"Cough in Children" New Perspectives

Edition-1

E-Book

PAST
KNOWLEDGE PEOPLE

2024

PABLO CORTES BORREGO M.D.

https://www.opastpublishers.com/

INDEX

Preface

There are continually important changes in our understanding of respiratory diseases in children, in their physio pathogenesis, epidemiology, genetics, molecular biology, in their pharmacotherapy, etc. Paradoxically, a relatively new field of research is the interpretation of cough as a generator of important data to diagnose the disease that produces it. Perhaps there are 2 exceptions in relation to this: the coughing spells of whooping cough and those produced by laryngotracheitis, whose presentations are very characteristic and to the clinician they strongly suggest both diagnoses.

Since cough can occur in both the upper and lower airways, who should diagnose and treat cough has been left relatively adrift. There is no doubt that cough in children should be managed by the pediatrician, however both otorhinolaryngologists and pulmonologists have studied cough from their particular points of view, that is, some from the upper airway and the others from the upper airway. low air, which has contributed little to its study and management in daily practice.

The ideal would be, as it has been interpreted until now, that all coughs would be treatable with a cough suppressant in syrup form and that this would reduce it significantly enough for the child to carry out his daily activities normally and sleep without annoying fits., which unfortunately does not usually happen. Medical records usually investigate the cough, in a rather "panoramic" way, so to speak, asking if it is wet or dry and if there is the presence of expectoration and its characteristics (when the child is able to expectorate). It is extremely difficult to make a diagnosis with these isolated data.

The fundamental purpose of this book is to facilitate finding characteristics in cough, which guide the professional to find the anatomical site of cough production, the causal mechanism and decide on a targeted treatment. It should not be very difficult to reconsider the semiological (not physio pathogenic) view of cough, I am convinced that with each illness. Its, children cough differently and/or show different data added to their cough, on which the clinician's attention can be focused to find the anatomical site where the stimulus to cough occurs and suggest its cause. The study of cough in children has been difficult because there is no strategy that carries an anatomical logic of the site and why the cough occurs according to stratifying various data on the cough itself and other underlying symptoms.

People around the world use a large number of home remedies in an attempt to relieve cough, largely because current medicine has not solved the diagnostic problem and because many of the causes of cough resolve spontaneously within a few days started.

During time immemorial, human beings have tried to cure the annoying cough, where tuberculosis surely played a predominant role since it caused chronic coughing (and coughing) until death, so that cough has also been considered a symptom. ominous, until relatively recently incurable and from which many of the homemade attempts to reduce it were surely born. Until much later, cough was considered to be part of a complex and nonspecific defense system. Even so, it is too annoying, often affecting the quality of life more than the disease that causes it. The history of the search for an effective antitussive is long, with the appearance of multiple medications, regardless of their cause and their site of production (upper or lower airway). Most have been ineffective, and those that were effective, such as codeine, are only usable in very special circumstances.

The cough caused by tuberculosis or bronchiectasis is very annoying, very chronic and represents a social impediment for those who suffer from it (even for children). On the other hand, trying to artificially suppress cough in these subjects represents a medical contradiction. To reduce cough in the previous examples, anti-tuberculosis medications must be given or remove the lung tissue injured by bronchiectasis if conditions allow it (for example, if they are located in a single lobe), those actions in those certain cases would be the best "cough suppressants."

Another example is cough caused by asthma, whose best cough suppressant with practically immediate action is specifically represented by bronchodilators, even when it is necessary to add anti-inflammatories to inhibit, to a greater or lesser extent, its recurrence and thus, each type or cause of cough requires a specific treatment. Until now, trying to treat cough nonspecifically, with a medication that treats both wet coughs and dry coughs, has been a pipe dream. In order to treat cough specifically, that is, to give each type of cough the treatment that exactly corresponds to it, a very solid diagnostic basis is required, starting with considering that non-specific cough, that dry cough that has no data sufficient companions to suggest a cause, it is rather rare. Cough is almost always accompanied by findings that we can rely on to direct the diagnostic route, whether the type of cough, the hours during the day of presentation, the age of the patient, the time of year, the time of evolution, etc.

This book aims to be a guide so that in a systematic way, through various stratifications, it is facilitated to find some characteristics of the cough that lead to an initial anatomical diagnosis, suggesting possible causal nosological entities and only from there, try to prescribe the directed treatment that precisely requires the child who coughs. Also, it presents some chapters that deal with the conditions and factors that surround the lives of children and that make them more susceptible to coughing, it also presents a system of the diagnostic process of cough, with several classifications in which the more we can do "fit" the characteristics of our coughing patients, the more the diagnosis can be facilitated. On the other hand, it presents an express chapter about postnasal drip syndrome, which is the most common cause of cough in the human being. Finally, chapters are presented related to an analysis of children who cough with the presence of frequent colds, hyperreactivity of both the upper and lower airways, a chapter about cough that remains as a sequel to a previous viral infection, ending with a panoramic view. of existing international guidelines for the evaluation of cough in children. In summary, it aims to be a useful tool to use cough as a key symptom in the diagnostic process of the respiratory diseases that cause it and subsequently establish a specifically targeted treatment in order to make it highly effective.

Author Biography:

Dr. Pablo Cortés Borrego is originally from Mexico City doing his undergraduate studies at the National Autonomous University of Mexico. He specialized in Clinical Pulmonology at the National Institute of Respiratory Diseases.

For 25 years he taught Pulmonology at the La Salle University and 8 years at the National Autonomous University of Mexico. He currently works as an adjunct professor of the subspecialty in Pneumopediatrics.

For several periods, he has been part of the Evaluation Committee as a Synod of Pediatricians for their Certification as Pediatric Pulmonologists in the National Council of Pulmonology. After completing his specialty, he continued working at said Institute in the Pediatrics Pavilion since 1987. At that time, the subspecialty of Pediatric Pulmonology did not exist. His areas of interest in children have been multiple, mainly, and in that order: Asthma, food allergies, Bronchiolitis, tuberculosis, palliative medicine, clinical pharmacology (leading him to study a university postgraduate degree) and particularly the study of cough in children, as well as in adults.

He has published articles in Mexican and international journals with topics mainly on pediatric respiratory pathology as well as book chapters. In this last aspect, he was caught by the knowledge of the ineffectiveness of current cough suppressants in relation to the common cold and other common pathologies in contrast to the amount of advertising and global sales of medications aimed at this purpose.

He is currently immersed in the development of a new intranasal antitussive medication that could be an interesting response to some very common types of cough in children and adults. The book Cough in children: New perspectives is a work that highlights the clinical aspects of cough in children that are useful for the daily practice of the doctor who is interested in diagnosing and treating cough more effectively.

Introduction

Parents, in general, and pediatricians, in particular, frequently confront children who cough persistently or recurrently. Treatment is often disappointing because, until now, making a definitive diagnosis and prescribing specific treatment has been difficult. Children with chronic cough are typically patients who have been taken from one doctor to another, subjected to multiple courses of antibiotics, expectorants, cough suppressants, or other types of medications. These medications are often administered in various combinations, doses, and durations that do not correspond to specific treatment regimens. Some have even undergone courses of immunotherapy against various allergens, or tried unconventional treatments like alternative medicine, homeopathy, or home remedies, the effectiveness of which has not been proven. This scenario reflects the desperation that persistent coughing creates, affecting both treating doctors, family members, and the children themselves.

This situation has been so exasperating that the medical literature[1,2] worldwide has introduced concepts such as "Expectable cough" and made recommendations like "continue to wait and reevaluate several weeks later." Most of the medical literature worldwide[3] accepts that chronic cough in pediatrics is a persistent or recurrent cough that lasts more than 3 weeks. This definition is likely based on the description of acute bronchitis, defined as "temporary inflammation of the trachea and main bronchi, primarily manifested by cough, usually resulting from a viral infection that typically resolves without any therapy within a period of no more than 2 weeks.[4,5]"

The definition of chronic bronchitis in pediatrics is not very clear because the clinically useful definition in adults, characterized by excessive mucus secretion and recurrent productive cough most days for at least 3 months per year for no less than two consecutive years[6,7], does not apply to children. For example, a child under 2 years of age, due to their age alone, could not be diagnosed with chronic bronchitis, even if they exhibited symptoms consistent with it. Moreover, anatomopathological alterations described in adults, such as increased bronchial wall thickness compared to glandular thickness, present challenges in pediatrics since children's respiratory epithelium naturally exhibits a significant increase in this ratio in normal bronchi[8]. This makes this data less relevant. Therefore, the definition of chronic bronchitis in adults is not applicable, neither clinically nor anatomopathologically, in the context of pediatric patients[9]. Consequently, chronic bronchitis in children is defined as the persistence of symptoms for more than 3 weeks following an acute injury, suggesting that the stimulus has continued for an extended period and that the bronchi have become affected, becoming a direct cause of cough.

Other terms like "extended bacterial bronchitis" (Protracted Bacterial Bronchitis[10]) defined as a wet cough lasting between 3 and 8 weeks with a positive culture in bronchoalveolar lavage (BAL) that resolves in 4 weeks with amoxicillin-clavulanic acid create confusion and do not provide clarity for the clinical diagnosis or treatment of cough in children. Chronic cough in pediatrics has also been associated with the concept of "Chronic Lung Disease," defined as a patient with respiratory symptoms of continuous evolution for a minimum of 3 months or recurrent evolution with six or more episodes within a 12-month period[11].

It is reasonable to consider that a child who coughs continuously for 3 to 6 months or more may have a chronic lung condition, provided that a cause related to the upper airways has been ruled out. Such cases have significant differences compared to children who have only coughed for slightly longer than 3 weeks, although some overlap in etiologies is inevitable, such as asthma. It can be expected that airway and lung parenchyma damage is more severe as the chronicity of the condition increases. This can occur as a result of significant perinatal events, such as prematurity, mechanical ventilation, congenital malformations, or during the first months of life. Chronic cough is only one of several common manifestations of "chronic lung disease." Therefore, the terms "chronic cough" and "chronic lung disease" cannot be synonymous, especially in the context of children. In pediatrics, there is often the recurrent nature of cough symptoms, and it has been conventionally stated that when there are more than four events per year, it is considered recurrent cough, indicating an ongoing or underlying disease[12].

Some authors suggest that on average, each child experiences 8 respiratory infections per year[13], with a peak of up to 10.4 cases per year in children from 6 months to one year of age[14]. This higher incidence at a younger age, consistently described in the literature, justifies considering age as a contributing factor to cough that is clinically significant. It is important to note that bronchitis, whether acute or chronic, is not the sole or most frequent cause of cough in childhood. Cough can often result from upper airway issues, such as rhinosinusitis, or from diseases that have already passed but have left consequences in the bronchi, for example, viral bronchiolitis.

It is important to emphasize that cough is not a disease in itself but is always a manifestation of an underlying condition. The most common cause of cough worldwide is postnasal drip syndrome (PNS) secondary to a viral upper airway infection, such as the common cold[15]. Normally, it should last no more than 7 to 10 days. If it persists for more than 3 weeks, this should raise concern, indicating that a complication has arisen, and a viral cause alone is unlikely. Chronic cough can also be due to more than one concurrent condition, such as asthma[16,17] or gastroesophageal reflux[18], or it may be the sole manifestation of these conditions.

Cough is one of the most common symptoms originating in the respiratory system. It is usually the most challenging to control, and often, it is the last symptom to disappear after appropriate treatment. The purpose of this book is to review the current state of diagnostic knowledge about cough in children, starting from the concept that cough differs significantly based on the disease causing it, the anatomical site of the stimulus, and the type of stimulus. These differences also depend on the epidemiology of the child's location, their age, and various other factors that impact a child's life when experiencing a cough.

The concept, therefore, is based on the understanding that cough is not a non-specific symptom, as some world literature has suggested6, and that it is valuable to stratify it based on various characteristics rather than simplifying it into just dry or wet cough. This leads us to explore efforts to determine the cause(s) of cough, with the notion that specific therapy, as opposed to nonspecific therapy, is more successful. This book, in relation to the variety of causes of cough, proposes a series of strategies and diagnostic approaches to assist healthcare professionals who encounter this condition daily. Given its multiple potential causes, successfully diagnosing and treating chronic (and acute) cough requires methodical and systematic research. It is essential not to treat only the symptom of coughing before considering the underlying process causing it. Such patients can almost always be diagnosed and treated successfully.

References

1. Chang, A. B., Landau, L. I., Van Asperen, P. P., Glasgow, N. J., Robertson, C. F., Marchant, J. M., & Mellis, C. M. (2006). Cough in children: definitions and clinical evaluation. Medical Journal of Australia, 184(8), 398-403.
2. Sacre Hazouri, J. A. (2010). Tos crónica en pediatría. Revisión y análisis. Revista Alergia de Mexico, 57(5).
3. Kamei R.K. M.D., Chronic cough in children Pediatric Clinics of North América 38, 3, June 1991 pp593.
4. Edwards, G. (1966). Acute bronchitis—Aetiology, diagnosis, and management. British Medical Journal, 1(5493), 963.
5. Park C.R.: Bronchitis, bronquiolitis and asthma. In Kelly, V.C. (ed): Practice of pediatrics. Vol IV. Hagerstown, Maryland, W.F. Pryor Co., 1979.
6. Bordow, R. A., Ries, A. L., & Morris, T. A. (Eds.). (2005). Manual of clinical problems in pulmonary medicine. Lippincott Williams & Wilkins.
7. Global Strategy for the Diagnosis, Management and prevention of Chronic Obstructive Pulmonary Disease 2006 ©GOLD.
8. Reid, L. (1960). Measurement of the bronchial mucous gland layer: a diagnostic yardstick in chronic bronchitis. Thorax, 15(2), 132.
9. Martinez, F. D., Morgan, W. J., Wright, A. L., Holberg, C. J., & Taussig, L. M. (1988). the Group Health Medical Associates' Personnel. Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. N Engl J Med, 319, 1112-1117.
10. Marchant, J. M., Masters, I. B., Taylor, S. M., Cox, N. C., Seymour, G. J., & Chang, A. B. (2006). Evaluation and outcome of young children with chronic cough. Chest, 129(5), 1132-1141.
11. Perez-Fernandez L., Gamboa L: A: Guide to the study of the “chronic pneumopathic” child: Pneumology and chest surgery: 57 (2), 1988:12-24.
12. Chemic, V., & Boat, T. F. (1998). Kendig's disorders of the respiratory tract in children 6th ed.
13. Loda, F. A., Glezen, W. P., & Clyde Jr, W. A. (1972). Respiratory disease in group day care. Pediatrics, 49(3), 428-437.
14. Denny, F. W., Collier, A. M., & Henderson, F. W. (1986). Acute respiratory infections in day care. Clinical Infectious Diseases, 8(4), 527-532.
15. Rs, I. (1998). Managing cough as a defense mechanism and as a symptom. Chest, 114, S133-S181.
16. McFadden Jr, E. R. (1975). Exertional dyspnea and cough as preludes to acute attacks of bronchial asthma. New England Journal of Medicine, 292(11), 555-559.
17. König, P. (1981). Hidden asthma in childhood. American journal of diseases of children, 135(11), 1053-1055.
18. Smyrnios, N. A., Irwin, R. S., & Curley, F. J. (1995). Chronic cough with a history of excessive sputum production: the spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. Chest, 108(4), 991-997.

Chapter - I

The Physio-Pathogenesis of Cough in Relation to Clinical Practice

This chapter provides a comprehensive analysis of cough mechanisms and serves as an introduction to managing the clinical nuances associated with these mechanisms. Understanding cough as a key symptom in the diagnostic process reflects the current trend in anatomical diagnoses of cough causes in children.

Cough presents itself uniquely in various aspects, including:

1. The individual experiencing it (age, gender, pharyngo-laryngeal size, etc.).
2. The underlying disease responsible for it.
3. The specific airway locations triggering the cough reflex, influencing its timing, exacerbating activities, and establishing patterns.
4. The nature of the stimulus (inhalation of particles, inflammation, secretions, bronchospasm, impaired swallowing, or a combination thereof).

Moreover, cough can:

- Be consciously produced or mimicked voluntarily.
- Serve as a means of communication.

Cough can be characterized by four defining features:

1. A deep inhalation.
2. A brief expiratory effort against a closed glottis.
3. Opening of the glottis with nasopharyngeal closure.
4. Vigorous exhalation through the mouth.

Variations exist, as seen in cases of cough accompanied by laryngospasm, where the depth of inspiration may significantly decrease between each cough, resulting in dyspnea ("dyspnea cough") due to limited or suspended inspirations after each bout of coughing, as is typically observed in whooping cough. Additionally, actions such as throat clearing, pharyngeal clearance, and expiratory effort with glottic closure caused by vocal cord or trachea contact (known as the “expiratory reflex”) may not fit the strict definition of a cough but can be fragments of cough[1].

The neurophysiological mechanisms underlying the various presentations and patterns of cough remain unknown. Presumably, differences may arise from various sensor types in the respiratory mucosa, the nature of stimuli, and their site(s) of origin. Nevertheless, for those studying patients with cough, it is possible, to some extent, to determine the causes by observing certain relatively simple clinical behaviors and considering specific cough characteristics unique to both the individual and the diseases causing it. This goes beyond merely distinguishing between a "wet" cough and a "dry" cough (see the chapter: Clinical Diagnosis of Cough). Locating the region(s) of the respiratory system where the cough stimulus occurs is of paramount importance. Whether the stimulus originates in the upper airway, exemplified by posterior nasal drip syndrome, or in the lower airway, as seen in acute bronchitis, asthma, pneumonia, bronchiolitis, or numerous other conditions, has significant diagnostic implications.

Predominantly, receptors or sensors initiating cough are located in the upper airways, where greater protection is required against foreign material entering the lower airways. Consequently, innervation from the pharynx to the larynx and the rest of the tracheobronchial tree[2] is primarily associated with the vagus nerve. When analyzing the sites of cough stimuli, it appears that the neural pathway responsible for cough may differ at various levels, both high and low in the airway.

Some evidence suggests that hypopharyngeal stimuli for cough may follow a different path than the vagus nerve, possibly explaining more conscious and "voluntary" coughing or initial coughing bouts in specific situations[3].

Although cough induced from the pharynx seems to deviate from the "vagal rule," with the pharynx primarily supplied by the glossopharyngeal nerve, a small pharyngeal branch of the superior laryngeal nerve from the vagus could mediate cough at this level, particularly in humans[4]. Given the elevated position of the larynx compared to the pharynx in children, this pathway may be even more active, especially in young children (see Figure 1).

