Therapeutics, Pharmacology and Clinical Toxicology
Vol XIII, Number 2, June 2009
Pages 196-204

CHRONIC COUGH IN CHILDHOOD: A CLINICAL AND THERAPEUTIC APPROACH

Doina Pleşca[1], Victoria Hurduc[1], Iulia Ioan[1], Anca Bădărău[2]

[1.] *Pediatrics and Pediatric Neurology Department, "Dr. Victor Gomoiu" Clinical Hospital for Children, UMF "Carol Davila", Bucharest*
[2.] *Department of Physiology, UMF "Carol Davila", Bucharest*

Abstract. The article is divided of two parts. In the first part, the authors discuss about the chronic cough, a subject of a great interest in pediatric practice. Physiopathology, the most important etiologic categories, clinical and paraclinical data, principles of therapy of chronic cough are reviewed.
The authors underline the importance of the history of the disease, in establishing the cause of chronic cough in children. A cough that worsens at night may be caused by sinusitis, asthma, or gastroesophageal reflux. The cough that disappears during sleep, suggests a psychogenic cause.
Clinical examination has to be thorough, complete and repeated, focused on ENT segment, chest, respiratory and cardio-vascular system. When clinical data and history cannot establish the cause of chronic cough, paraclinical evaluation is necessary. Any child with chronic cough, no matter the age, must have chest X-Ray examination to eliminate aspiration of foreign body or another severe disease (congenital anomaly, cystic fibrosis, bronchiectasis, cardiomegaly, mediastinal mass).
In the second part, the authors present the main clinical entities (cough variant asthma and eosinophilic bronchitis, cough during and after respiratory infections, allergic rhinitis, chronic sinusitis and rhinoadenoiditis, passive smoking, gastroesophageal reflux, bronchiectasis, aspiration syndrome / foreign body aspiration, deglutition difficulties, vocal cords dysfunction, compression syndrome, psychogenic cough, otogenic causes - Arnold ear – cough reflex, cough as a side effect of the medication) and the etiologic treatment.
The indications of an etiologic treatment have to be influenced by a detailed history of the disease and by clinical examination. In the absence of an etiologic factor, the patient will receive symptomatic treatment only if the cough is responsible for awakeness, vomiting and fatigue. Tolerability of cough is the element that determines the indications for inhibitors of cough.
Keywords: algorithmic approach to the diagnosis, chronic cough, child

General data

The respiratory diseases in childhood account for a third of the family physician visits. The main symptom of the respiratory diseases is coughing; cough is a very common complaint initiating visits in pediatric offices; approximately 6% of pediatric office visits involved children who presented with cough.

In USA, a survey in 1995-1996 regarding the reasons for pediatric office visits showed there were approximately 24 million visits only for children who presented with cough. Among them, 47,7% involved children up to 15 years of age.

In the UK, cough, not associated with infections, had an estimated prevalence of 28.5% in boys and of 30,3% in girls. Other two surveys (Chang AB

Prof. Dr. Doina Pleşca, MD, PhD
Pediatrics and Pediatric Neurology Department,
"Dr. Victor Gomoiu" Clinical Hospital for Children,
21, Basarabiei Blvd, sect.2, Bucharest
Phone: 021.323.22.30; 021.321.20.42

and co., 2001), using an electronic registry, showed how often the healthy children had presented with cough. Cough paroxysms average in 24 hours was 11,3 with large variations between one and 34.

The respiratory symptoms are usually caused by common, self-limited diseases, but there are many serious diseases that may also result in cough (including congenital pulmonary malformations, congenital heart defects, cystic fibrosis, bronchiectasis, etc.).

Cough lasting more than three weeks is conventionally considered "chronic cough", and it seldom creates difficulties regarding the differential diagnosis.

Pediatric cough can be classified in many ways, regarding etiology, duration, features and specific and nonspecific cough. The pediatric chronic cough is estimated by its duration of 3 – 12 weeks. A prospective study showed that the residual cough after upper respiratory tract infections tends to spontaneously remit in 1 – 3 weeks. A prospective cohort study of preschool children showed that they also had a residual cough even in the twenty-fifth day after an upper respiratory tract infection.

