotic may continue for a maximum 3-4 weeks (21). In the case of cough and failure to respond to initial treatment or in case of nervous tic cough, the parents should be ensured that no special treatment is needed.

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