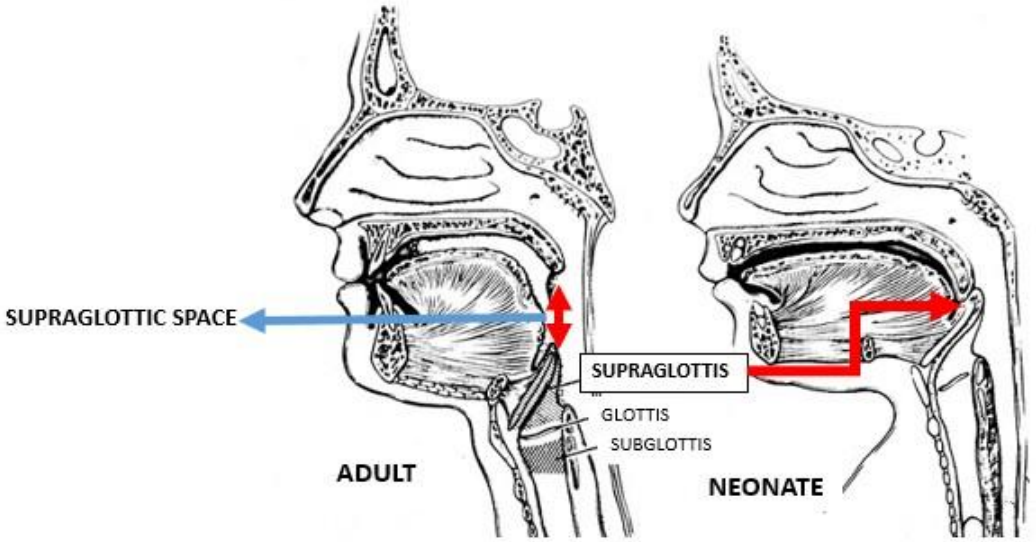


Figure 1: Position of the epiglottis with respect to the soft palate in adults and neonates (in the rest of the mammals there is no downward displacement, acquired with age, so the variety of sounds they emit is very limited) life (Modified from Sasaki C, Isaacson G. 1988 Otol clin North Am 21(4) W, Sanders, Co.)

In newborn newborn and during the first months of life, in which the epiglottis (upper part of the larynx) occupies a very high place, in firm contact with the back of the soft palate, it is possible that fibers of the vagus nerve and the glossopharyngeal occupy similar or at least very close regions, so both fibers could be stimulated in the same regions. This pharyngo-laryngeal conformation produces the necessary nasal breathing during the first 6 months of life and the ability to breastfeed (with a true "drain" of milk at the periphery of the epiglottis) at the same time that breathing occurs (figure 2).

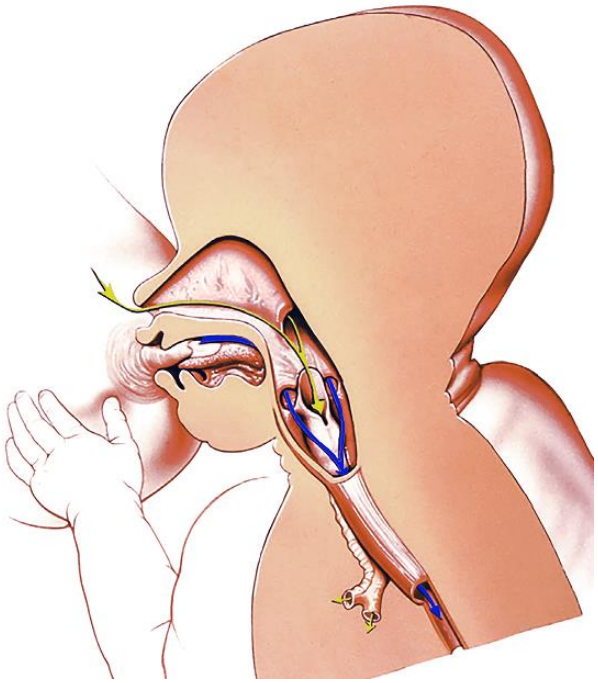


Figure 2: The air flow in the neonate is continuous, occupying a central channel (yallow arrow). The flow of milk (blue arrow) is also continuous through the lateral parts of the larynx, connecting with the esophagus, thanks to the contact of the epiglottis and soft palate (Modified from Laitman and Reidenberg 2013[5].

It is suggested that cough sensitivity, particularly in the upper airways, is primarily limited to the larynx during the first months of life, with a clear vagal distribution. The development of cough sensitivity in the hypopharynx, as well as on the upper surface and periphery of the epiglottis, appears to occur later. This delay may be due to a shift in afferent activity, possibly initiated by the glossopharyngeal nerve or the described branch of the superior laryngeal (vagal) nerve that extends to parts of the hypopharynx. It is likely that this latter pathway undergoes maturation during the early months of life, similar to other systems in the body.

As children grow, the epiglottis and other laryngeal structures descend into lower regions, possibly as a crucial part of the aforementioned maturation process. This descent enables oral breathing, later speech development, and may provide a more optimal distribution of glossopharyngeal and vagal receptors, as well as a stronger connection of the superior laryngeal nerve with the hypopharynx. In older children, other cough triggers, such as postnasal drip, may be associated with inflammation caused by conditions like nasopharyngitis or sinusitis, potentially leading to the dispersion of inflammatory mediators into the lower airways.

Cough Receptors

Understanding the neural pathways involved in the cough reflex can enhance our comprehension of diagnostic strategies and the development of new treatments. This chapter aims to define the categories of afferent vagal nerves that innervate the airways and their roles in regulating cough. In the airways, at least three classes of afferent nerves have been identified: rapidly adaptive mechanoreceptors (RRAs), slowly adaptive mechanoreceptors (MRLAs), and demyelinated C-fibers.

Rapidly Adaptive Receptors (RRAs)

Sustained lung inflations can act as cough stimuli. RRAs are distinct from other airway afferent nerves due to their rapid adaptation (1-2 seconds) to sustained lung inflations. They are also sensitive to lung collapse, alterations in lung dynamic adaptability (and, consequently, their sensitivity during bronchospasm). RRAs might be better described as dynamic receptors that respond to changes in airway mechanical properties such as diameter, length, and interstitial pressures. This explains the need to cough in patients experiencing asthma exacerbation, particularly during forceful exhalation.

In some cases, factors like mucus hypersecretion and bronchial inflammation (common in bronchospasm) can trigger cough. It is not surprising that substances like histamine, capsaicin, substance P, and bradykinin can activate RRAs and be counteracted by bronchodilators to prevent their effects, such as increased mucus secretion or bronchospasm.

Slowly Adaptive Mechanoreceptors (MRLAs)

MRLAs, like RRAs, exhibit activity during the respiratory cycle, with heightened activity during inspiration and maximal activity just before expiration begins. They appear to be associated with the smooth muscle of the intrapulmonary airways. Activation of MRLAs leads to central inhibition of respiration, inhibition of cholinergic airway regulation, reduced phrenic nerve activity, and decreased smooth muscle tone (due to the suspension of cholinergic neural activity)[6,7]. The exact role of MRLAs in cough is not fully understood, but their profound influence on respiratory patterns suggests involvement not only in cough but also in other defensive reflexes. Their action might be related to facilitating cough through second-order neurons known as pump cells at the brain stem level[8].

C-Fibers

C-Fibers are demyelinated afferent fibers that differ from RRAs and MRLAs in their relative insensitivity to mechanical stimulation and lung inflation. Instead, they are directly activated by bradykinin and capsaicin. Interestingly, the response of C-Fibers to capsaicin and bradykinin is not inhibited by prior bronchodilator treatment. C-Fibers can synthesize neuropeptides, which are then transported to their central and peripheral nerve terminals. In some species, such as rats and guinea pigs, activation of C-fibers triggers peripheral neuropeptide secretion (via axonal reflex), leading to bronchospasm and neurogenic-type inflammation[9,10].

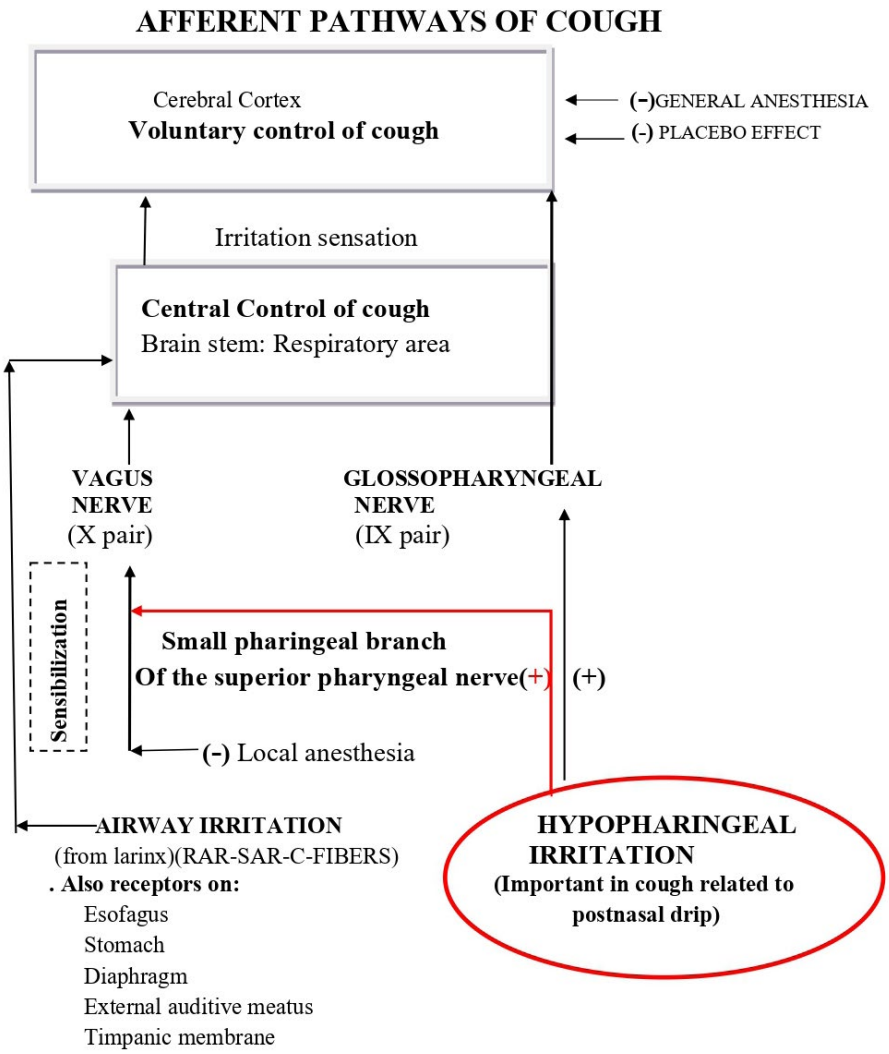
In illness, cough sensors can exhibit an exaggerated response to stimuli that may be irritating to the airway. This increased sensitivity in RRA and C-fiber receptors can result from a combination of factors, including exposure to viral infections, ozone, cigarette smoke, allergens, and various inflammatory mediators[11].

Compelling evidence suggests that neurotrophins, particularly nerve growth factor, play a role in regulating sensory nerves by increasing their activity. Neurotrophins are potent compounds that can alter nerve phenotypes. In sensory nerves, especially C-fibers, nerve growth factor appears to be the primary active neurotrophin, possibly secreted by various cell types, including mast cells[12].

RRA receptors can be sensitized by airway mucus, leading to subsequent smooth muscle contraction and mucosal edema[13,14]. Structural changes in nerve receptors, particularly in their intracellular mediators, have been linked to increased sensitivity. Similar changes have been observed in jugular ganglion node cells and afferent pathways at the brainstem's entry point, potentially holding significant relevance.

The schematic model below illustrates various factors influencing afferent pathways, including types of pathways, stimulus production sites, and factors related to the reduction or elimination of their activity at both central and peripheral levels.

Afferent Pathways of Cough



Scheme Description

The process initiates in the airway, where neural sensors in the tracheobronchial tree or the hypopharynx (lower part of the diagram) are stimulated by irritation. This irritation can result from various inflammatory or mechanical changes, which may or may not lead to secretion, or from the inhalation of chemical irritants, allergens, or mechanical actions. In experimental settings, involuntary coughing appears to originate exclusively from structures innervated by the vagus nerve and its branches[15,16]. These receptors are predominantly located in the larynx, the proximal tracheobronchial tree, the lower part of the oropharynx, small bronchi, the tympanic membrane, and the external auditory meatus.

There is a notable exception to vagus-mediated coughing, which is voluntarily initiated coughing[17,18]. This type of coughing can also be consciously inhibited, at least for a brief period. This coughing originates in the hypopharynx, primarily supplied by the glossopharyngeal nerve (IX cranial nerve). Additionally, a small pharyngeal branch of the superior laryngeal nerve, itself a branch of the vagus nerve, contributes to this pathway.

These crucial pathways originating from the hypopharynx account for the most common type of cough in humans, typically triggered by posterior nasal drip. The vagus nerve conveys afferent impulses to the brainstem's respiratory region, home to the cough control area. In contrast, the glossopharyngeal nerve transmits impulses to subcortical regions associated with voluntary cough control, where it appears to suppress coughing, such as during general anesthesia and the placebo effect.

Recent research has examined the role of the cerebral cortex in influencing coughing[19]. While we can voluntarily initiate or inhibit coughing, there are limitations, particularly when attempting to inhibit coughing caused by contact with secretions on the vocal cords. The placebo effect has been suggested to act at both subcortical and cortical levels. The diagram illustrates a possible neuronal system that includes the cerebral cortex.

The significance of higher cough centers is underscored by observations of weak or absent cough reflexes in stroke patients and altered cough patterns in individuals with Parkinson's disease[20]. Local anesthetics, which effectively block sensory

nerve traffic in both myelinated and unmyelinated nerves, are potent antitussive agents. However, their use must be cautious as they can eliminate all protective reflexes from the lungs and potentially trigger bronchospasm[22].

Symptoms suggestive of gastroesophageal reflux in children with chronic cough, wheezing, and recurrent pneumonia are common. Anti-reflux treatment has been linked to symptom reduction, indicating a causal connection. Possible mechanisms include micro-aspirations of esophageal contents into the tracheobronchial tree and stimulation of an esophagus-tracheobronchial neural reflex.

Gastroesophageal reflux is associated with relaxation and/or immaturity of the lower esophageal sphincter. Symptoms like hiccups, food regurgitation, heartburn, throat clearing, dysphonia, and the Sandifer's position may suggest reflux, although cough alone accounted for 75% of patients in one study[23].

Recent studies combining pH monitoring with esophageal impedance measurements have not demonstrated an increase in reflux events in coughers compared to healthy volunteers. Notably, subjects (adults) with reflux symptoms did not exhibit a higher degree of acid exposure than those without associated symptoms. However, subjects with reflux symptoms displayed increased cough reflex sensitivity (when exposed to citric acid), suggesting a sensitization mechanism in esophageal afferent sensors and/or central sensitization at the brainstem level[24].

Along these lines, central nervous pathways related to cough exhibit interactions and plasticity, similar to peripheral mechanisms described previously[25-27]. For instance, afferent fibers from RRA receptors and C-fibers converge in the nucleus solitarius tract, with the neurokinins secreted by these fibers enhancing RRA receptor activity, especially in cough and bronchoconstriction reflexes. This potentiation is heightened by ongoing C-fiber activity. A prime example of this central plasticity is evident in some cases of gastroesophageal reflux, where esophageal afferent activity, which normally does not trigger coughing, can activate the cough reflex when sensitization occurs.

These mechanisms that lower the cough threshold may be crucial for reflux-induced coughing, explaining why ant reflux medications and proton pump inhibitors have limited sensitivity and specificity in reducing cough symptoms, even when frank reflux symptoms are present[28].

Thus, evaluating a patient with chronic cough, confirming the presence of gastroesophageal reflux, and determining if reflux is the cause of the cough remains a clinical challenge[29]. Standard diagnostic tests for acid reflux, such as 24-hour pH monitoring, may fall within normal ranges in terms of reflux events, even when reflux is the underlying cause of chronic cough. Ultimately, multiple factors may contribute to cough, involving both upper and lower airways simultaneously. Factors to consider include:

• Impaired nasal function leading to inadequate air conditioning and potential reduction of natural bronchodilators like nitric oxide.

• Possible interactions between the nasal and bronchial neural pathways, potentially increasing receptors (e.g., nasobronchial reflex).

• Inflammation originating in the upper airways spreading to the lower airways or through systemic pathways[12].

References

1. Widdicombe JG: A brief overview of mechanisms and therapy. In Cough causes mechanisms and therapy. Chung KF, Widdicombe JG, Boushey HA Oct 2003, Wiley-Blackwell Publishing Ltd, Maiden Mass, USA

2. Fuller, R. W., & Jackson, D. M. (1990). Physiology and treatment of cough. Thorax, 45(6), 425.

3. Chung KF, Widdicombe JG: Cough. Murray and Nadel's textbook of respiratory medicine. Copyright 2010, Saunders an inprint of Elsevier Inc. 5th Edition. China.

4. addington, w. r., stephens, r. e., gilliland, k., & miller, s. p. (1998). tartaric acid-induced cough and the superior laryngeal nerve evoked potential1. american journal of physical medicine & rehabilitation, 77(6), 523-526.

5. Laitman, J. T., & Reidenberg, J. S. (2013). The evolution and development of human swallowing: the most important function we least appreciate. Otolaryngologic clinics of North America, 46(6), 923-935.

6. Joad, J. P., Kott, K. S., & Bonham, A. C. (1997). Nitric oxide contributes to substance P-induced increases in lung rapidly adapting receptor activity in guinea-pigs. The Journal of Physiology, 503(Pt 3), 635.

7. Schelegle, E. S., & Green, J. F. (2001). An overview of the anatomy and physiology of slowly adapting pulmonary stretch receptors. Respiration physiology, 125(1-2), 17-31.

8. Shannon, R., Baekey, D. M., Morris, K. F., & Lindsey, B. G. (1998). Ventrolateral medullary respiratory network and a model of cough motor pattern generation. Journal of applied physiology, 84(6), 2020-2035.