Irwin and Madison (2000) classify cough in three categories: acute cough with a shorter duration (approximately 3 weeks), subacute cough (between 3 and 8 weeks) and chronic cough (over 8 weeks). This classification excludes many cases with self-limited cough. The acute upper respiratory tract infections, the most common pediatric diseases (70-90%, Jeremy Hull, 2008), are the main causes of acute cough. Patients with subacute cough may have a recent history of upper respiratory tract infection or seasonal allergic rhinitis. Patients with chronic or recurrent cough may have an underlying disorder which has to be discovered and treated.

2. Physiopathology of cough

Cough is an airway protective reflex triggered by two main mechanisms namely direct stimulation of cough by secretions or foreign particles and the increase of receptors' sensitivity by decreasing the cough threshold.

The main trigger organs are the larynx and the lower airways. The cough is initiated by mechanical, inflammatory and chemical stimuli. In the cough reflex three distinct types of receptors are involved: some are located in the muscular wall of the bronchi (*slow adapting receptors*), some are located in the airways mucosa (*rapidly adapting receptors*) and the *"C" fibers*, which trigger the cough by releasing neuropeptides, such as substance P, are located in the tracheobronchial mucosa.

These receptors, stimulated by different agents, send out information to the central nervous system or to other cough regulating systems. Cough is initiated from organs innervated by the afferent pathway through the vagus nerve (larynx, lower airways, tympanic membrane and the outer ear, esophagus, intraabdominal organs) that relays with the cough control center in the respiratory area of the brainstem. The efferent pathway of the reflex arch through the recurrent nerves, intercostal nerves and phrenic nerve transmit impulses toward the diaphragm and the intercostal muscles, causing them to contract (figure 1).

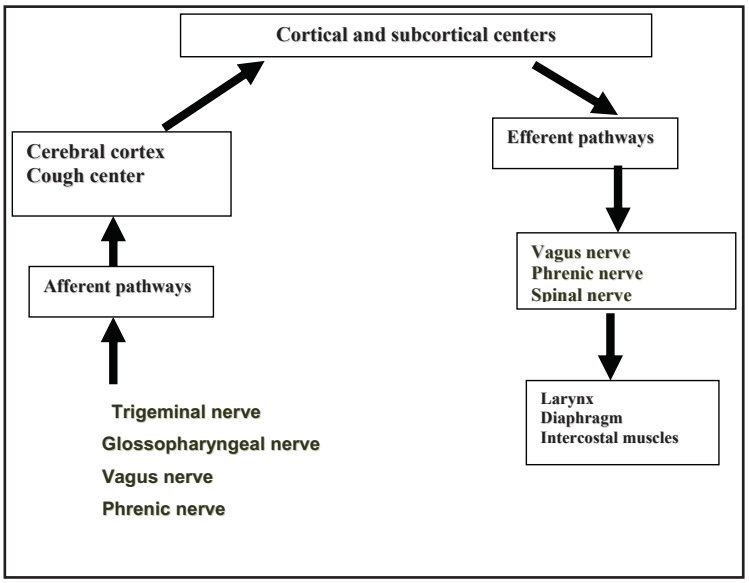

Figure 1. The components of cough reflex

3. Etiology

The causes of pediatric cough vary with several parameters: age, duration, character, the timing of the onset, association to other signs and symptoms, exposure to different pollutants, family history, etc. The main disorders presented with pediatric cough are listed in Table I.

1. Congenital malformations:
- of airways / esophagus
- Laryngotracheomalacia
- Bronchopulmonary malformations
- Congenital mediastinal tumors
- Congenital heart defects associated with congestive heart failure

2. Infectious or post-infectious cough
- Recurrent viral infections
- Chlamydia, Bordetella pertusis, Mycoplasma pneumoniae infections
- Granulomatous infection (fungal infection)
- Suppurative lung diseases (cystic fibrosis, foreign bodies, ciliary dyskinesia)
- Immunodeficiencies (primary, secondary)

3. Asthma
- cough-variant asthma
- eosinophilic bronchitis

4. Rhinitis
- allergic
- rhino-sinusitis
- vasomotor rhinitis

5. Gastroesophageal reflux
6. Vocal cords dysfunction
7. Aspiration (of fluid substances)
8. Foreign body aspiration
9. Physical and chemical irritation
- active or passive smoking,
- dust, volatile substances, moisture

10. Psychogenic cough
11.Habitual cough

Table I. Causes of chronic cough (adaptation from Henty Milgrom, 2003)

4. Evaluation of cough

Evaluation of chronic cough involves a complete history, a complete physical examination, laboratory tests and imaging studies, in order to establish an appropriate diagnosis and treatment.