9. Lee, L. Y., & Pisarri, T. E. (2001). Afferent properties and reflex functions of bronchopulmonary C-fibers. Respiration physiology, 125(1-2), 47-65.

10. Barnes, P. J. (2001). Neurogenic inflammation in the airways. Respiration physiology, 125(1-2), 145-154.

11. Carr, M. J. (2007). Plasticity of the afferent innervation of the airways: The role of ion channels. Pulmonary Pharmacology & Therapeutics, 20(4), 412-415.

12. Togias, A. (2000). Unique mechanistic features of allergic rhinitis. Journal of allergy and clinical immunology, 105(6), S599-S604.

13. Mazzone SB, Canning BJ: Plasticity of the cough reflex. Eur Respir Rev 12:236-242, 2002.

14. Canning, B. J. (2002). Interactions between vagal afferent nerve subtypes mediating cough. Pulmonary Pharmacology & Therapeutics, 15(3), 187-192.

15. Widdicombe, J. G. (1995). Neurophysiology of the cough reflex. European Respiratory Journal, 8(7), 1193-1202.

16. Widdicombe, J. G. (1998). Afferent receptors in the airways and cough. Respiration physiology, 114(1), 5-15.

17. Lee, P. C. L., Cotterill-Jones, C., & Eccles, R. (2002). Voluntary control of cough. Pulmonary pharmacology &

therapeutics, 15(3), 317-320.
18. Eccles, R. (2002). The powerful placebo. Do we need antitussives. Pulm Pharmacol Ther, 15, 303-8.
19. Eccles, R. (2003). Placebo effects of antitussive treatments on cough associated with acute upper respiratory tract infection. Cough: causes, mechanisms and therapy, 259-268.
20. Stephens, R. E., Addington, W. R., & Widdicombe, J. G. (2003). Effect of acute unilateral middle cerebral artery infarcts on voluntary cough and the laryngeal cough reflex. American journal of physical medicine & rehabilitation, 82(5), 379-383.
21. Karlsson, J. A., Sant'Ambrogio, G. U. I. S. E. P. P. E., & Widdicombe, J. O. H. N. (1988). Afferent neural pathways in cough and reflex bronchoconstriction. Journal of applied physiology, 65(3), 1007-1023.
22. Karlson J-A, Airway anaesthesia and the cough reflex. Bull Eur Physiopathol Respir 1983;23(suppl10):29-36S.
23. Birring SS, Pavord ID: 2013 ed.: Clinical respiratory medicine pp247 Chapter 18. Cough 4th ed. 2013 S. Spiro, G. Silvestri, A. Agusti Saunders/Elsevier B.V.
24. Smith, J. A., Decalmer, S., Kelsall, A., McGuinness, K., Jones, H., Galloway, S., ... & Houghton, L. A. (2010). Acoustic cough—reflux associations in chronic cough: potential triggers and mechanisms. Gastroenterology, 139(3), 754-762.
25. Kollarik, M., & Undem, B. J. (2003). Plasticity of vagal afferent fibres mediating cough. Cough: causes, mechanisms and therapy, 181-192.
26. Fontana GA: Motor mechanisms and mechanics of cough. Chung, K. F., Widdicombe, J. G., & Boushey, H. A. (2003). Cough: Causes, Mechanisms and Therapy., Oxford: Blackwell, pp 193-206.
27. Bonham, A. C., Sekizawa, S. I., & Joad, J. P. (2004). Plasticity of central mechanisms for cough. Pulmonary pharmacology & therapeutics, 17(6), 453-457.
28.Lacy, B. E., Weiser, K., Chertoff, J., Fass, R., Pandolfino, J. E., Richter, J. E., ... & Vaezi, M. F. (2010). The diagnosis of gastroesophageal reflux disease. The American journal of medicine, 123(7), 583-592.
29. Dicpinigaitis, P. V. (2011). Cough: an unmet clinical need. British journal of pharmacology, 163(1), 116-124.

Chapter - II

Factors that Increase the Incidence of Cough

Chronic cough often results from not just one, but multiple disorders or diseases, each of which can independently cause chronic cough. These diseases can intersect with various factors that influence the lives of children, and the combination of both can significantly increase the incidence of cough. These factors or conditions that coexist with cough can not only lead to more frequent coughing spells but can also contribute to its chronicity.

Sometimes, these factors exert such a strong influence that they can lead doctors to mistakenly consider them as the direct cause of the cough. This can occur in certain cases, with gastroesophageal reflux serving as a typical example. Reflux can exacerbate coughs caused by, for instance, upper respiratory infections or asthma. Treating only the reflux, which is a contributing factor, will likely not alleviate the cough. The cough will likely subside when addressing the infection or asthma in the first place. However, it's important to note that in some children, gastroesophageal reflux may be the primary or main cause of the cough, especially given that reflux can contribute to infections or asthma exacerbations.

Understanding this concept is crucial in the broader context of cough etiology. In the example mentioned earlier, treating reflux and the infection simultaneously can make it challenging to discern which factor primarily led to the disappearance of the cough. This may result in unnecessary and prolonged use of antireflux medications.

It's worth noting that increased intra-abdominal pressure from coughing can lead to ineffective or partially ineffective lower esophageal sphincter function, especially in young infants and preschoolers, and this reflux can trigger coughing via a reflex esophageal pathway or, less commonly, due to upper airway irritation and/or bronchial aspiration.

Determining whether reflux is the main cause of the cough involves a stepwise approach. Initially, treat the most apparent and frequent cause, and only after exhausting that possibility should you consider a contributing factor with significant weight in sustaining the cough (refer to "Various Causes of Cough in a Child"). Below, we analyze some of these factors.

The factors that increase the incidence of cough in children encompass a set of characteristics inherent to both the child's environment and the child's personal history or constitution. These characteristics can vary in their specific influence, ranging from highly significant to relatively insignificant. Therefore, it is advisable to address them when possible.

These characteristics or factors can either trigger acute cough or contribute to its persistence, thereby meeting the criteria for chronic cough. Each of these factors independently increases the likelihood of cough, and they can be cumulative, meaning that the more factors present in the child, the greater the probability of chronic and/or recurrent cough. Additionally, managing such a cough may become more challenging. For example, a child under 2 years of age whose parents smoke, attends daycare during the winter, and experiences a temporary decrease in IgA levels may experience prolonged bouts of coughing. The causes may include recurrent viral or bacterial infections and/or bronchial hyperreactivity.

It's essential to emphasize that cough typically doesn't occur in the absence of an underlying disease or disturbance. In other words, these factors increase the likelihood of cough manifesting through a disease that inherently causes some degree of cough. The factors listed below are not ordered by their specific influence on cough production, as this influence varies for each patient based on their unique characteristics:

1. Age under 5 years
2. Winter season
3. Respiratory history of the lower respiratory tract
4. Abnormal perinatal history
5. Passive smoking
6. Allergies
7. Environmental pollution
8. Nursery attendance
9. Local epidemiology
10. Climate
11. Socioeconomic status
12. Inadequate medical treatment
13. Gastroesophageal reflux

Age under 5 Years: The immune system undergoes pre- and postnatal maturation. During the first 6 months of life, maternal immunoglobulins provide valuable protection to the newborn and subsequently to the infant, resulting in reduced rates of acute respiratory viral infections worldwide[1].

Young infants typically experience between 3 and 8 upper respiratory tract infections annually[2,3], and many of them develop chronic or recurrent cough due to successive upper respiratory tract infections. Most reports concur on a significant increase in the number of infections starting at 6 months of age, which gradually declines but remains noteworthy until around the age of 5. A prospective Australian community study found an average of 2.2 person-year episodes for children under 10, each lasting 5.5 to 6.8 days[4], indicating the significance of this phenomenon. Approximately 35% of preschoolers report coughing in any given month[5].

This implies a direct correlation with the immunological maturation process, with a notable inverse relationship, particularly with the production capacity of different immunoglobulins (see Figure 1).

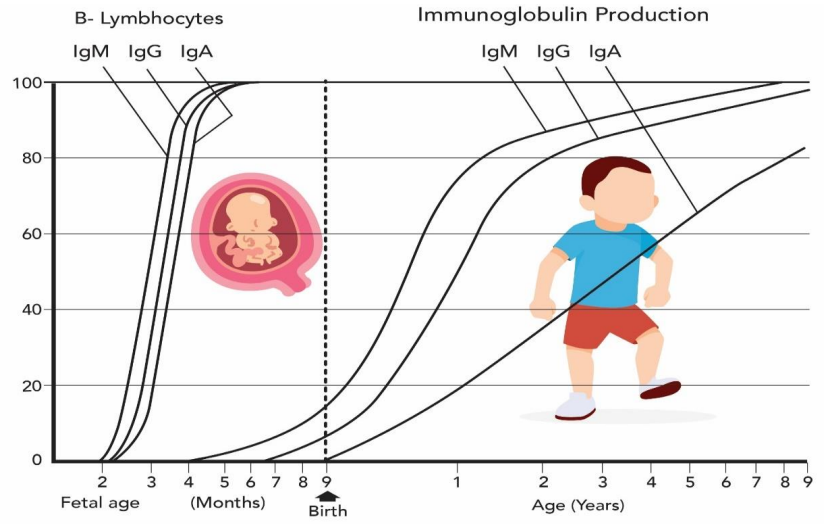


Figure 1: Transition from passive immunity from maternal antibodies in the fetus to the production of immunoglobulins from birth. (Modified from: Loughlin "Respiratory disease in children": figure 4.3 page 41)

The capacity for endogenous production of immunoglobulins is not necessarily an isolated fact. The influence of external factors, such as daycare centers, can affect this production and in turn, impact the frequency of upper respiratory tract viral infections (as shown in the graph). This connection necessitates further studies. However, when we encounter a child with a deficiency in certain immunoglobulins, such as the not uncommon case of children with transient deficiency in immunoglobulin A, production, the importance becomes evident. Affected children experience not only respiratory infections but also enteric infections, often occurring consecutively and proving challenging to control until their immunoglobulin levels return to normal.

"The Viral Respiratory Season"

The so-called "Viral Respiratory Season[6]", which spans from October-November through March-April in the Northern Hemisphere (and from April to September in the Southern Hemisphere), witnesses a significant increase in viral respiratory infections. A proportion of these infections lead to complications, resulting in various causes of chronic cough[7]. In a study involving 100 healthy subjects who were monitored, it was observed that the average frequency of cough was higher during the cold winter months and lower during the warm summer months[8]. Using influenza as a representative example of the "Viral Respiratory Season," characterized by annual epidemics, here present the graphs for the 2003-13 seasons.

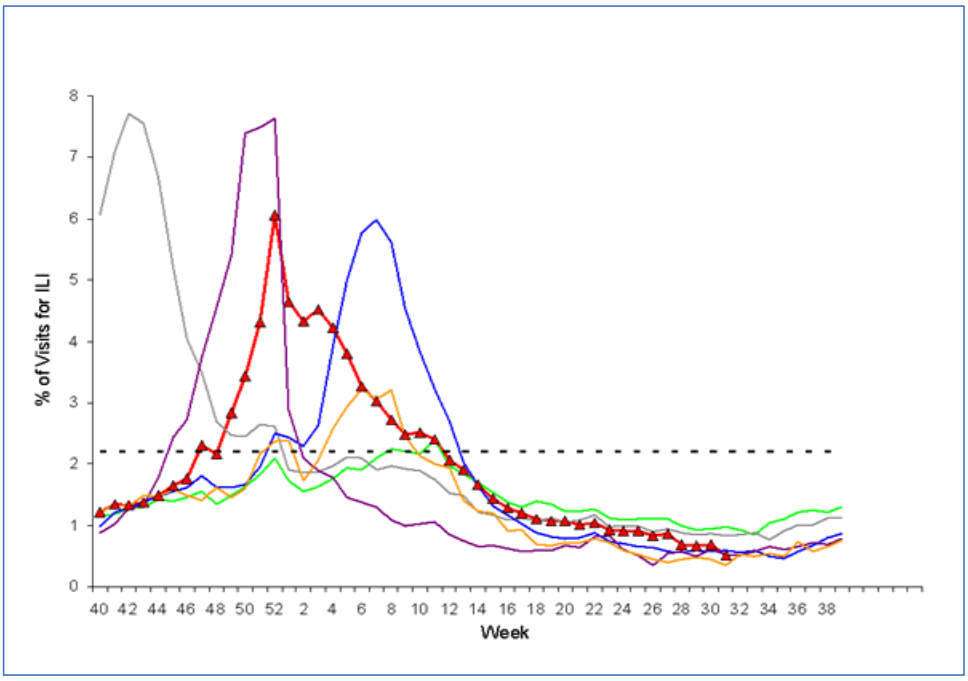


Figure 2. Percentage of Visits of Influenza-like visits (ILI) reported by U.S. Outpatient Influenza like Surveillance Network (ILINET). Weekly National Summary, 2003-2013 (Note in grey color the pandemic season preview in 2009).

On the other hand, in Canada, the United States, and Mexico, we observe a significant increase in emergency room visits for asthma exacerbations during the month of September each year (from week 36 to 40 of the year). This month each year, experiences the highest number of emergency room visits in all three countries, possibly due to the fact that children begin school, leading to a corresponding increase in rhinovirus cases[9]. Interestingly, the same phenomenon occurs in the southern hemisphere, but with a six-month difference, in the month of February, coinciding with the start of the school year after the southern summer vacation[10].

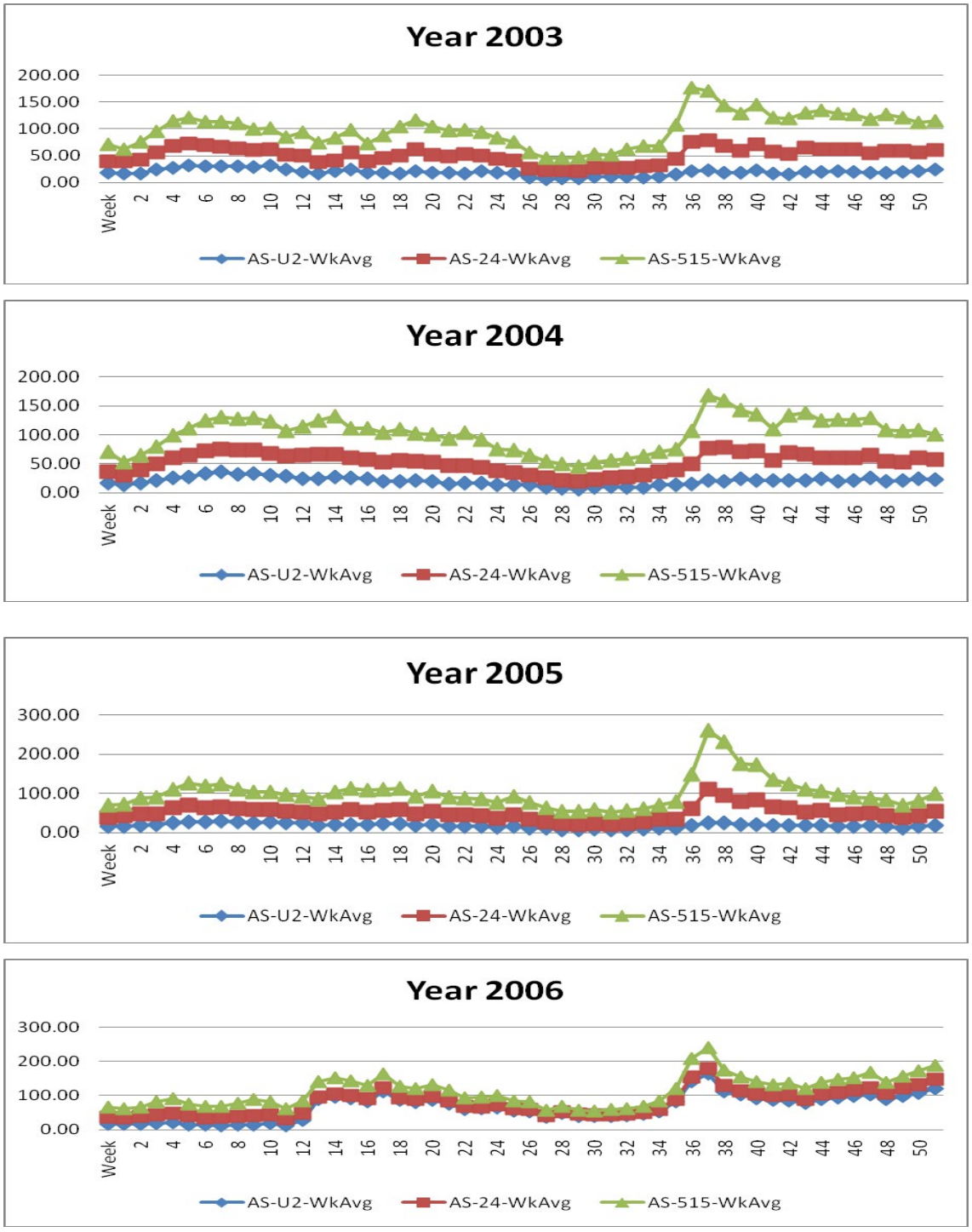


Figure 4: Average weekly visits for asthma exacerbations to emergency departments in Ontario Canada in 2001 a2006. (AS-U2: age less than 2 years (blue), AS-24: age 2 a4 years (red), AS-515: Age 5 a15 years (green) Data, contributed by Dr. Neil Johnston.