4.1. History

A methodical approach to the assessment of a case of chronic cough is of great importance. The history is essential; the timing of the onset of cough, the onset age, the recurrent character and the dry and irritant or productive character should all be sought. The time of day when cough occurs, its triggers and exacerbating factors (during the day or at night, in decubitus position, exercise – induced, exposure to cold air) also need to be explored. The medical history will determine the importance of the environment, mainly the influence of passive smoking.

The onset and duration of the symptoms also suggest the character of the cough: acute, subacute or chronic. The child's age may influence the differential diagnosis. Certain pathological conditions (bronchial hyperreactivity, chronic rhinorrhea, infections etc.) are common causes of cough during childhood, while other may be present only in certain ages (Table II).

Infants
- Respiratory tract infections: Chlamydia trachomatis, Bordetella pertussis, Pneumocystis carinii
- Post-infectious causes: RSV, parainfluenza V, influenza V, rhinoviruses, adenoviruses
- Aspiration/gastroesophageal reflux
- Exposure to tobacco smoke
- Cystic fibrosis
- Congenital malformations (pulmonary and cardiac)
- Deglutition disorders
- Airway hyperreactivity/asthma

Preschoolers (1-6 years) - early childhood
- ENT infections (acute, subacute, chronic or mixed sinusitis and rhinitis)
- Postinfectious (RSV bronchiolitis, whooping cough)
- Chronic adenoid/tonsillar hypertrophy
- Atopia/allergic rhinitis
- Asthma
- Passive exposure to tobacco smoke
- Gastroesophageal reflux disease
- Foreign body aspiration
- Cystic fibrosis
- Bronchopulmonary malformations
- Sequelae of esophageal atresia
- -Immunodeficiency syndrome

School-age child – late childhood
- Asthma
- Maxillary sinusitis (acute, subacute, chronic), rhinitis
- Gastroesophageal reflux disease
- Psychogenic cough
- Passive exposure to tobacco smoke/smoking

Table II. Causes of chronic cough according to age

- Respiratory tract infections (Mycoplasma, B. pertussis)
- Cystic fibrosis
- Immunodeficiencies
- Mediastinal tumors
- Episodic laryngeal dysfunction
- Bronchial dilatation

Adolescent

- Asthma
- Sinusitis, rhinitis
- Gastroesophageal reflux disease
- Psychogenic cough
- Smoking
- Respiratory tract infections (Mycoplasma, B. pertusis)
- Cystic fibrosis

Table II (continued) Causes of chronic cough according to age

The timing of the cough's onset is essential for the diagnosis. For example, the presence of a nighttime cough is consistent with asthma or sinusitis/rhinosinusitis. Cough upon awakening is characteristic of bronchiectasis or cystic fibrosis. Exercise – induced cough may be seen in asthma, bronchiectasis or cystic fibrosis. Cough accentuated in the decubitus position may be caused by sinusitis, rhinitis, asthma or gastroesophageal reflux disease. Contrarily, cough which disappears at night suggests a psychogenic etiology.

Another factor to consider in the diagnosis is the character of cough. A productive cough is an important sign, characteristic of an infection or an airway reactive disease, a brassy cough usually suggests a tracheitis or, sometimes, a psychogenic cough. A "barking" cough is consistent with laryngeal edema and croup, a paroxystic cough is characteristic of whooping cough, a tracheobronchial foreign body, a respiratory tract infection with atypical bacteria (*Mycoplasma pneumoniae, Chlamydia, etc.)*.

Other associated signs and symptoms may aid in finding the etiology of cough (Table III). Fever, weight loss, night sweats, weakness, may be symptoms of a serious systemic disorder (malignant disorders, juvenile chronic arthritis, cystic fibrosis) or a serious infection (TB - tuberculosis, histoplasmosis, mononucleosis, HIV etc.).