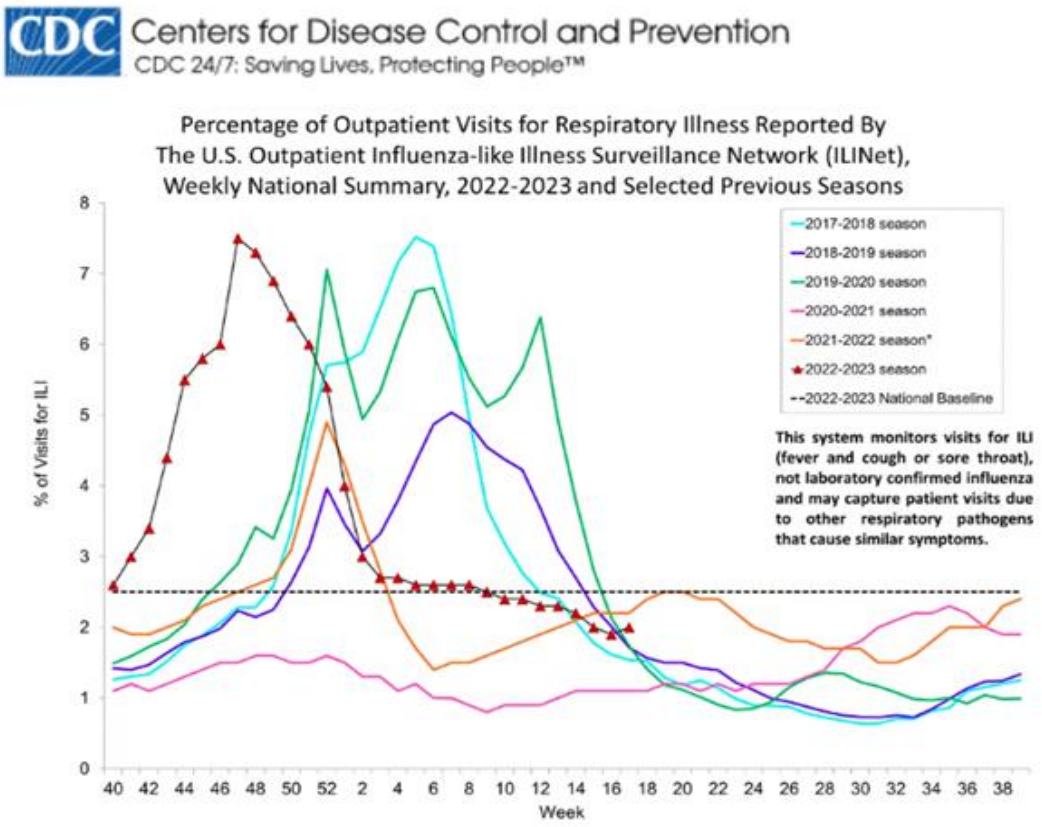


Figure 5: Twenty years later they paractically no changed for the same northern hemisphere (EEUU) and something similar happens in Mexico.

Pathological History of the Lower Respiratory Tract

Some lower respiratory tract pathologies resolve without obvious long-term effects. However, frequently, they leave functional issues that become symptomatic in specific situations. A common example is bronchiolitis resulting from respiratory syncytial virus infection6, often referred to as "bronchopneumonia" in some Latin American countries. After recovery from the acute event, bronchospastic events similar to asthma exacerbations can occur. These events are often triggered by viral infections of the upper airways caused by different pathogens than respiratory syncytial virus[11,12] or by bacterial sinusitis[13].

Bronchiolitis and rhinosinusitis are not the sole examples of such aggression to the airway. Even less severe conditions can lead to various degrees of respiratory dysfunction, as seen in the case of croup[14] (laryngotracheobronchitis) that occurs in early childhood. In particular, recurrent croup can result in significant reductions in FVC, FEV1, FEF 25-75%, and bronchial hyperreactivity that persist up to 10 or 12 years later[15].

Infants typically experience an average of 3 to 8 colds per year2, and many children develop chronic or recurrent coughs due to consecutive upper respiratory tract infections. Occasionally, a single respiratory tract infection, both upper and lower, particularly those caused by adenovirus, influenza, Bordetella pertussis, or mycoplasma, can lead to a lingering cough that may last several months due to potential ciliary abnormalities, which can persist for up to 10 weeks after infection with these agents. Other less frequent events, such as near drowning due to immersion or ingestion of hydrocarbons, can also cause coughing.

Perinatal History

Often, the conditions surrounding a child's birth are downplayed as time passes. For example, when a newborn experiences transient tachypnea, it's commonly assumed that once the child overcomes it, their lungs will remain normal for the rest of their life. However, there is growing evidence linking such perinatal events with later respiratory issues during childhood or even adulthood. Children who had tachypnea at birth may be more prone to early wheezing, asthma[19,20,21], or even Chronic Obstructive Pulmonary Disease (COPD) in adulthood, especially if exposed to tobacco smoke. This area presents a substantial area for research.

Other significant or abnormal perinatal factors, such as premature birth, low birth weight, meconium aspiration, neonatal apnea, mechanical ventilation, or hyaline membrane disease, are often major factors in the subsequent presentation of chronic cough or recurrent cough in childhood, especially when combined with the use of mechanical ventilation[22]. These factors can contribute to bronchopulmonary dysplasia, which leads to increased coughing due to inflammation, bronchial hyperreactivity, and a heightened susceptibility to lower respiratory tract infections.

Passive Smoking (PS)

Exposure to passive smoking, especially when one of the parents is a smoker, particularly the mother, has been associated with a greater number of coughing episodes and more frequent exacerbations in asthmatic children[23]. Some associations, like the American Academy of Pediatrics, even consider passive smoking an independent cause of cough and serious chest diseases, especially in children under 2 years of age[24]. Notably, parental smoking has a statistically significant effect on cough frequency, particularly in children under 11 months. In households without smoking, frequent cough was reported in 35% of boys and 32% of girls. This percentage increased to 42% and 40%, respectively, if one of the parents smoked, and up to 48% and 52% in homes where both parents smoked[25]. There's limited information on parental smoking cessation as a successful treatment for children's cough[26], likely because passive smoking not only causes coughing spells but also increases airway susceptibility to diseases like bronchiolitis and croup, which can promote alterations sufficient to cause chronic or recurrent cough.

Active smoking should also be suspected in preadolescents and adolescents. In a British study of high school children who had smoked regularly for one or two years, it was found that they experienced more cough, dyspnea, and discharge than non-smokers of the same age and height[27]. Contrary to this, the Tuczon cohort reported that "cough was not associated with parental smoking during the first decade of life," which contrasts with previous studies28, suggesting that passive smoking may be only a contributing factor.

Allergy

Parents often suspect allergies as a potential cause of their children's chronic cough. It is challenging to differentiate between excessive nasopharyngeal secretions due to allergies and those caused by viral or bacterial infections, especially if symptoms have persisted for several weeks or occur recurrently. The physical characteristics of nasal secretions can be very similar in both cases, especially when they are not purulent, which is more suggestive of a bacterial infection. Therefore, sometimes the main cause of these secretions can only be determined with appropriate antibiotic treatment. If the secretion noticeably decreases with antibiotic treatment, it should be continued for 15 to 21 days. If the secretion only partially disappears, a more effective antibiotic may be necessary. Combining an antihistamine with the treatment can complicate the interpretation of results because it is difficult to determine whether it was the antibiotic or the antihistamine that reduced or eliminated the secretion. Another cause can be added like reflux or asthma[29].

Allergy is undoubtedly a significant factor in coughing. However, studies often fail to establish the precise mechanism by which allergies alone lead to cough. "Allergic cough" remains a poorly defined condition, even in adults, and its relationship with cough is likely an overlap with asthma, non-asthmatic eosinophilic bronchitis, allergic rhinitis, adenoid and tonsillar hypertrophy[30]. High levels of dust can cause coughing due to both mechanical irritation and allergic reactions. Allergic rhinitis can potentially lead to cough due to postnasal drip[31]. It is important to note that positive skin tests and elevated IgE levels related to cough do not necessarily establish a cause-and-effect relationship.

One explanation for the increasing global prevalence of asthma is that children spend extended periods indoors exposed to household allergens. Poorly ventilated homes with increased humidity encourage the proliferation of fungi and dust mites in mattresses, carpets, and floors[32]. This can influence bronchial hyperreactivity in susceptible children. The introduction of pets into homes has been associated with asthma and its difficulty in control[33].

Environmental Pollution

Elevated levels of suspended particles and gases such as carbon monoxide and sulfur dioxide, stemming from automotive and industrial combustion, as well as high ozone levels, can provoke nasal and bronchial responses that lead to coughing or exacerbate pre-existing coughs. Increased environmental pollution has been linked to a rise in emergency room visits by asthmatic patients in various cities, including Barcelona, Atlanta, and Mexico City[34-36]. There are also reports of increased coughing and worsening of asthma in children residing near roads with high traffic levels[37,38].

In a town in Israel, the incidence of nighttime cough and the production of phlegm without colds in high school children were significantly higher than in low-pollution areas, emphasizing the detrimental effects of environmental pollution[39]. After the reunification of Germany, studies conducted in the same geographic regions but with varying levels of environmental pollution revealed that industrialized cities with high sulfur dioxide pollution had a higher prevalence of bronchitis in the child population[40,41]. A similar trend was observe in Eastern Europe[42].

In China, growing reports highlight the negative impacts of increasing environmental pollution. In districts with high environmental pollution, boys and girls have an increased risk of coughing at night, producing phlegm without colds, and experiencing symptoms such as wheezing and chronic cough. To preserve children's respiratory health, it's imperative that countries implement strong policies to combat environmental pollution[43]. Notably, indoor pollution may be even more influential than outdoor pollution, especially for young children who spend significant time indoors. Studies have focused on homes and schools, considering factors such as humidity, fungal growth, insect infestation, dust mites, construction materials, heating systems, ventilation, nitrogen dioxide, and tobacco smoke[44]. Both passive smoking and products from gas stove combustion, as well as the presence of allergens, pets, and cleaning solvents, can contribute to coughing independently or in combination with other factors.

Assistance to Nurseries

The data support the notion that at least in the first years of life there is an increase in the incidence of respiratory infections in children who are cared for in daycare centers, Considering the

risk of viral diseases in this age group, a large number of infants and children are affected as long as they have the opportunity to grow and demonstrate immunological and respiratory stability, with notable differences between those who are cared for in daycare, those who are cared for at home and those who have or do not have siblings (see graph below)

.

Pathological History of the Lower Respiratory Tract

Some lower respiratory tract pathologies resolve without obvious long-term effects. However, frequently, they leave functional issues that become symptomatic in specific situations. A common example is bronchiolitis resulting from respiratory syncytial virus infection6, often referred to as "bronchopneumonia" in some Latin American countries. After recovery from the acute event, bronchospastic events similar to asthma exacerbations can occur. These events are often triggered by viral infections of the upper airways caused by different pathogens than respiratory syncytial virus[11,12] or by bacterial sinusitis[13].

Bronchiolitis and rhinosinusitis are not the sole examples of such aggression to the airway. Even less severe conditions can lead to various degrees of respiratory dysfunction, as seen in the case of croup[14] (laryngotracheobronchitis) that occurs in early childhood. In particular, recurrent croup can result in significant reductions in FVC, FEV1, FEF 25-75%, and bronchial hyperreactivity that persist up to 10 or 12 years later[15].

Infants typically experience an average of 3 to 8 colds per year2, and many children develop chronic or recurrent coughs due to consecutive upper respiratory tract infections. Occasionally, a single respiratory tract infection, both upper and lower, particularly those caused by adenovirus, influenza, Bordetella pertussis, or mycoplasma, can lead to a lingering cough that may last several months due to potential ciliary abnormalities, which can persist for up to 10 weeks after infection with these agents[16]. Other less frequent events, such as near drowning due to immersion[17] or ingestion of hydrocarbons[18], can also cause coughing.

Perinatal History

Often, the conditions surrounding a child's birth are downplayed as time passes. For example, when a newborn experiences transient tachypnea, it's commonly assumed that once the child overcomes it, their lungs will remain normal for the rest of their life. However, there is growing evidence linking such perinatal events with later respiratory issues during childhood or even adulthood. Children who had tachypnea at birth may be more prone to early wheezing, asthma[19-21], or even Chronic Obstructive Pulmonary Disease (COPD) in adulthood, especially if exposed to tobacco smoke. This area presents a substantial area for research.

Other significant or abnormal perinatal factors, such as premature birth, low birth weight, meconium aspiration, neonatal apnea, mechanical ventilation, or hyaline membrane disease, are often major factors in the subsequent presentation of chronic cough or recurrent cough in childhood, especially when combined with the use of mechanical ventilation[22]. These factors can contribute to bronchopulmonary dysplasia, which leads to increased coughing due to inflammation, bronchial hyperreactivity, and a heightened susceptibility to lower respiratory tract infections.

Passive Smoking (PS)

Exposure to passive smoking, especially when one of the parents is a smoker, particularly the mother, has been associated with a greater number of coughing episodes and more frequent exacerbations in asthmatic children[23]. Some associations, like the American Academy of Pediatrics, even consider passive smoking an independent cause of cough and serious chest diseases, especially in children under 2 years of age[24]. Notably, parental smoking has a statistically significant effect on cough frequency, particularly in children under 11 months. In households without smoking, frequent cough was reported in 35% of boys and 32% of girls. This percentage increased to 42% and 40%, respectively, if one of the parents smoked, and up to 48% and 52% in homes where both parents smoked[25]. There's limited information on parental smoking cessation as a successful treatment for children's cough[26], likely because passive smoking not only causes coughing spells but also increases airway susceptibility to diseases like bronchiolitis and croup, which can promote alterations sufficient to cause chronic or recurrent cough.

Active smoking should also be suspected in preadolescents and adolescents. In a British study of high school children who had smoked regularly for one or two years, it was found that they experienced more cough, dyspnea, and discharge than non-smokers of the same age and height[27]. Contrary to this, the Tuczon cohort reported that "cough was not associated with parental smoking during the first decade of life," which contrasts with previous studies[28], suggesting that passive smoking may be only a contributing factor.

Allergy

Parents often suspect allergies as a potential cause of their children's chronic cough. It is challenging to differentiate between excessive nasopharyngeal secretions due to allergies and those caused by viral or bacterial infections, especially if symptoms have persisted for several weeks or occur recurrently. The physical characteristics of nasal secretions can be very similar in both cases, especially when they are not purulent, which is more suggestive of a bacterial infection. Therefore, sometimes the main cause of these secretions can only be determined with appropriate antibiotic treatment. If the secretion noticeably decreases with antibiotic treatment, it should be continued for 15 to 21 days. If the secretion only partially disappears, a more effective antibiotic may be necessary. Combining an antihistamine with the treatment can complicate the interpretation of results because it is difficult to determine whether it was the antibiotic or the antihistamine that reduced or eliminated the secretion. Another cause can be added like reflux or asthma[29].

Allergy is undoubtedly a significant factor in coughing. However, studies often fail to establish the precise mechanism by which allergies alone lead to cough. "Allergic cough" remains a poorly

defined condition, even in adults, and its relationship with cough is likely an overlap with asthma, non-asthmatic eosinophilic bronchitis, allergic rhinitis, adenoid and tonsillar hypertrophy[30]. High levels of dust can cause coughing due to both mechanical irritation and allergic reactions. Allergic rhinitis can potentially lead to cough due to postnasal drip[31]. It is important to note that positive skin tests and elevated IgE levels related to cough do not necessarily establish a cause-and-effect relationship.

One explanation for the increasing global prevalence of asthma is that children spend extended periods indoors exposed to household allergens. Poorly ventilated homes with increased humidity encourage the proliferation of fungi and dust mites in mattresses, carpets, and floors[32]. This can influence bronchial hyperreactivity in susceptible children. The introduction of pets into homes has been associated with asthma and its difficulty in control[33].

Environmental Pollution

Elevated levels of suspended particles and gases such as carbon monoxide and sulfur dioxide, stemming from automotive and industrial combustion, as well as high ozone levels, can provoke nasal and bronchial responses that lead to coughing or exacerbate pre-existing coughs. Increased environmental pollution has been linked to a rise in emergency room visits by asthmatic patients in various cities, including Barcelona, Atlanta, and Mexico City[34-36]. There are also reports of increased coughing and worsening of asthma in children residing near roads with high traffic levels[37,38].

In a town in Israel, the incidence of nighttime cough and the production of phlegm without colds in high school children were significantly higher than in low-pollution areas, emphasizing the detrimental effects of environmental pollution[39]. After the reunification of Germany, studies conducted in the same geographic regions but with varying levels of environmental pollution revealed that industrialized cities with high sulfur dioxide pollution had a higher prevalence of bronchitis in the child population[40,41]. A similar trend was observe in Eastern Europe[42].

In China, growing reports highlight the negative impacts of increasing environmental pollution. In districts with high environmental pollution, boys and girls have an increased risk of coughing at night, producing phlegm without colds, and experiencing symptoms such as wheezing and chronic cough. To preserve children's respiratory health, it's imperative that countries implement strong policies to combat environmental pollution[43]. Notably, indoor pollution may be even more influential than outdoor pollution, especially for young children who spend significant time indoors. Studies have focused on homes and schools, considering factors such as humidity, fungal growth, insect infestation, dust mites, construction materials, heating systems, ventilation, nitrogen dioxide, and tobacco smoke[44]. Both passive smoking and products from gas stove combustion, as well as the presence of allergens, pets, and cleaning solvents, can contribute to coughing independently or in combination with other factors.

Assistance to Nurseries

The data support the notion that at least in the first years of life there is an increase in the incidence of respiratory infections in children who are cared for in daycare centers, Considering the risk of viral diseases in this age group, a large number of infants and children are affected as long as they have the opportunity to grow and demonstrate immunological and respiratory stability, with notable differences between those who are cared for in daycare, those who are cared for at home and those who have or do not have siblings (see graph below).

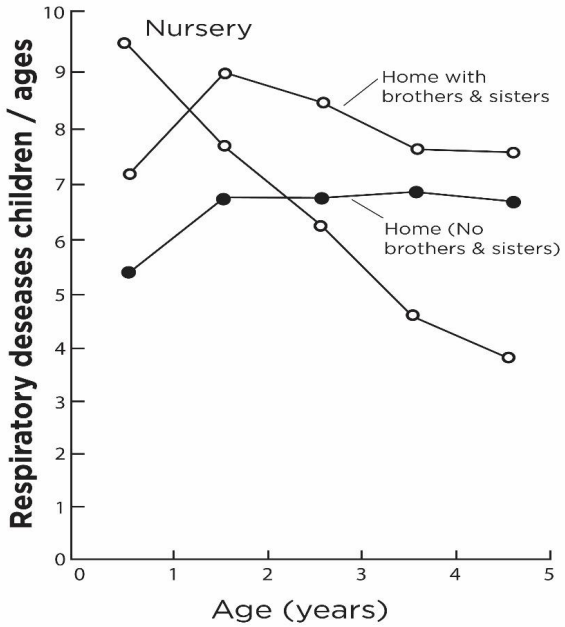


Figure 5: Comparative incidences of respiratory diseases in different environments in which children live. Note how daycare children get sicker during the first year, but during the 3rd year the number of illnesses decreases below the figures for other children from environments considered “healthier.” Modified from Pediatrics in Review,1986 (Vol. 8 Page 532, Fig. 2)

Measures to Mitigate the Impact of Daycare

Various measures have proven effective in reducing the impact of daycare-related factors. These include practices such as regular handwashing, adherence to immunization schedules, and segregating febrile children. It's undeniable that other measures, such as administering vaccines against pneumococcus, Haemophilus influenzae type B, and the annual influenza vaccine, hold significant potential to reduce infectious symptoms in general and, more specifically, cough within daycare settings. We anticipate that the effectiveness of these measures will be most noticeable in such environments.

Epidemiology of the Child's Environment

Certain populations are characterized by conditions like endemic tuberculosis. In these populations, which often face challenges such as poverty, malnutrition, overcrowding, and low sociocultural levels, tuberculosis becomes a much more frequent cause of cough. Consequently, it plays a pivotal role in the differential diagnosis compared to populations in regions with more robust health controls, where tuberculosis is rather rare. This highlights the importance of adapting the differential diagnosis of cough to the epidemiological conditions of the child's environment. In children with persistent chronic cough, an inquiry into family and cohabitants' history of tuberculosis is advisable, particularly for younger children who are more likely to have had contact with tuberculosis at home.

Climate

Children living at sea level experience a higher proportion of asthma cases compared to those in higher altitude regions in Canada, the United States, and Mexico[45]. Climate and temperature influence these differences, though areas with higher altitudes may have other factors at play, such as increased environmental pollution or pronounced temperature changes[46]. The effect of temperature should not be underestimated, as demonstrated by an Australian study that correlated temperature variations with Maximum Expiratory Flow (PEF) measurements and respiratory symptoms in children. The study revealed a linear relationship, meaning that greater temperature fluctuations led to more significant changes in PEF and respiratory symptoms[47].

Socioeconomic Factors

Socioeconomic factors, particularly poverty and residence in marginalized areas, encompass a wide range of influences that impact the presentation of various diseases, including respiratory ailments with cough as a primary manifestation. These factors often include low income, poor nutrition, low birth weight, young maternal age, overcrowding, inadequately ventilated living spaces, delays in seeking medical attention, and passive smoking[48]. In extreme poverty situations, mothers may resort to cooking with firewood in poorly ventilated areas, alongside their children.

In contrast, a Spanish epidemiological study noted that parental smoking was associated with higher socioeconomic levels, and their children were more likely to experience bronchitis and cough[49]. While pneumonia, especially in rural areas, remains a leading cause of cough and mortality in children under 5 years old, asthma in preschoolers in low-income regions may be significantly underdiagnosed or misdiagnosed as pneumonia. This misdiagnosis can lead to increased coughing, heightened morbidity, and mortality.

Gastroesophageal Reflux

Most newborns experience some degree of reflux in the neonatal period, with regurgitation and vomiting being common in the first year of life. The vast majority of infants with symptomatic reflux-related symptoms during their first year tend to resolve most of their symptoms between 9 months and 2 years of age[50]. Establishing a cause-effect relationship between reflux and respiratory symptoms is often challenging. The link between asthma, bronchitis, or pneumonia and gastroesophageal reflux is not easy to confirm, even when reported cases attempt to demonstrate it[51-53] Gastroesophageal reflux can trigger cough through local and central reflex mechanisms and micro aspirations. One possible mechanism through which reflux worsens cough is increased intra-abdominal pressure during coughing spells, combined with decreased efficiency of the lower esophageal sphincter, often due to immaturity.

A self-perpetuating positive feedback loop of cough and reflux (or reflux and cough) has been proposed. In this cycle, cough due to any cause can precipitate reflux[54]. Evidence of this cycle has been found in studies of infants and children, indicating that the antitussive effect of antireflux therapy persists long after antireflux therapy has been discontinued[55].

Insufficient Medical Treatment

In some cases, a secondary cause of chronic or recurrent cough is a treatment that has not been directed towards the underlying cause of the cough or has been administered for an insufficient duration. Various cough suppressants and remedies with different mechanisms of action are available in the market. This implies that all coughs have the same cause and pathophysiology, which is not the case[56,57]. Additionally, serious and even fatal adverse events have been reported in association with some of these medications. Often, parents turn to these over-the-counter remedies, which do not require a written medical prescription, in an attempt to alleviate their child's cough before seeking medical evaluation. This practice can lead to delays in diagnosis and proper treatment or even cause serious adverse events[58].

The market for cough suppressants thrives on the self-limiting nature of most diseases that cause acute cough, coupled with the strong placebo effect that exists. In fact, the placebo effect can be as high as 85% in adults[59]. Consequently, parents may perceive improvement, regardless of whether their child receives medication, a placebo, or no treatment at all. One study reported that parents who wanted medication at the initial visit reported improvement regardless of whether the child received medication, placebo, or no medication. Treatment, comparing parents who did not request medication or preferred not to administer anything[60].

For the treatment of cough, it is important to identify the specific cause of cough and tailor treatment accordingly. Different causes of cough, such as asthma and tuberculosis, require distinct treatments, not a one-size-fits-all approach. The current trend is to determine the specific cause of cough and treat it directly. For chronic cough (lasting more than three weeks), the use of cough suppressants is discouraged. It's important to recognize that cough is a common and bothersome symptom, but it is essential to address the root cause of the cough rather than merely alleviate the symptom.

Conclusion

These factors play a critical role in a child's susceptibility to cough, and many of them can be mitigated or treated effectively. In some cases, comprehensive treatment can overcome these factors, but in others, only partial success may be achieved. In such cases, it is crucial for healthcare providers to focus on treating the underlying cause of the cough and to manage it effectively. The nature and specific factors influencing the cough should be carefully evaluated for each child under study. This approach can lead to more successful management and improved outcomes for children with cough-related conditions.

References

1. Denny, F. W., Collier, A. M., & Henderson, F. W. (1986). Acute respiratory infections in day care. Clinical Infectious Diseases, 8(4), 527-532.
2. Cherry JD. The common cold. In Feigin & Cherry (Eds) Textbook of pediatric infectious disease. 2 nd edn. Pp.155-160, WB Saunders Co. Philadelphia. 1987
3. Monto, A. S., & Ullman, B. M. (1974). Acute respiratory illness in an American community: the Tecumseh study. Jama, 227(2), 164-169.
4. Leder, K., Sinclair, M. I., Mitakaki, T. Z., Hellard, M. E., Forbes, A., & Fairley, C. K. (2003). A community-based study of respiratory episodes in Melbourne, Australia. Australian and New Zealand journal of public health, 27(4), 399-404.
5. Thomson, F., Masters, I. B., & Chang, A. B. (2002). Persistent cough in children and the overuse of medications. Journal of paediatrics and child health, 38(6), 578-581.
6. Wohl, M. E. B. (1978). Bronchiolitis: state of arts. Am Rev Resppir Dis, 118, 759-781.
7. Cypcar, D., & Busse, W. W. (1993). Role of viral infections in asthma. Immunology and allergy clinics of North America, 13(4), 745-767.
8. Loudon, R. G., & Brown, L. C. (1967). Cough frequency in patients with respiratory disease. American Review of Respiratory Disease, 96(6), 1137-1143.
9. Johnston, N. W., Johnston, S. L., Duncan, J. M., Greene, J. M., Kebadze, T., Keith, P. K., ... & Sears, M. R. (2005). The September epidemic of asthma exacerbations in children: a search for etiology. Journal of Allergy and Clinical Immunology, 115(1), 132-138.
10. Lister, S., Sheppeard, V., Morgan, G., Corbett, S., Kaldor, J., & Henry, R. (2001). February asthma outbreaks in NSW: a case control study. Australian and New Zealand journal of public health, 25(6), 514-519.
11. Wittig, H. J., & Glaser, J. (1959). The relationship between bronchiolitis and childhood asthma: a follow-up study of 100 cases of bronchiolitis in infancy. Journal of Allergy, 30(1), 19-23.
12. Eisen, A. H., & BACAL, H. L. (1963). The relationship of acute bronchiolitis to bronchial asthma—A 4-to-14-year follow-up. Pediatrics, 31(5), 859-861.
13. Evans, D., Levison, M. J., Feldman, C. H., Clark, N. M., Wasilewski, Y., Levin, B., & Mellins, R. B. (1987). The impact of passive smoking on emergency room visits of urban children with asthma. American Review of Respiratory Disease, 135(3), 567-572.
14. Slavin, R. G. (1992). Asthma and sinusitis. Journal of allergy and clinical immunology, 90(3), 534-537.
15. Gurwitz, D., Corey, M., & Levison, H. (1980). Pulmonary function and bronchial reactivity in children after croup. American Review of Respiratory Disease, 122(1), 95-99.
16.Loughlin, G. M., & Taussig, L. M. (1979). Pulmonary function in children with a history of laryngotracheobronchitis. The Journal of pediatrics, 94(3), 365-369.
17. Carson, J. L., Collier, A. M., & Hu, S. C. S. (1985). Acquired ciliary defects in nasal epithelium of children with acute viral upper respiratory infections. New England Journal of Medicine, 312(8), 463-468.
18. Laughlin, J. J., & Eigen, H. (1982). Pulmonary function abnormalities in survivors of near drowning. The Journal of Pediatrics, 100(1), 26-30.
19. Gurwitz, D., Kattan, M., Levison, H., & Culham, J. A. G. (1978). Pulmonary function abnormalities in asymptomatic children after hydrocarbon pneumonitis. Pediatrics, 62(5), 789-794.
20. Birnkrant, D. J., Picone, C., Markowitz, W., El Khwad, M., Shen, W. H., & Tafari, N. (2006). Association of transient tachypnea of the newborn and childhood asthma. Pediatric pulmonology, 41(10), 978-984.
21. Liem, J. J., Huq, S. I., Ekuma, O., Becker, A. B., & Kozyrskyj, A. L. (2007). Transient tachypnea of the newborn may be an early clinical manifestation of wheezing symptoms. The Journal of pediatrics, 151(1), 29-33.
22. Saigal S,,O'Brodovich,. The respiratory system in the newborn. Clinics in Perinatology 1987,14(3): 661-678.
23. Morgan W.J., Taussig L.M. Chronic Bronchitis. The Pediatric Clinics of North America 31(4) 1983.
24. Rantakallio, P. (1978). Relationship of maternal smoking to morbidity and mortality of the child up to the age of five. Acta Paediatrica, 67(5), 621-631.
25. Charlton, A. (1984). Children's coughs related to parental smoking. Br Med J (Clin Res Ed), 288(6431), 1647-1649.
26. Brand, P. L., & Duiverman, E. J. (1998). Coughing and wheezing children: improvement after parents stop smoking. Nederlands Tijdschrift voor Geneeskunde, 142(15), 825-827.
27. Adams, L., Lonsdale, D., Robinson, M., Rawbone, R., & Guz, A. (1984). Respiratory impairment induced by smoking in children in secondary schools. Br Med J (Clin Res Ed), 288(6421), 891-895.
28. Stein, R. T., Holberg, C. J., Sherrill, D., Wright, A. L., Morgan, W. J., Taussig, L., & Martinez, F. D. (1999). Influence of parental smoking on respiratory symptoms during the first decade of life: the Tucson Children's Respiratory Study. American journal of

epidemiology, 149(11), 1030-1037.
29. Khoshoo, V., Edell, D., Mohnot, S., Haydel Jr, R., Saturno, E., & Kobernick, A. (2009). Associated factors in children with chronic cough. Chest, 136(3), 811-815.
30. Lack, G. (2001). Pediatric allergic rhinitis and comorbid disorders. Journal of allergy and clinical immunology, 108(1), S9-S15.
31. König, P. (1981). Hidden asthma in childhood. American journal of diseases of children, 135(11), 1053-1055.
32. Platts-Mitis, T. A., Sporik, R. B., Chapman, M. D., & Heymann, P. W. (1995). The role of indoor allergens in asthma. Allergy, 50, 5-12.
33. Sporik, R., Ingram, J. M., Price, W., Sussman, J. H., Honsinger, R. W., & Platts-Mills, T. A. (1995). Association of asthma with serum IgE and skin test reactivity to allergens among children living at high altitude. Tickling the dragon's breath. American journal of respiratory and critical care medicine, 151(5), 1388-1392.
34. Castellsague, J., Sunyer, J., Saez, M., & Anto, J. M. (1995). Short-term association between air pollution and emergency room visits for asthma in Barcelona. Thorax, 50(10), 1051-1056.
35. White, M. C., Etzel, R. A., Wilcox, W. D., & Lloyd, C. (1994). Exacerbations of childhood asthma and ozone pollution in Atlanta. Environmental Research, 65(1), 56-68.
36. Romieu, I., Meneses, F., Sienra-Monge, J. J. L., Huerta, J., Velasco, S. R., White, M. C., ... & Hemandez-Avila, M. (1995). Effects of urban air pollutants on emergency visits for childhood asthma in Mexico City. American Journal of Epidemiology, 141(6), 546-553.
37. Studnicka, M., Hackl, E., Pischinger, J., Fangmeyer, C., Haschke, N., Kuhr, J., ... & Frischer, T. (1997). Traffic-related NO2 and the prevalence of asthma and respiratory symptoms in seven year olds. European Respiratory Journal, 10(10), 2275-2278.
38. Ciccone, G., Forastiere, F., Agabiti, N., Biggeri, A., Bisanti, L., Chellini, E., ... & Viegi, G. (1998). Road traffic and adverse respiratory effects in children. SIDRIA Collaborative Group. Occupational and environmental medicine, 55(11), 771-778.
39. Goren, A. I., Goldsmith, J. R., Hellmann, S., & Brenner, S. (1991). Follow-up of schoolchildren in the vicinity of a coal-fired power plant in Israel. Environmental health perspectives, 94, 101-105.
40. Nowak, D., Heinrich, J., Jorres, R., Wassmer, G., Berger, J., Beck, E., ... & Magnussen, H. (1996). Prevalence of respiratory symptoms, bronchial hyperresponsiveness and atopy among adults: west and east Germany. European Respiratory Journal, 9(12), 2541-2552.
41. Østergaard, M. S., Nantanda, R., Tumwine, J. K., & Aabenhus, R. (2012). Childhood asthma in low income countries: an invisible killer?. Primary Care Respiratory Journal, 21(2), 214-219.
42. Bråbäck, L., Breborowicz, A., Julge, K., Knutsson, A., Riikjärv, M. A., Vasar, M., & Björkstén, B. (1995). Risk factors for respiratory symptoms and atopic sensitisation in the Baltic area. Archives of disease in childhood, 72(6), 487-493.
43. Gao, Y., Chan, E. Y., Li, L., Lau, P. W., & Wong, T. W. (2014). Chronic effects of ambient air pollution on respiratory morbidities among Chinese children: a cross-sectional study in Hong Kong. BMC public health, 14(1), 1-11.
44. Hynes, H. P., Brugge, D., Osgood, N. D., Snell, J., Vallarino, J., & Spengler, J. (2004). Investigations into the indoor environment and respiratory health in Boston public housing. Reviews on environmental health, 19(3-4), 271-290.
45. Conference for North American Environmental Cooperation, Montreal Canada November 2003.
46. Vargas, M. H., Sienra-Monge, J. J., Díaz-Mejía, G., & DeLeón-González, M. (1999). Asthma and geographical altitude: an inverse relationship in Mexico. Journal of asthma, 36(6), 511-517.
47. Li, S., Baker, P. J., Jalaludin, B. B., Guo, Y., Marks, G. B., Denison, L. S., & Williams, G. M. (2014). An Australian national panel study of diurnal temperature range and children's respiratory health. Annals of Allergy, Asthma & Immunology, 112(4), 348-353.
48. Brochu, P. J., Yanosky, J. D., Paciorek, C. J., Schwartz, J., Chen, J. T., Herrick, R. F., & Suh, H. H. (2011). Particulate air pollution and socioeconomic position in rural and urban areas of the Northeastern United States. American journal of public health, 101(S1), S224-S230.
49. JD, B. E., JI, C. M., & JC, C. M. (1990). Repercussion of risk factors associated with the development of chronic bronchial pathology on pulmonary function in children. Anales Espanoles de Pediatria, 32(5), 399-406.
50. Hillemeier, A. C. (1996). Gastroesophageal reflux: diagnostic and therapeutic approaches. Pediatric Clinics, 43(1), 197-212.
51. Ott, D. J., Wu, W. C., & Gelfand, D. W. (1981). Reflux esophagitis revisited: prospective analysis of radiologic accuracy. Gastrointestinal Radiology, 6, 1-7.
52. Allen, C. J., & Anvari, M. (2002). Preoperative symptom evaluation and esophageal acid infusion predict response to laparoscopic Nissen fundoplication in gastroesophageal reflux patients who present with cough. Surgical endoscopy, 16, 1037-1041.
53. Pratter, M. R., Bartter, T., Akers, S., & DuBois, J. (1993). An algorithmic approach to chronic cough. Annals of internal medicine, 119(10), 977-983.
54. Redington A.E, Morice A.H. Acute and chronic cough 2005. (205)261-262. Taylor & Francis Group. Boca Raton Fl.
55. Buts, J. P., Barudi, C., & Otte, J. B. (1987). Double-blind controlled study on the efficacy of sodium alginate (Gaviscon) in reducing gastroesophageal reflux assessed by 24 h continuous pH monitoring in infants and children. European journal of pediatrics, 146, 156-158.
56. Schroeder, K., & Fahey, T. (2002). Should we advise parents to administer over the counter cough medicines for acute cough? Systematic review of randomised controlled trials. Archives of disease in childhood, 86(3), 170-175.
57. Schroeder, K., & Fahey, T. (2001). Over-the-counter medications for acute cough in children and adults in ambulatory settings. The Cochrane Database of Systematic Reviews, (3), CD001831-CD001831.
58. Gunn, V. L., Taha, S. H., Liebelt, E. L., & Serwint, J. R. (2001). Toxicity of over-the-counter cough and cold medications. Pediatrics, 108(3), e52-e52.
59. Chang, A. B., Landau, L. I., Van Asperen, P. P., Glasgow, N. J., Robertson, C. F., Marchant, J. M., & Mellis, C. M. (2006).