Ocular and/or nasal irritation (itching and runny nose, nasal and eye congestion, tearing eyes) suggest an allergic disorder, and rarely, an exposure to irritants. Recurrent sinopulmonary and otic infections may be seen with humoral immunodeficiency (hypogammaglobulinemia) or with structural abnormality (ciliary dyskinesia).

Pointers	Possible causes
Cough exacerbated in decubitus position	Sinusitis, postnasal drip, asthma, gastroesophageal reflux disease (GERD)
Cough which disappears with sleep	Psychogenic cough
Harsh, "brassy", stridorous cough	Pertussis, psychogenic cough, laryngeal anatomic anomalies
Harsh cough in an infant with respiratory distress and triggered by food	Double aortic arch, vascular ring, eso-tracheal fistula
Throat clearing	Rhinitis, sinusitis, GERD
Productive cough	Infections, asthma
Dry cough	Asthma, allergic rhinitis, foreign body
Exercise – induced cough	Asthma
Cough induced by weather changes	Allergic rhinitis, asthma
Constitutional signs and symptoms	Systemic diseases, infections, immunodeficiencies
Ocular and/or nasal irritation, runny nose, nasal congestion, tearing eyes, ocular and/or nasal pruritus	Allergic disorders, exposure to irritants
Sinopulmonary infections or recurrent otitis media	Immunodeficiencies, primary ciliary dyskinesia
Pyrosis, nausea, chest pain or retrosternal discomfort or sourness	Gastroesophageal reflux disease
Swallowing or choking on food or other substances / objects weeks before the onset of cough	Foreign body aspiration

Table III. The medical history: pointers to specific cause of cough

Gastrointestinal symptoms (pyrosis, nausea, retrosternal discomfort, sourness, etc.) are consistent with gastroesophageal reflux disease. Recurrent vomiting associated with failure to thrive or weight loss suggest gastroesophageal reflux disease in infancy.

The familial history of atopic diseases, asthma, cystic fibrosis, exposure to environmental pollution (smoking, toxics, kerosene etc.), the onset of coughing when cleaning the house (allergic sensitivity to house dust), should be assessed.

Exposure to passive smoking may be present in about 30 % of family houses. Parental smoking must be enquired during evaluation of chronic cough in a child because the single and most efficient "treatment" is avoiding smoking exposure.

The specific history data (preterm birth, baby bottle feeding problems, presence of pulmonary or cardiac malformations, bronchiolitis, eczema, asthma), the living environment, if the child goes to nursery school, kindergarten or school or if he ever had a contagious disease transmitted from the persons around him (communicable disease) should be recorded.

Data about the immunization schedule, recent history of contact with an infected person, assessment of risk factors for tuberculosis and IDR to PPD should be considered.

4.2. Physical examination

In a child with chronic cough, the clinical examination has to be thorough, complete and repeated, focused on ENT segment, chest, respiratory and cardiovascular systems.

Failure to thrive (in height and weight) is consistent with a chronic disorder, chronic cough being a secondary symptom.

The characteristic facial features (dysmorphic, adenoid features etc.) are an important clue which helps to diagnose an ENT disorder. Sensitivity to pressure or tapping over the maxillary and/or frontal sinuses associated with other symptoms (nasal obstruction, rhinorrhea) lasting more than 7 or 10 days, is highly suggestive of sinusitis or rhinosinusitis. A foreign body present in the external auditory meatus may sometimes stimulate the cough reflex. Hoarseness associated with harsh, "brassy" cough is consistent with a vocal cord dysfunction.

An increased anteroposterior diameter of the chest and hyperresonance on percussion is characteristic for hyperinflation of the lungs. This is frequently related to asthma or cystic fibrosis.

Pointers	Possible causes
Allergic features or Morgan lines (Dennie sign), pallor of nasal mucosa or rhinorrhea, paving stones appearance of the nasal and posterior pharyngeal mucosa	Allergic rhinitis
Sensitivity to pressure or tapping over the maxillary and/or frontal sinuses	Sinusitis
Hyperinflation	Asthma, cystic fibrosis
Unilateral pulmonary hyperresonance or dullness to chest percussion	Foreign body aspiration, atelectasis, pleural effusion
Wheezing during spontaneous respiration or during forced exhalation	Asthma
Stridor or severe wheezing	Tracheal stenosis, tracheomalacia or intraluminal tracheal masses
Digital clubbing	Cystic fibrosis, bronchopulmonary suppurations
Nasal polyps	Cystic fibrosis
Eczema	Allergies / Asthma
Dyspnea/tachypnea	Any parenchymatous pulmonary disease or respiratory tract disease
Dyspnea on exertion	Any parenchymatous pulmonary disease or respiratory tract disease
Deformation of the chest wall	Any parenchymatous pulmonary disease or respiratory tract disease
Neurological development anomalies	Pulmonary aspiration

Table IV. The physical exam pointers to specific cause of cough

Unilateral pulmonary hyperresonance or dullness to percussion suggest bronchial obstruction due to foreign body aspiration, atelectasis or pleural effusion.

The careful examination of the skin may reveal the presence of hemangiomas; these may also coexist in the airways wall. Skin lesions located on the face or on the extension areas of limbs suggest an atopic disorder.

Stridor or severe wheezing may be related to narrowing of the trachea, tracheomalacia or an intraluminal tracheal obstacle. Infants with severe wheezing audible in the sternal area may suggest a compression syndrome due to a vascular ring.

The cardiovascular exam has to be carefully performed because cough may be a symptom of the congestive heart failure associated with a congenital heart defect (ventricular septal defect etc.). Other heart lesions resulting in an atrial or pulmonary artery dilatation may determine airways compression, cough and wheezing.

Table IV presents the main clinical features associated with chronic cough helpful for the etiologic diagnosis.

Figures no. 2 and 3 show a diagnostic algorithm for evaluating pediatric chronic cough according to age.