Cough in children: definitions and clinical evaluation. Medical Journal of Australia, 184(8), 398-403.
60. Hutton, N., Wilson, M. H., Mellits, E. D., Baumgardner, R., Wissow, L. S., Bonuccelli, C., ... & DeAngelis, C. (1991). Effectiveness of an antihistamine-decongestant combination for young children with the common cold: a randomized, controlled clinical trial. The Journal of pediatrics, 118(1), 125-130.

Chapter - III

The Diagnostic Process of Pediatric Cough

While cough is one of the primary signs and symptoms in humans, it has only recently become a prominent area of research. Historically, it was seldom considered a central diagnostic indicator for the disease causing it. This oversight arose from the perception of cough as a non-specific symptom that could result from almost any respiratory disease. Physicians often sought diagnostic clues in accompanying general symptoms, such as expectoration, dyspnea, wheezing, fever, and more, rather than examining cough itself.

Another reason for the limited use of cough as a diagnostic tool was the absence of a dedicated medical specialty that comprehensively addressed it. Otorhinolaryngologists handled cough stemming from upper airway issues, while pulmonologists dealt with cough arising from lower airway conditions. Some diseases, such as laryngo-tracheo-bronchitis, fell under the purview of both specialties. Pediatricians found themselves responsible for addressing both upper and lower airway issues, necessitating a breadth of knowledge spanning both domains. While research on adult cough is relatively recent, the study of cough in children, particularly in clinical practice, lags even further behind.

In some instances, parents may seek medical attention for their children because they recognize that cough can be a precursor to a severe asthma attack or because they are concerned about various discomforts associated with coughing, such as insomnia, vomiting, headache, difficulties in physical activity, reduced appetite, fever, a sensation of suffocation, and musculoskeletal pain[1]. Chronic cough can lead to complications that range from simple irritation of the pharyngo-laryngeal and tracheo-bronchial areas, which can perpetuate the cough, to more severe consequences, including vomiting, muscle fatigue, and, in rare cases, serious complications like rib fractures, pneumothorax, pneumomediastinum, and rectus abdominis muscle rupture.

In some cases, parents' concerns regarding their child's cough may be extreme, driven by fears of severe intrathoracic damage or even death. The clinical approach to cough in children significantly differs from that in adults. For instance, children may have congenital or perinatal causes of cough, and foreign body aspiration is a concern unique to children. This chapter aims to emphasize cough as a crucial diagnostic symptom in children and to guide its treatment effectively. It's essential to understand that cough varies from one disease to another, and recurrent coughing episodes in a child may indicate the recurrence of the same disease.

To differentiate cough as a symptom, an accurate description of the cough itself is indispensable. A clinical focus that considers the cough's characteristics can often establish connections with certain pathophysiological events and, subsequently, with the most common diseases that explain it. While some data are highly specific, others are less so. A prime example is distinguishing between a wet cough and a dry cough, as many seemingly "dry" coughs can be attributed to secretions, even when they are scant, particularly in children.

The following sections provide six tables with suggested diagnostic methods based on different characteristics of the cough, the patient, and simple chest X-ray findings. For cough persisting longer than ten days, each patient should undergo all five diagnostic approaches. If the cough continues for over eight weeks, Table VI is recommended. This comprehensive table explores various causes, necessitating more in-depth and invasive investigations, as it encompasses a wide range of diagnostic possibilities.

The 6 Tables are:

I. Typical cough (Very specific for each disease)

II. Very Frequent Cough (The great frequency with which these diagnoses occur determines that they are considered in all patients).

III. Cough According to Age (Each age group influences the frequency of diseases that cause cough).

IV. Cough that subsides or decreases with specific therapy (The frank response to a single treatment suggests a diagnosis specific).

V. Cough with normal chest x-ray (It usually initially rules out, although with reservations, a good number of diagnoses).

VI. Chronic cough, more than 8 weeks. (Other diagnoses to consider).

I. Typical Cough

Typical coughs are highly suggestive of a specific disease, characterized by distinct features that often point to one or two potential diagnoses, and sometimes even reveal the underlying cause. Such coughs are typically so distinct and characteristic of a particular ailment that finding an alternative diagnosis can be challenging.

One unique example is the cough now colloquially referred to as the "seal cough" due to its resemblance to the sound of a barking seal. It is also described as "barking," "metallic," or "tracheal"

due to the dry quality of the cough. In most cases, a definitive diagnosis can be made simply by listening to the child cough. This is especially true if the cough is accompanied by symptoms like dysphonia and stridor, as it allows physicians to easily rule out conditions like laryngotracheomalacia, which primarily affects younger children. The terms "coughing fits" or "coughing spells" refer to groups of multiple coughing episodes rather than isolated coughs.

A "clearing" cough is one accompanied by the act of "clearing the throat" or "pharyngeal clearing" with varying frequency. The presence of this throat-clearing action can offer insight into the pathophysiological process responsible for the cough. Typically, it is associated with posterior nasal drip syndrome, a condition where secretions, to be effectively swallowed, require prior clearance from the surface of the posterior wall of the hypopharynx. This clearance is achieved through the action of clearing the throat to facilitate the necessary propulsive pressure for proper swallowing. In some cases, this excessive secretion and associated inflammation can lead to dysphonia.

Although intense throat clearing can also occur following high gastroesophageal reflux events that reach the upper airways, both throat clearing and reflux events are more frequently observed in adolescents and adults. In children, gastroesophageal reflux has been linked to recurrent croup[2]. Given the prevalence of postnasal drip syndrome (PNS) as one of the most common causes of cough, it warrants further discussion below.

(Postnasal Drip Syndrome or Upper Respiratory Disease Cough Syndrome): PNS refers to the presence of secretions that flow from the posterior part of the nasopharynx to the posterior oropharyngeal wall, and sometimes further downward to the hypopharynx and even the lower airways. SGNP, either in isolation or combination, stands out as the most frequent cause of acute and chronic cough in both children and adults, often prompting them to seek medical attention. SGNP can induce both dry cough (in approximately 30% of cases) and wet cough (in about 60% of cases)[3]. These characteristics, however, are not the primary criteria for diagnosis since wet cough can result from a broad spectrum of diseases characterized by excessive mucus production, as shown in the table. A wet cough offers the advantage of allowing further evaluation of the secretion (expectoration or anterior and/or posterior rhinorrhea), which gives it the distinctive moist quality that defines it.

Moving forward in our exploration of "typical cough," nocturnal coughs—occasionally confused by some parents as "coughs due to cold weather" (even in warm regions)—and morning coughs are specific to posterior nasal drip. They are closely tied to recumbent positions, which lead to improved gravity-driven sinus drainage. These coughs may also occur when children change their position from recumbent to an upright one, particularly in the trunk and head areas. In such instances, accumulated secretions in the hypopharynx during the night are mobilized by gravity, resulting in coughing. These episodes occur both at night and in the morning, though in some children, one of the two periods may exhibit a more pronounced occurrence.

When children experience coughing spells during physical activity, it suggests bronchial hyperreactivity, often associated with asthma or early wheezing. Parents might report that their child only coughs during vigorous exercise. A more precise query would be: "Does your child cough frequently when they engage in vigorous physical activity, such as running?" Typically, the answer is affirmative for these children, even when measures are taken to pause their play to prevent coughing. Coughing during intense laughter or forceful exhalations is also common in these cases.

Extended coughing spells culminating in stridor are highly indicative of whooping cough.

I. Typical Cough

Quality of cough Probable diagnosis

1.-) **"SEAL" "TRACHEAL", "METALLIC" OR "DOGGY"**	***LARYNGO-TRACHEO-BRONCHITIS (CRUP)** -Laryngotracheomalacia -Psychogenic cough
2.-) **"THROATING" COUGH** (associated with mechanism of oropharyngeal clearance)	**POSTERIOR NASAL DRIP SYNDROME: Rhinopharyngitis or rhinosinusitis (If more than 10 days)**
3.-) **NIGHT COUGH** (decubitus)	**POSTERIOR NASAL DRIP SYNDROME** Asthma, Gastroesophageal reflux
4.-) **WHEN GETTING UP BY THE MORNINGS**	**POSTERIOR NASAL DRIP SYNDROME** (causes both night and morning cough) **Bronchiectasis** (more likely if accompanied by pulmonary suppuration)
5.-) **DURING OR AFTER THE EXERCISE** (also when laughing, or forcefully exhale)	**ASTHMA or EARLY WHEEZING (If less than 6 years)**
6.- **PAROXYSTIC** (long bouts of short, uncontrollable coughs)	**WHOOPING COUGH** (very typical with final stridor). POSTERIOR NASAL DRIP SYNDROME

7.-) **Goose honking** (cough similar to to an old car horn)	**PSYCHOGENIC COUGH**
STACCATO COUGH (from newborn to 3-4 months old)	**CHLAMYDIA TRACHOMATIS**
9.-) **PRODUCTIVE MOLD COUGH BRONCHIAL**	**ASTHMA** PLASTIC BRONCHITIS

***In bold when the diagnosis is very feasible given the typical nature of the cough.**

Psychogenic cough is a diagnosis that should be made through exclusion. While not very common, it tends to predominate in the pre-pubertal and adolescent stages. However, it can also be observed in preschool children, especially in female patients and in situations of emotional tension, such as school competition, difficulty in relating to peers, or instances of bullying.

Both in adults and children[4], anxiety is recognized as an independent risk factor for chronic cough[5]. Psychological issues can lead to coughing in children independently or coexist with an organic etiology, such as Tourette syndrome, motor or vocal tics, and be contributing factors for the cough.

Addressing the organic cause can significantly alleviate the cough, but it may persist as long as the underlying emotional tension remains unresolved or is not managed from a psychological perspective[6]. Ideally, both aspects need to be addressed.

Psychogenic cough has been described as similar to the sound made by Canada geese, with a quack that is slightly deeper and more "hollow" than the sound of common ducks, or akin to an old car horn.
It is often assumed that in cases of psychogenic cough, there is an emotional or affective gain, such as capturing the attention of parents. At times, an anxiolytic treatment might be more effective than traditional cough medications, though the primary goal is to address the psychological factors or mitigate the socio-affective environment contributing to the cough.

Chlamydia Cough

The staccato cough is characteristic of pneumonia secondary to Chlamydia trachomatis infection, especially in the neonatal period. The term "staccato" is borrowed from music and indicates that the notes, or in this case, the coughs, are played separately and detached[7], like distinct musical notes. In other words, it is characterized by isolated coughing spells.
In rare instances, a cough accompanied by the production of bronchial molds can primarily result from an asthmatic attack or the uncommon occurrence of plastic bronchitis.

II. Very Frequent Cough

These are the most commonly encountered types of cough in daily medical practice and often require significant attention. Unfortunately, some characteristics of these coughs are less specific for making diagnoses compared to other clinical approaches.

Wet Cough and Dry Cough

Traditionally, the literature describes "dry cough" and its counterpart, "wet cough." However, parents frequently misinterpret one for the other[8], so it should not be assumed that a dry cough is free of any secretion.

A productive cough doesn't necessarily generate expectoration, and even when the cough results from secretions, it's not always expectorated. In some cases, it may be perceived as dry. Children and women typically have limited ability to expectorate, influenced by factors like age, pharyngeal and laryngeal anatomy, strength, the nature of the secretion, and more. Therefore, a wet or productive ("thick") cough in children might be synonymous with a cough that generates secretion, even when there's no actual ability to expectorate. Mothers' observations regarding the characteristics of the secretion, whether it's observed as expectoration during a coughing episode or as vomit (in the case of an emetic cough), are valuable. This helps with characterization, as a mucohyaline secretion suggests a viral etiology, while mucopurulent secretion points more toward a bacterial etiology, especially if it persists for more than 10-12 days.

II. Very Frequent Cough

Description	Probable Diagnosis
1.- Cough predominantly nocturnal (during recumbency)	POSTERIOR NASAL DRIP SYNDROME LATER - Disease due to gastroesophageal reflux
2.- During or after running **(or laughing out loud)**	-ASTHMA (or early wheezing)
3. During or after meals	**-** Gastroesophageal reflux - Ineffective swallowing mechanism
4.- Dry* (Considered the most nonspecific cough) It is mandatory to look for accompanying characteristics such as rhinorrhea, nocturnal and morning predominance (SGNP), or wheezing, dyspnea or increased cough with exertion (asthma).	**PSTERIOR NASAL DRIP SYNDROME** (By far the most common cause, especially if it occurs more at night and/or in the morning, as well as if it is accompanied by rhinorrhea, even if this is very slight) **ASTHMA** OR **EARLY WHEEZING** Particularly at the beginning of an exacerbation) - "IRRITATIVE" COUGH **(After a viral infection)**

5.- Productive	POSTERIOR NASAL DRIP SYNDROME: Rhinopharyngitis or rhinosinusitis (if more than 10-12 days) Asthma, gastroesophageal reflux, bronchitis, bronchiolitis, pneumonia, bronchiectasis, CF, pulmonary edema, bronchiectasis, etc. etc

*It should not be assumed that there are no secretions in children with cough interpreted by parents as “dry cough”

By definition, expectoration is the act of expelling materials from the trachea, bronchi, or lungs through coughing. These materials originate from the thorax[9]. However, in children with a productive cough, the secretions (materials) may not necessarily originate from the lower airways. They can result from secretions produced in the upper airways. Therefore, children who exhibit expectoration may also have conditions like rhinosinusitis, allergic rhinitis, or the common cold, in addition to diseases causing lower airway secretions, such as asthma, bronchitis, or pneumonia.

Furthermore, it becomes more challenging for younger children to expectorate, even when their secretions are excessive. This is why the terms "wet" or "thick cough" are often used interchangeably to describe a productive cough.

III. Diagnosis According to Age

MINOR INFANT **(1 a12 months)**	**1.- Viral infections upper airways, recurrent or concatenated (PNDS)** 2.- Early wheezing/asthma 3.- Viral airway infections lower E.g.: Bronchiolitis 4.- Postbronchiolitis sequelae 5.- Reflux disease gastroesophageal 6.- Bronchopulmonary dysplasia Congenital malformations

OLDER INFANT AND PRESCHOOLER (1 A5 YEARS)	**1.- Rhinopharyngitis (viral) or rhinosinusitis (bacterial) + PNDS** **2.- Viral infections of the airways recurrent discharges + PNDS** 3.- Early wheezing/asthma 4.- Respiratory Disease Postbronchiolitis 5.- Pneumonia 6.- Gastroesophageal reflux 7.- Foreign body
SCHOOLS AND ADOLESCENTS (6 A16 YEARS)	**1.-Rhinopharyngitis (viral) or rhinosinusitis (bacterial) +PNDS** 2.- Asthma 3.- Recurrent superior respiratory tract infections (PNDS) 4.-Gastroesophageal reflux 5.- Psychogenic cough

PNDS: Postnasal drip syndrome

In conclusion, it should not be assumed that children, regardless of their age, can never expectorate, nor should it be assumed that a cough considered dry implies an absence of secretions in the airways.

III. Cough According to Age

The pediatric stage encompasses a wide range of ages, from newborns to adolescents. Understanding the common disorders associated with each age group is crucial for diagnostic guidance. Age influences the susceptibility and underlying causes of subacute or recurrent cough. In the early stages of life, factors like immaturity or malformation of bodily systems (see factors increasing cough incidence) play a significant role, but their influence diminishes as other factors become more important. In this context, there remains a debate about whether asthma, considering the natural course of the disease, can be largely attributed to an immaturity of the body's adaptation to its environment. This may explain why many children initially diagnosed with wheezing see their symptoms decrease and even disappear as they age.

Diagnostic Age Groups

From the 29th day of the neonatal period and throughout the first year, cough-related illnesses are typically of viral origin or may manifest as persistent wheezing. Other not uncommon causes of cough at this stage include gastroesophageal reflux and lesions resulting from prematurity, mechanical ventilation, or bronchopulmonary dysplasia in premature infants. It's essential to consider the possibility of congenital malformations during this period.

In older infants and preschoolers, while they remain susceptible to viral infections throughout life, bacterial infections in the upper respiratory tract become more common causes of cough. Bacterial infections may not resolve as quickly as viral ones, which usually last 7 to 10 days. Infections often target the paranasal

sinuses, with rhinosinusitis being a frequent complication of the common cold, extending the cough beyond the typical 10-12 days associated with viral upper airway infections, also known as the common cold or rhinopharyngitis. Rhinosinusitis can present as recurrent cough, lasting for 2 weeks to a month, disappearing, and reappearing 15 to 30 days later.

Bronchiolitis and the bronchial hyperreactivity it leaves in its wake are additional causes of recurrent cough. Wheezing is a characteristic accompanying sign, and sometimes dyspnea may also be present, leading to emergency room visits. Coughing during vigorous physical activity can be an early indicator of bronchial hyperreactivity.

Any of the aforementioned causes of cough can be complicated by pneumonia. In this age group, Broncho aspiration of foreign bodies is more frequent and should be considered, even without maternal disclosure or suspicion. Additional supportive evidence, such as stridor, atelectasis, a valve phenomenon with pulmonary hyperinflation, sudden onset of cough and/or wheezing, or simply maternal doubt regarding a potential event, should lead to bronchoscopy.

Cough That Improves or Resolves With Specific Therapy

With the exception of morphine and codeine, there are no effective nonspecific cough suppressants for all types of cough. Medications designed to address the underlying cause of the cough are more effective. For instance, children with cough due to asthma benefit from bronchodilators. Therapeutic tests can sometimes be useful for suggesting a diagnosis or understanding the pathophysiological mechanism. The placebo effect can significantly influence the outcome of a therapeutic test[10]. The interpretation of a therapeutic test can be challenging, considering the many variables involved in cough-related diseases. Objectivity in evaluation is vital. Asthma, particularly cough-variant asthma, is easier to diagnose through treatment[11]. Bronchodilator treatment can reliably confirm the diagnosis in children under 5 years of age, where spirometry cannot be performed due to a lack of cooperation.

The use of antimicrobials for apparent infectious causes of cough may seem logical, but it is not without potential problems like subtherapeutic doses, too short administration periods, or resistance. Antihistamines and decongestants can also be used for specific tests, mainly to address postnasal drip as the primary cause of cough. However, it's important to note that these are prohibited in children under 2 years of age[12]. Cough due to gastroesophageal reflux is often associated with bronchospasm, leading to an increase in abdominal pressure, which can promote or exacerbate reflux. This makes the interpretation of therapeutic tests challenging[13]. For patients with reflux-related cough, the test is simpler when it's associated with symptoms like frequent vomiting or regurgitation related to food.

In conclusion, a therapeutic test can range from easily interpretable, as in the case of asthma, to quite challenging, as in gastroesophageal reflux disease. Sometimes, short antimicrobial treatments for infectious cough may be insufficient, leading to partial responses or recurrent cough. Directed therapeutic tests, involving a single medication for a specific diagnosis, can be useful when interpreted with caution. Ongoing research suggests promising results for addressing cough due to posterior nasal discharge in children with the common cold, although the study is not yet complete due to the COVID-19 pandemic.

Experimental Control

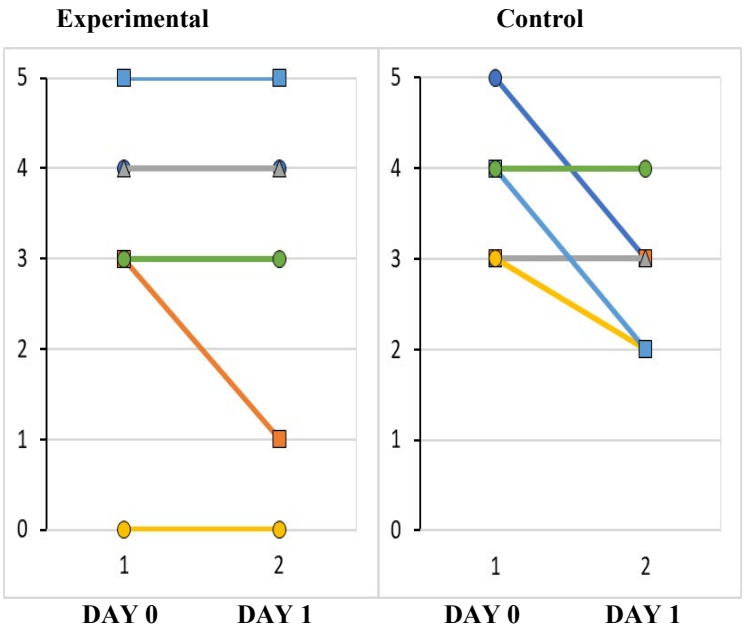


Figure 1: A study is shown with 10 children with cough secondary to a common cold (48-72 hours of onset) who were administered intranasally: placebo (control) the aqueous combination of intranasal oxymetazoline-ipratropium (experimental) (Patent US20018034472) Data not yet published.

BRONCHODILATORS		**ASTHMA/EARLY WHEEZING**
ANTIHISTAMINE DECONGESTANT PO	+	**COMMON COLD** (postnasal drip **syndrome**) - Allergic rhinitis - Vasomotor rhinitis
ANTIBIOTIC		**-RHINOSINUSITIS** -Bronchitis -Bacterial rhinopharyngitis other bacterial infections of the respiratory tract
GASTROKINETICS/PROTON PUMP INHIBITORS OR H_2 BLOCKERS		**GASTROESOPHAGEAL REFLUX**
ANSIOLYTIC?		**PSYCHOGENIC COUGH**
VASOCONSTRICTOR + ANTICHOLINERGIC (nasal topical)		**COMMON COLD** (Postnasal drip syndrome) **RHINOSINUSITIS**

Psychogenic cough is more commonly observed during puberty and early adolescence, especially in patients facing school and/or family pressures, which can often be elicited through targeted questioning. It is a diagnosis considered after ruling out other potential causes and, therefore, it is inherently a diagnosis of exclusion. The exclusion process can be notably complicated when ambiguous results are obtained from the conducted studies.

V. Cough With Normal Chest X-Ray

A normal chest radiograph is an invaluable tool for ruling out lung parenchymal diseases, with some exceptions[14]. Among these exceptions are certain opacities that may not be easily discernible behind the cardiac silhouette or below the diaphragmatic levels in the posteroanterior projection, particularly in the left hemithorax. These opacities could indicate conditions such as bronchiectasis or small areas of pneumonia. Additionally, intrathoracic abnormalities, such as small effusions or congenital malformations located in the mediastinum (e.g., duplication cysts) or in the lung parenchyma, like early-stage pulmonary fibrosis.

-POSTERIOR NASAL DRIP SYNDROME

-ASTHMA/EARLY WHEELS

-GASTROESOPHAGEAL REFLUX

-FOREING BODY IN AIRWAYS

VI. Chronic Cough

When a child has been coughing continuously for more than 8 weeks, it may indicate a severe disorder that could jeopardize not only the patient's development but also their life. This persistent cough could be a result of lung disease, systemic illness, or a sequel to a previously inactive process, such as bronchiolitis obliterans resulting from a prior pathogenic event. The diagnostic possibilities significantly broaden, encompassing a wide range of conditions found in pediatric pulmonology textbooks.

Just as with diseases at other levels, a thorough clinical history should guide further investigations. Subtle details, along with physical and radiological findings, can be of paramount importance. Chronic cough typically necessitates deeper and more invasive studies, in addition to the information provided by the medical history and chest X-ray.

Certain types of cough may suggest specific diagnoses. For example, morning cough with pulmonary suppuration might indicate conditions like bronchiectasis resulting from previous infections or cystic fibrosis. Another example is sudden-onset cough following a choking incident, which could be attributed to foreign body aspiration.

Chronic tracheal cough, often accompanied by laryngotracheomalacia-related stridor, or cough occurring during feeding and associated with swallowing disorders, as well as postprandial cough due to gastroesophageal reflux, are other examples. Nonetheless, a significant proportion of chronic cough cases may not provide sufficient data to suggest a specific diagnosis.

Below is a table listing suggested studies for making a diagnosis. Please note that this is just a sample, as the range of potential diagnoses in pediatric pulmonology is extensive.

CHRONIC COUGH	MORE THAN 8 WEEKS	TRACHEO-BRONCHOMALACIA	**FIBROBRONCHOSCOPY**
		BRONCHIOLITIS OBLITERANTS BRONCHIECTASIA	**CT (high resolution) of the Chest**
		BACTERIAL PROTRACTED BRONCHITIS	**FIBROBRONCHOSCOPY SMEAR AND CULTIVES**
		TUBERCULOSIS	**BACILLOSCOPY (in gastric lavage or BAL) Quantiferon**
		GASTROESOPHAGEAL REFLUX	**pHmetry/SEGD/ lipophages in BAL**
		ASTHMA	**Spirometry/Oscillometry bronchodilator response**
		CYSTIC FIBROSIS	**Electrolytes in sweat**
		BRONCHOPULMONARY DYSPLASIA	**Perinatal history/criteria**
		CONGENITAL HEART DISEASE	**Echocardiography**
		PULMONARY FIBROSIS	**Lung biopsy**

PSYCHOGENIC COUGH	**Diagnosis by exclusion**
CILIARY DYSKINECIA	**NASAL EXHALED NITRIC OXIDE. BRONCHIAL BIOPSY WITH ELECTRON MICROSCOPY**

Chronic cough can represent a difficult diagnostic challenge in some cases requiring a lung biopsy, especially in interstitial diseases in which the causes are very diverse.

Multiple Concurrent Causes of Chronic Cough in the Same Patient

In two adult studies conducted by Dr. Richard Irwin[15], 18% and 23% of patients with challenging-to-diagnose chronic cough had two contributing causes, respectively. Additionally, 3% of the total cases exhibited more than two contributing disorders triggering the cough. These studies treated postnasal drip syndrome as a single cause, even though, in many instances, multiple factors contributed to its occurrence, such as rhinosinusitis and allergic rhinitis occurring simultaneously. In the case of children, it may not differ significantly, and it is evident that one cause does not necessarily exclude the presence of a second cause. Occasionally, as noted in the mentioned studies, a third contributing factor for the cough is observed.

In fact, at times, one cause of cough can make it more likely for a second cause to emerge. An illustrative example is an asthmatic child who contracts viral rhinopharyngitis. Initially, the child presents a cough due to postnasal drip, often accompanying the forward nasal discharge typical of rhinopharyngitis. Consequently, the child typically experiences more pronounced coughing, primarily at night and in the morning. On the other hand, rhinopharyngitis can serve as a catalyst for an asthma exacerbation or bronchospasm, especially in early wheezing.

Bronchospasm, in and of itself, accompanied by bronchial hypersecretion, is also a cause of cough with this new bronchial origin. As a result, the child is now coughing for two different reasons, each necessitating individualized treatment. In the example above, a bronchodilator can alleviate the cough resulting from bronchospasm. However, if the postnasal drip is not addressed, the child will continue to experience coughing, primarily at night and in the morning, until this manifestation, corresponding to rhinopharyngitis, either naturally subsides within 7 to 10 days or is treated.

Certain diseases are more likely to combine with other conditions or specific factors to provoke cough. The following is a list of common combinations.

Common Disease Combinations

Allergic rhinitis	**Asthma**
Allergic rhinitis	**Rhinosinusitis**
Rhinosinusitis	**Asthma**
GE Reflux	**Asthma**
GE Reflux	**Recurrent pneumonia**
BP dysplasia	**Early whistler/ Recurrent pneumonia**

The diseases listed above can be combined to a greater or lesser degree with the factors that increase the incidence of cough. and that may require highly specialized management.

Thus, you can have a child who was born prematurely and required mechanical ventilation for 2 weeks, under 2 years old and who attends daycare. If the mother smokes[16], then she will be much more susceptible to suffering from concatenated viral infections of the upper respiratory tract and developing bronchospasm in each event. This patient will have a higher level of complexity to be diagnosed and managed and it is clear that it will not be enough for the mother to stop smoking.

Allergic rhinitis is frequently combined with asthma since both frequently share atopy as a physiopathogenic background.

Likewise, allergic rhinitis makes children more susceptible to rhinosinusitis[17,18] given that the inflammatory process of the Nasal mucosa also includes mucosa of the drains and meatuses of the paranasal sinuses with consequent obstruction and increased possibility of becoming secondarily infected and manifesting as chronic or recurrent cough due to the consequent post-nasal drip syndrome.

Obviously, cough is an interesting process with several components and a wide variety of factors and diseases that can affect it; Breaking down the causes, giving them their fair weight, as well as an appropriate treatment for each of them, is precisely the job of the doctor who in his daily consultation sees children with respiratory diseases.

References

1. Holinger, L. D., & Sanders, A. D. (1991). Chronic cough in infants and children: an update. The Laryngoscope, 101(6), 596-605.
2. Gilger, M. A. (2003). Pediatric otolaryngologic manifestations of gastroesophageal reflux disease. Current gastroenterology reports, 5(3), 247-252.
3. Irwin, R. S. (1999). Managing cough as a defense mechanism as a symptom. A consensus panel report of the American College of Chest Physicians. Chest, 115(2), 602-603.
4.Gay, M., Blager, F., Bartsch, K., Emery, C. F., Rosenstiel-Gross, A. K., & Spears, J. (1987). Psychogenic habit cough: review and case reports. The Journal of clinical psychiatry, 48(12), 483-486.
5.Lúdvíksdóttir, D., Björnsson, E., Janson, C., & Boman, G. (1996). Habitual coughing and its associations with asthma, anxiety, and gastroesophageal reflux. Chest, 109(5), 1262-1268.
6. Powell, C., Brazier, A. (2004). Psychological approaches to the management of respiratory symptoms in children and adolescents. Pediatric Respir Rev 5, 214-224.
7. Moliner Mary. Dictionary of the use of Spanish, p.1212 Editorial Gredos, SA Madrid 20th printing.
8. Chang, A. B., Landau, L. I., Van Asperen, P. P., Glasgow, N. J., Robertson, C. F., Marchant, J. M., & Mellis, C. M. (2006). Cough in children: definitions and clinical evaluation. Medical Journal of Australia, 184(8), 398-403.
9. Save Publishers. Terminological dictionary of medical sciences 1968 Barcelona Spain.
10. Hutton, N., Wilson, M. H., Mellits, E. D., Baumgardner, R., Wissow, L. S., Bonuccelli, C., ... & DeAngelis, C. (1991). Effectiveness of an antihistamine-decongestant combination for young children with the common cold: a randomized, controlled clinical trial. The Journal of pediatrics, 118(1), 125-130.
11.GINA. (2018). Global strategy for asthma management and prevention pp.103. www.ginasthma.
12. Thomson, F., Masters, I. B., & Chang, A. B. (2002). Persistent cough in children and the overuse of medications. Journal of paediatrics and child health, 38(6), 578-581.
13. Rs, I. (1990). Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. Am Rev Respir Dis, 141, 640-647.
14. Palombini, B. C., Villanova, C. A. C., Araujo, E., Gastal, O. L., Alt, D. C., Stolz, D. P., & Palombini, C. O. (1999). A pathogenic triad in chronic cough: asthma, postnasal drip syndrome, and gastroesophageal reflux disease. Chest, 116(2), 279-284.
15.Irwin, R. S., Corrao, W. M., & Pratter, M. R. (1981). Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. American Review of Respiratory Disease, 123(4), 413-417.
16.Charlton, A. (1984). Children's coughs related to parental smoking. Br Med J (Clin Res Ed), 288(6431), 1647-1649.
17. Van, Bever. H. P., Desager, K. N., Hegendorens, M. (2002). Critical evaluation of prognostic factors in childhood asthma. Pediatric Allergy Immunol 13:77-83.
18. Lombardi, E., Stein, R. T., Wright, A. L., Morgan, W. J., & Martinez, F. D. (1996). The relation between physician-diagnosed sinusitis, asthma, and skin test reactivity to allergens in 8-year-old children. Pediatric pulmonology, 22(3), 141-146.

Chapter - IV

Posterior Nasal Drip Syndrome (PNDS) as a Cause of Cough

Posterior nasal drip refers to the drainage of secretions from the nasal mucosa and paranasal sinuses, which flow into the nasopharynx and hypopharynx, located behind the nose. Normally, this flow of secretions is minimal and is unconsciously swallowed into the digestive tract. However, when the quantity and characteristics of these secretions change, it becomes a common cause of acute and chronic cough in both children and adults[1,2].

Posterior nasal drip syndrome (PNDS), also known as rhinosinusitis cough syndrome (RS-CS), has seen a change in nomenclature due to the fact that, in some cases, it can irritate or inflame upper airway structures, directly stimulating cough receptors, even without excessive secretion beyond the norm. Therefore, posterior nasal drip is not always a prerequisite for inducing cough[1].

Throughout this chapter, postnasal drip syndrome (PNDS) and rhinosinusal cough syndrome (RS-CS) will be used interchangeably. The clinical manifestation of PNDS includes a persistent cough that tends to worsen in a supine position, especially at night. Patients may describe a sensation of "something flowing downward" through the posterior pharyngeal wall, originating from the upper and posterior portions of the nasopharynx and oropharynx. This sensation often prompts the need to clear the throat, as it results from a tickling sensation in the hypopharynx, leading to occasional, hard-to-suppress coughing spells. Throat clearing is an attempt to prevent secretions from descending further, which inevitably triggers coughing.

Throat clearing can first manifest in patients as early as one year of age. In older patients, it may be described as an itchy or prickly feeling, often referred to as a "dusty" sensation that provokes hypopharyngeal tickling and subsequent coughing. Some patients may report "throat discomfort" or a "dry throat," but without actual pharyngeal pain.
Patients suffering from PNDS typically exhibit at least one of the following characteristics:
1. Posterior pharynx drainage with frequent throat clearing.
2. Anterior nasal discharge, which may or may not resemble the posterior discharge, varying in consistency from watery to mucopurulent.
3. A "cobblestone" appearance on the mucosa of the posterior oropharyngeal wall.
4. The presence of mucopurulent or mucohyaline material at this level.
5. Some patients may only experience nasal obstruction due to vascular congestion.

Regardless of the physical characteristics of the secretion, it can be highly irritating to the structures it contacts along its path, such as the posterior oropharyngeal wall, hypopharynx, and sometimes even laryngeal structures. When it affects the latter, it can result in dysphonia, and coughing while speaking is a common characteristic, though nonspecific and potentially associated with other cough causes.
Dysphonia may result not only from inflammatory conditions of the larynx and vocal cords but also from the secretion's downward flow. Clinically, diagnosis in adolescents and adults primarily relies on the patient's description of a sensation that something is dripping or flowing down the posterior pharyngeal wall. In children around the age of 4 or 5, throat clearing and the observation of anterior nasal discharge can aid in diagnosis.

These sensations strongly stimulate the cough reflex, and children may have difficulty expressing this discomfort. Mothers tend to report cough (dry or wet) with a clear tendency to occur at night or in the morning, often accompanied by emesis. Watery or mucopurulent rhinorrhea is frequently noted, and throat clearing is sometimes observed but less commonly than in older children and adolescents.

In infants and preschoolers, instead of throat clearing, mothers may notice pharyngeal crackles, described as similar to the sound of crumpling tissue paper, which can become palpable as thrills upon reaching the lower airways.

One of the most suggestive indicators of RS-CS is a noticeable exacerbation of cough during the night, particularly shortly after bedtime and in the morning. Asthma often causes nighttime coughing, so inquiring about wheezing is important. In some cases, patients may experience nighttime cough due to both asthma and RS-CS simultaneously.

The most typical physical finding is the presence of mucoid or mucopurulent secretion on the posterior oropharyngeal wall, although its absence does not rule out the diagnosis. Even minimal secretion or its absence, known as "silent SGNP," can trigger severe and frequent coughing spells.

The diagnosis of rhinosinusal cough syndrome or RS-CS is best established through a combination of criteria, including symptoms, physical examination, radiographic findings, and response to treatment.

Pathophysiology of Cough Due to Posterior Nasal Drip Syndrome and Its Connection with Swallowing
Normally, secretions from the rhinosinusal passages that reach the posterior oropharyngeal wall are swallowed. However, the mechanisms and structures involved in swallowing material from the sinonasal region may not operate in the same way as those for salivary secretions and oral boluses. Postnasal drip syndrome can lead to a form of swallowing that differs from the standard oral swallowing process.

The initial phase of swallowing has been primarily studied in the context of understanding swallowing disorders and their relation to respiratory diseases[3]. These disorders can lead

to bronchoaspiration, recurrent pneumonia, and bronchial hyperreactivity. Extensive neurological damage can affect the brain stem and the swallowing mechanism, leading to pneumonia caused by bronchoaspirations, ranging from mild and infrequent to severe and frequent. Some patients may require a gastrostomy for feeding, yet this may not prevent bronchoaspiration of normal oral and upper airway secretions, given the inefficiency of their swallowing.