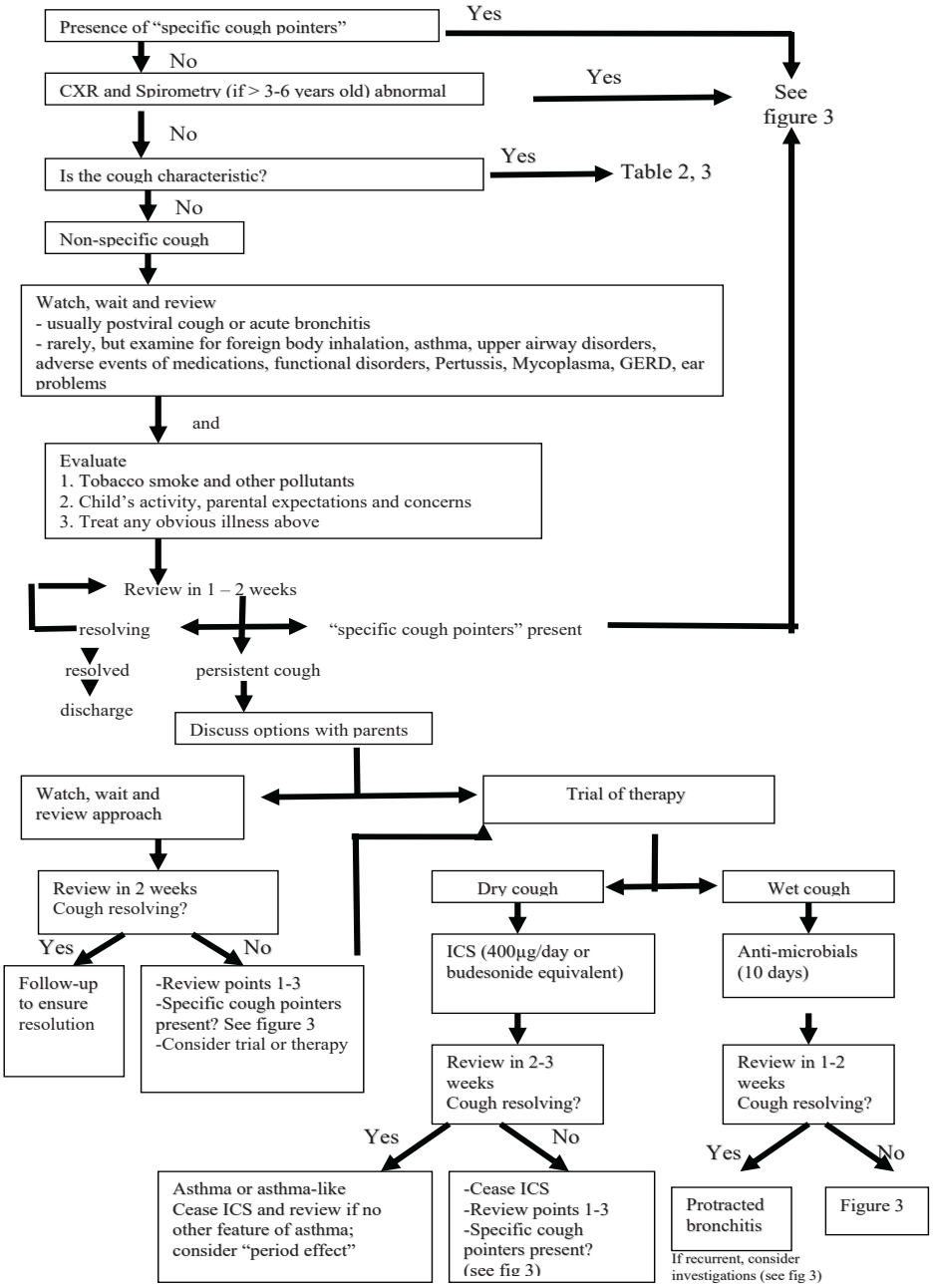

Figure 2

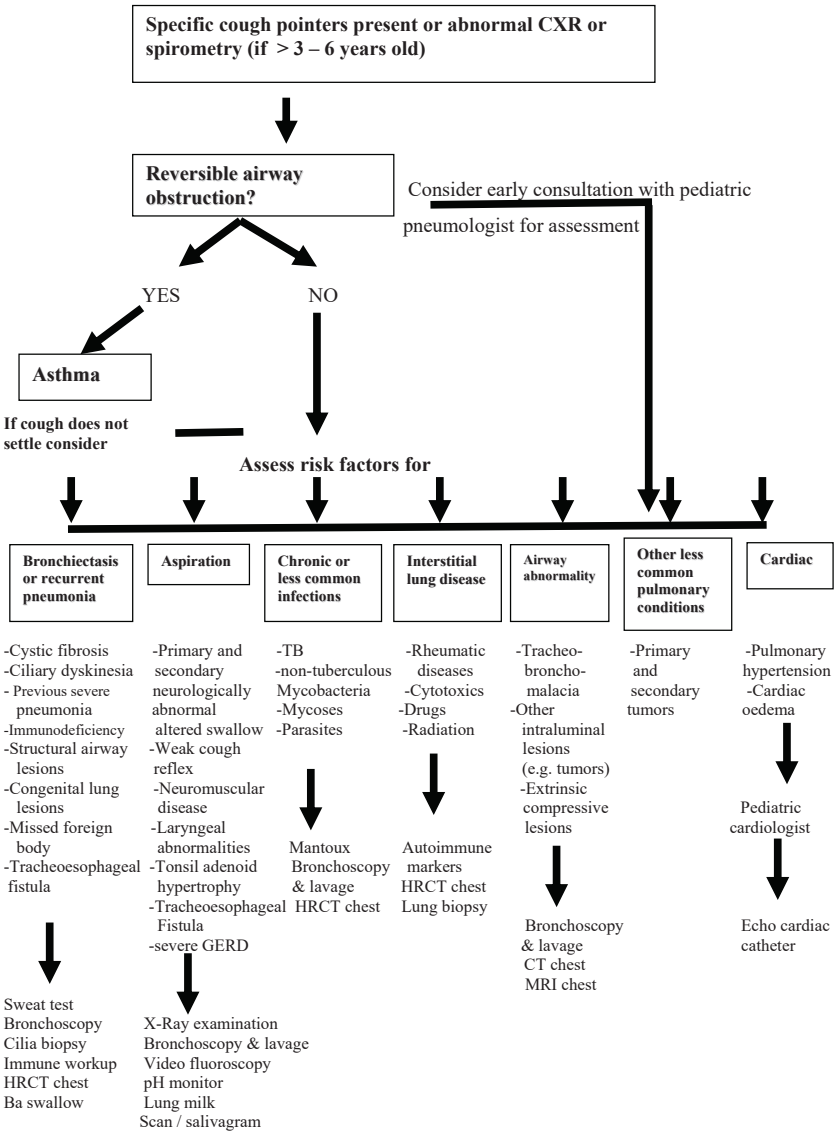

Figure 3

4.3. Laboratory studies

If the medical history and the physical examination do not establish an etiologic diagnosis for the chronic cough, detailed laboratory studies are required.

Table V presents the main laboratory studies recommended in the assessment of chronic cough in childhood

For any child at any age, with unexplainable chronic cough, a chest X-ray is recommended in order to exclude a foreign body aspiration or a serious disorder (congenital anatomical anomalies, bronchiectasis, cardiomegaly, mediastinal masses etc.). When the chest X-ray is normal or it shows hyperinflation or thickening of the peribronchovascular interstitium, it is recommended to perform pulmonary function testing before and following a bronchodilator administration. If the response following the bronchodilator is favorable, it is highly suggestive of asthma. If after a week, the patient's symptoms do not improve, it is necessary to extend the investigations.

If the chest X-ray is normal, the pulmonary function testing is normal and the child is over 5 years of age, bronchial provocation tests or effort tests can be performed for a better assessment of the bronchial hyperreactivity.

If the patient presents with bronchorrhea, the sputum examination is essential, appreciating the color, volume and odor. Bronchorrhea may be seen by strongly pressing down the base of the tongue with a tongue depressor (strongly coughing maneuver which allows the sputum to be expectorated in the laryngeal orifice where it can be seen).

Tuberculin skin test will be performed when the cause of the cough is not discovered and the child

Test	Indication
Chest X-ray	Chronic unexplainable cough at any age
Pulmonary function testing (before and following the bronchodilator administration)	The chest X-ray is inconclusive and the child is over 5 years of age
Bronchial provocation test (histamine, methacholine)	Pulmonary function testing results are normal and the child is over 5 years of age
Pulmonary function testing in early childhood (limited availability)	Chronic cough or wheezing in children up to 3 years of age
Barium radiology	Stridorous cough in children, right aortic arch seen on chest X-ray, suspicion of gastroesophageal reflux disease (GERD)
Flexible bronchoscopy	Suspicion of foreign body aspiration, unexplainable cough with anomalies on chest X-ray
Tuberculin skin test	Weight loss, recurrent fever, night sweats, anomalies on chest X-ray, history of tuberculosis contact
Paranasal sinuses X-ray / CT	Cough predominantly at night, rhinorrhea lasting more than 7 days, facial sensitivity
Sputum examination (Gram staining, AFB staining, cultures)	Productive cough at any age
Sweat test	Recurrent respiratory tract infections, more than 2 episodes of pneumonia per year, failure to thrive, pansinusitis, digital clubbing

Table V Laboratory and imaging studies for the evaluation of chronic cough
(adaptation from Meeghan Hart, 2001)

presented with malaise, weight loss, night sweats, history of tuberculosis contact or he is from an endemic area.

Sweat test will be performed on any child presented with chronic cough, persistent wheezing, nasal polyposis or who had more than two episodes of pneumonia per year. Pansinusitis, failure to thrive, digital clubbing are indications to perform the sweat test.

If there is a suspicion of gastroesophageal reflux disease or aspiration syndrome, barium radiology and an esophageal pH monitoring have to be performed.

A complete hemogram for assessing the number of leukocytes and eosinophils, and determining the E immunoglobulines are necessary to discover an infection or an allergic disorder.

If there is suspicion of a foreign body aspiration as cause of chronic cough, a bronchoscopy will be performed. If the cough is associated with an unilateral pulmonary infiltrate / opacity, a flexible fiberoptic bronchoscopy is indicated. If there are no particular signs or symptoms in the physical exam or radiological studies, bronchoscopy will bring supplemental information only in 5 % of cases.

The whooping cough incidence is increasing and its diagnosis may be difficult to establish in previously immunized children that have nonspecific symptoms. *Bordetella pertussis* may be found in the nasal exudate (ELISA, PCR, cultures).

Pulmonary CT is the "gold standard" for evaluating the structural integrity of small airways and is more sensitive than the spyrometric indices. The utility of CT-scan must be counterbalanced by the increase of the risk for cancer which depends on age and dose. Although the risk is negligible, children have a 10 times higher risk than adults of average age. For a single CT-scan of 200 mA, the mortality risk for cancer is of 1 in 1000 – 2500 for a child of 2.5 years of age. So, while CT-scan, and especially CT-scan of sinuses, have very well-defined roles in evaluating pediatric cough, they do not have to be routinely performed if there are no other symptoms. It is recommended to first visit a pediatric pneumologist because different types of CT-scan (conventional, spiral and high resolution) have different indications and exposure to radiations and depend on the type of the suspected lesion.

Bibliograpy

1. Brown M., Erika von Mutius, Morgan WJ, Clinical Assessment and diagnostic Approach to Common Problems in Pediatric Respiratory Medicine, **Taussing LM, Landau LI, Martinez F.(eds), second edition, Mosby Elsevier, 2008, 117-120**

2. Chang AB., Glomb WB., Gudelines for Evaluating

Chronic Cough in Pediatrics:ACCP Evdence-based Clinical Practice Guidelines, *CHEST* **2006; 129; 260-283**

3. Chang AB, Phelan PD, Randomised controlled trial of inhaled salbutamol and beclomethasone for recurrent cough. *Arch. Cis Child* **1998; 79:6-11**

4. Hart M. Kercsmar, Chronic cough in children: a systemic approach, *The Journal of Respiratory Diseases for Pediatricians,* **nr. 3, pg.155-165, 2001**

5. Vital and Health Statistics: National Ambulatory Medical Care Survey: 1995-1996, **summary, nr. 142**

6. Singh D., Arora V., Chronic/recurrent cough in rural children in Ludhiana, *Indian Pediatr.* **2007, 39, pg. 23-29**

7. Chang A.B., Phelan PD., Frequency and perception of cough severity, *J. Paediatr. Child Health,* **37, pg. 142-145, 2001**

8. Munyard P., Bush A., How much coughing in normal?, *Arch. Dis. Child,* **74, pg. 531-534, 1996**

9. Irwin RS, Madison JM, The diagnosis and treatment of cough, *N. Engl. Journ. Med.* **343, pg. 1715-1721, 2000**

10. Chang RS, Harrhy VA, Simpson J., Cough, airway inflammation and mild asthma exacerbation, *Arch. Dis. Clild,* **86, pg.270-275, 2002**

11. Ehlenfield DR., Cameron K., Welliver RC., Eosinophilia at the time of respiratory syncitial virus bronchiolitis predicts childhood reactive airway disease, *Pediatrics,* **105, pg. 79-83, 2000**

12. Chang A.B., Asher M.I., A review of cough in children, *Journal of Asthma,* **38, pg. 299-309, 2001**

13. Chang A.B, Cough, cough receptors and asthma in children, *Pediatr. Pulmonol.,* **28, pg. 59-70, 1999**

14. Milgrom H., Chronic cough, în Leung D.Y.M., Sampson HA, Geha RS. (eds):Pediatric Allergy- Principles and Practice, *Mosby,* **pg. 321-334, 2003**

15. Delacourt C, Physiopathologie de la toux, *Arch.pediatr.,* **vol.8-suppl.3, pg.600-603, 2001**

16. Dutaut G. Et. al., La toux chronique de l enfant: grandes etiologies et arbre decisionnel, *Arch.pediatr.,* **vol.8-suppl.3, pg.610-623, 2001**

17. Manach Y., Toux chronique d origine ORL, *Arch.pediatr.,* **vol.8-suppl.3, pg.635-638, 2001**

18. Roger G et al., Dysfonction laryngee episodique, *Arch. pediatr.,* **vol.8-suppl.3, pg.650-655, 2001**

19. Bacharier LD., Strunk RC., Vocal cord dysfuncțion: A practical approach, *The Journal of Respiratory Diseases for Pediatricians,* **nr. 3, pg. 33- 48, 2001**

20. Oommen A., Lambert PC, Efficacy of a short course of parent-initiated oral prednisolone for viral wheeze in children aged 1-5 years: randomised controlled trial., *Lancet* **2003; 326:1433-1438**