In contrast, the relationship between normal swallowing in healthy individuals and its influence on cough has received limited analysis to date, despite the crucial connection between the upper airway and the digestive tract in the nasopharyngeal, laryngeal, and esophageal areas.

The physiology of oropharyngeal swallowing is exceptionally intricate, involving the coordination of numerous structures that work in a precise, orderly manner, combining voluntary and involuntary actions, all while briefly interrupting breathing.

Swallowing has been studied through various methods, including esophago-gastro-duodenal series with fluoroscopy, manometry with pressure sensors at various levels[4], topographic manometry, and their combination[5]. Additionally, studies have explored innervation and its relationship with the central nervous system. Below, we'll analyze swallowing phases using a combination of manometry and fluoroscopy, with a focus on the connection to posterior nasal drip syndrome and cough in individuals with normal swallowing.

Swallowing Phases in Manofluorography

Swallowing can be divided into four phases to facilitate understanding:

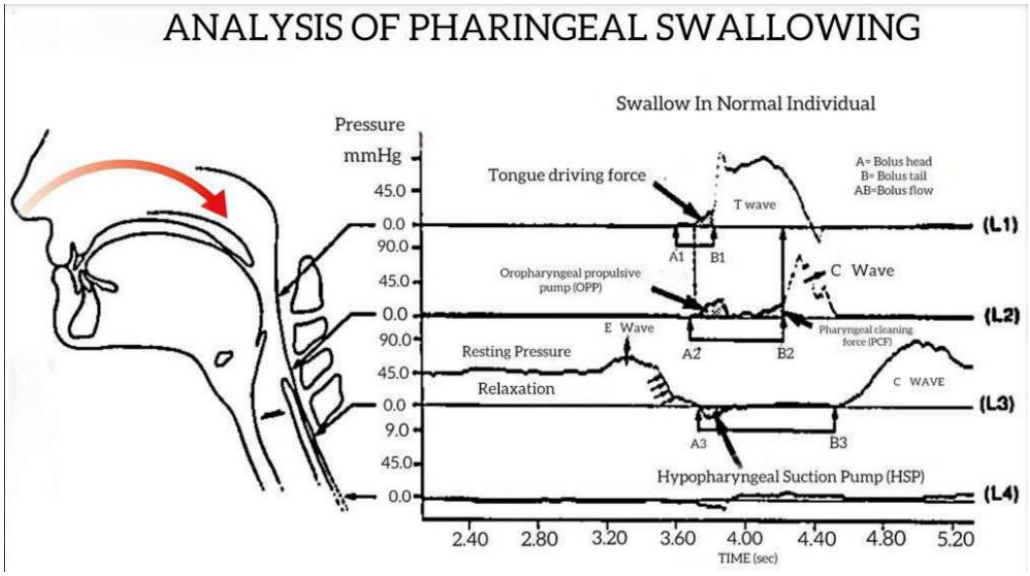
1st Phase: Oral Preparation

This phase begins with the elevation and forward displacement of the hyoid bone, the larynx in general, and the base of the tongue. This repositions the bolus in an oral position, surrounded by the anterior and medial parts of the tongue, as well as the palate. During this phase, the material to be swallowed is chewed and moistened through salivary hypersecretion, forming a compact and lubricated bolus. In manofluorography studies, the elevation and forward displacement of these structures are accompanied by an increase in pressure at the L3 sensor, corresponding to the Pharyngo-Esophageal (PE) segment, known as the E wave (for Elevation).

2nd and 3rd Phases: Buccal and Pharyngeal

This phase commences with the tongue adopting a backward sliding motion toward the oropharynx, coupled with sequential elevation of its anterior and middle thirds. This sequential movement of the tongue actively propels the bolus. When the bolus reaches the oropharynx, voluntary swallowing ceases[6]. The base of the tongue moves backward, compressing the bolus against the pharyngeal wall, causing it to advance rapidly. The compressive force of the base of the tongue against the pharyngeal wall measures around +18mmHg.

In the diagram, this force of the lingual base against the pharynx is called Propulsive Lingual Force, represented by the T wave (for “tongue” in English) and is exerted on the head of the bolus (A 1) and is observed in the L1 sensor or pharyngeal.



Manofluorogram of a normal swallow. The pressure patterns of 4 leads are illustrated: L1: Oropharynx, L2: Laryngeal introitus, L3: PE (Pharyngo-esophageal) segment and L4: Esophageal. Swallowing begins with the E wave (elevation of the larynx) in the oral preparation phase. Secretions from the rhinosinus passage are not swallowed with the same efficiency as those from the mouth. (Modified from McConnel FMS, Cerenko D, Mendelsohn M. Clin Otol North Am (4)1988.

Then, Two Almost Simultaneous Events Occur:

1. The lingual propulsive force (in L1) transmits pressure through the bolus, with the head transferring the pressure to the bolus's tail, resulting in increased pressure in L2 (laryngeal introitus). This is known as Transmitted Lingual Propulsive Force.

2. The suction pump activates when the larynx lowers (after previously rising and initiating the E wave in L3) and its muscles relax. This causes an increase in volume, resulting in a negative pressure of approximately -20mmHg.

As a result, the forces—Propulsion of the base of the tongue at +18mmHg and the hypopharyngeal suction pump at -20mmHg—combine to create a pressure gradient of 38mmHg, which propels the bolus forward.

Finally, the larynx contracts again before reaching its resting tone. This new elevation is referred to as the C wave in L3 and L4. Importantly, it generates the Laryngeal Cleansing Force in the laryngeal introitus (L3), which is transmitted to the pharyngo-laryngeal segment (L4). This force clears any food residues that might remain and, if left uncleared, could lead to bronchoaspiration.

4th Phase: Esophageal

This phase involves involuntary esophageal peristalsis. There are several factors within swallowing that are important concerning cough:

a) The pharyngeal bolus transits due to a pressure gradient, with two primary forces at play: the piston-like thrust force of the tongue and the pharyngeal suction pump. These forces combine to create a pressure gradient of 38mmHg.

b) The initial laryngeal elevation (E wave) combined with the backward movement of the tongue causes epiglottic closure.

c) Swallowing can vary based on the bolus's characteristics, such as its size, dryness, consistency, texture, and temperature. It also depends on the subject's position and the orientation of their head and neck during swallowing. Swallowing is most efficient when the head is upright, and the face is facing forward.

d) Swallowing differs significantly depending on whether the material to be swallowed originates in the oral cavity or the rhinosinusal passage, which can be a reason for cough due to SGNP.

Swallowing of Material from the Sinus Passage and the Production of Cough

Normally, secretions in the nasal-sinus passage are swallowed unconsciously. The rhinosinusal passage comprises structures and spaces designed for conducting air and secretions, characterized by a pseudostratified ciliated epithelium specialized for this purpose.

The quantity and consistency of secretions are typically sufficient for the functioning of the mucociliary apparatus. However, certain stimuli, like inhalation of particles, viral or bacterial infections, exposure to odors, allergens, temperature changes in inhaled air, or even ingestion of specific foods (e.g., spicy foods), can alter their physical-chemical properties, potentially increasing flow and making them harder to handle and swallow.

In these cases, cough usually occur, especially if the secretion moves beyond the hypopharynx. The efficiency of the drainage system for paranasal sinuses is higher in the supine position due to gravity, leading to an increase in secretion, making proper swallowing more challenging. This is the reason for the characteristic nocturnal cough in this syndrome.

Additionally, during sleep, swallowing may not be as efficient as during wakefulness, which can exacerbate the issue, particularly in patients with obstructive sleep apnea syndrome. In this regard, Jäghagen found subclinical swallowing abnormalities in 7% of normal subjects, a percentage that rose to more than 50% in patients with obstructive sleep apnea syndrome[7].

Swallowing of Secretions Coming from the Rhinosinusal Passage and Its Relationship with Cough

When swallowing secretions from the rhinosinusal passage, it differs from swallowing from the oral cavity in several ways. In these cases, there may be no bolus formation, compaction, lubrication, or the usual speed associated with swallowing from the oral cavity. The lingual propulsive force and sequential movements may be interrupted by secretions, complicating the swallowing process.

The "C" wave or pharyngeal cleaning force becomes more critical, both at the pharyngeal and laryngeal introitus (L2) levels, along with the hypopharyngeal pump, to keep these areas free from secretion residues and prevent them from triggering the cough reflex. If the secretion cannot be cleared, coughing is the final defensive measure to stop the secretion flow. If the secretion is not removed through coughing and subsequent swallowing, it may enter the larynx, causing more coughing, which can lead to bronchitis or pneumonia if these defense mechanisms fail.

Clinical Presentation of Posterior Nasal Drip Syndrome (Difference From Adults)

In both children and adults, cough is often more prevalent at night or in the morning upon waking, and it can be wet or dry. In adolescents and adults, additional symptoms may include a sensation of secretion draining into the hypopharynx, nasal congestion, and anterior nasal discharge. Dysphonia or loss of vocal clarity, especially after prolonged speaking, can also occur. Sometimes there is a clear history of having previously suffered from an upper airway disease (for example, the common cold or viral nasopharyngitis) that left the cough as a subacute, chronic or recurrent sequel to the aforementioned characteristics. Cough induced by SGNP may also be associated with abundant amounts of mucopurulent secretion, reaching more than 30cc in 24 hours in adolescents and adults and whose most common etiology is chronic rhinosinusitis[8].

In the child, the parents' reference to their questioning, is a similar beginning, that is, with a probably viral rhinopharyngitis in the previous 7 to 10 days and which continued with mucopurulent rhinorrhea (or at least the formation of meliceric, yellow or greenish scabs or greenish, from mucus in the nasal passages) and cough in frequent attacks (wet or dry) predominantly at night and/or in the morning upon waking, which can be so intense that it disturbs the sleep of the child and his parents.

Posterior nasal or retronasal discharge usually causes emesis due

to stimulation of the vomiting reflex at the pharyngeal level by the secretion, more frequently in children than in adults. This is a cough that produces vomiting as opposed to vomiting that produces cough (more related to gastroesophageal reflux as a cause). If the cause is posterior nasal discharge, vomiting can cause a significant reduction in cough, even if momentary. It seems that the flow of the vomit itself functions as a certain "washing" mechanism of the areas previously stimulated by the secretion.
On the other hand, the syndrome may be accompanied by nasal congestion and/or mucohyaline nasal discharge, which may change days later to mucopurulent, which could already suggest bacterial involvement.

In the case of frequent recurrences, it may be concatenated viral infections; however, these patients should be studied for probable bacterial rhinosinusitis, especially in the case of subsequent mucopurulent discharge, or even if it is mucohyaline, with more than two or three weeks of evolution. Long-standing mucohyaline rhinorrhea may correspond, in addition to bacterial rhinusinusitis as mentioned above, to perennial or seasonal allergic rhinitis, non-allergic rhinitis with eosinophilia, post-infectious rhinitis, rhinitis due to physical or chemical irritants that can occur in children in a context of intra-domiciliary contamination rather than in an occupational context (more typical of adults) and medicinal rhinitis.

All these cases of rhinitis, whatever their cause, can be (and are not uncommon) superimposed by rhinosinus bacterial infections that increase the intensity of the cough. Therefore, the treatment is also directed towards the infection, in addition to treating the cause of rhinitis, since treating only one of the causes of cough usually only achieves partial improvements, at best.

A minority of patients will have no signs or symptoms suggesting retronasal discharge as the cause of their cough, which is called a "silent" retronasal discharge, especially in children who cough more when lying down at night and who partially respond to decongestant/antihistamine therapy[9].

It is not common for a child to complain of the characteristic frontal headache that increases when bending over or of facial pain resulting from sinus congestion as happens in adults, but it does tend to frequently manifest with respect to the ear, the main manifestation of which is pain like consequence of extension of inflammation and sometimes secretion towards portions of the middle ear with bulging of the tympanic membrane and eventually, the presence of suppurative otitis media.

Given the above, the characteristics of cough in children, produced by posterior nasal drip syndrome, as well as the signs and symptoms that accompany it, can be highly suggestive of its etiology. Even so, a definitive diagnosis can be made only from a combination of criteria that include symptoms, physical examination, radiographic findings and finally the frank response to a specific therapy[10].

Posterior Nasal Discharge and Cough

Typically, posterior nasal or retronasal discharge causes emesis due to the stimulation of the vomiting reflex in the pharynx, more commonly in children than in adults. However, in adults, it can lead to increased coughing. This type of cough is known for producing vomiting rather than the other way around, which is more related to gastroesophageal reflux. In some cases, nasal congestion and mucous nasal discharge can change to mucopurulent, especially in adolescents and adults, indicating chronic rhinosinusitis as a common cause. In cases of frequent recurrence, there may be repeated viral infections. These patients should be evaluated for possible bacterial rhinosinusitis, particularly if the discharge persists or evolves over several weeks.

Prolonged mucohyaline rhinorrhea may indicate bacterial rhinosinusitis or other conditions, including allergic rhinitis, non-allergic rhinitis with eosinophilia, post-infectious rhinitis, rhinitis due to irritants, or medicinal rhinitis. These conditions can also be superimposed with bacterial infections, further complicating the cough. The treatment should target both the underlying cause of the cough and the infection when present, as addressing just one aspect often leads to partial improvement at best.

A minority of patients may not display obvious signs or symptoms of retronasal discharge as the cause of their cough. This "silent" retronasal discharge is more common in children, especially when they experience more nighttime cough while lying down. It may partially respond to decongestant and antihistamine therapy. In such cases, a complete diagnosis typically depends on a combination of criteria, including symptoms, physical examination, radiographic findings, and a positive response to specific therapy.

Differential Diagnosis of Posterior Nasal Drip Syndrome (PNS) or Sinusitis Cough Syndrome (STERS)

1. Common Cold/Rhinopharyngitis (Acute Cough): The common cold is one of the most frequent infectious diseases in humans, especially among children. It shares common symptoms with posterior nasal drip syndrome, including cough, congestion, and throat clearing.
2. Bacterial Rhinosinusitis: Rhinosinusitis can often develop as a bacterial complication of viral infections, especially in children. It is more frequent in children compared to adults and is a common cause of subacute, chronic, or recurrent cough.
3. Allergic Rhinitis: Allergic rhinitis can lead to congestion, nasal discharge, and other symptoms, which might trigger coughing in certain individuals.
4. Other Less Common Diagnoses (Predominantly in Adults): This category includes fungal rhinosinusitis, rhinitis due to anatomical abnormalities, rhinitis resulting from physical and chemical irritants, occupational rhinitis, rhinitis medicament, and pregnancy rhinitis, which can cause cough when superimposed with rhinosinusitis.

1. Viral Rhinopharyngitis / Common Cold and SGNP

It is one of the most common infectious diseases in humans[2].

In the US, adults experience 2 a4 colds a year, in children this varies according to age, and 6 can be considered normal and up to 12 a year in young infants and preschoolers[11].

At least 200 viruses have been identified capable of causing the common cold[12] with histological effects on the respiratory mucosa ranging from the absence of changes to epithelial necrosis. In general, most produce vasodilation and hypersecretion as well as variable degrees of inflammation. The clinical syndrome is more or less common to all these infections and is characterized by most of the following: nasal congestion, nasal and retronasal discharge of watery or mucohyaline secretion, pharyngeal clearance (throat clearing), sneezing and cough predominantly nocturnal and/or in the morning when you get up. Sometimes also fever is present for one or several days.

There are no prospective studies, but the common cold has long been considered the most common cause of acute cough. A randomized, double-blind study of cough and common cold[12] demonstrated a statistically significant association between cough, throat clearance, and postnasal drip. The cough improved as pharyngeal clearance and postnasal drip improved. Treatment with an association of an antihistamine (first generation: bromopheniramine) and a decongestant allowed a more rapid improvement of the 3 symptoms when compared with placebo, concluding that the primary cough-producing mechanism was post-nasal drip induced by the virus.

Interestingly, it is proposed in this study that the inflammatory mediators produced by the infection could increase the sensitivity of cough receptors through the afferent sensory neural fibers of the upper airways, particularly those located at the level of the hypopharynx..

In this regard, another double-blind, randomized study[13] demonstrated that naproxen (non-steroidal anti-inflammatory drug) decreased cough, supporting the idea of the contribution of inflammation in the pathogenesis of both the common cold and cough.

Nasal examination is not very specific, however, watery rhinorrhea, hyaline bridges suggestive of viral infection or allergy, meliceric crusts suggestive of bacterial superinfection, turbinate hypertrophy, hyperemia and violet coloration of the turbinates suggestive of allergy, etc. can be observed. Both oral mucosa and ocular conjunctivae may present a surface with granulia, that is, the presence of stippling instead of the completely smooth mucosal surfaces that denote normality, given that viruses affect the mucous membranes more generally than bacterial involvement, certainly more locally.

The treatment of acute cough due to the common cold has been controversial. Traditionally, antihistamines have been used alone or combined with a decongestant. The literature mentions that first generation antihistamines are more effective in stopping cough given their greater cholinergic effect compared to more recent antihistamines[14].
In general terms, the literature agrees regarding antihistamines, in 2 aspects:
1.- They should not be used in children under 2 years of age
2.- The cough suppressants on the market do not reduce cough significantly enough to be recommended.
On the other hand, a promising therapy is the combination of an intranasal -adrenergic agent and a topical anticholinergic agent that can be used in the short term, with the idea of reducing the posterior nasal discharge that causes cough, even when it does not We currently have prospective data on its effectiveness. Topical anticholinergic therapy has been shown prospectively to reduce rhinorrhea and sneezing; however, unfortunately this study did not evaluate cough[15].
Specific antiviral therapies are limited by the large number of possible viral causes and their side effects[16].
A cause that frequently perpetuates the cough of the common cold and/or rhinopharyngitis, and this is rhinosinusitis (reason for the next section). It is difficult to make the diagnosis of acute bacterial rhinosinusitis in the presence of an acute viral infection, since it involves both the nasal and sinus mucosal surfaces, so simple radiological and tomographic studies of the paranasal sinuses do not have good specificity for bacterial infection during the first week from the onset of rhinopharyngitis[17]. The above makes the decision to institute antimicrobial treatment difficult, under these conditions.
When rhinopharyngitis appears more likely to be of viral origin, the symptoms usually subside no later than 7 to 10 days, but the cough persists beyond this period; diagnosis could be postviral cough, which is, due to its frequency, discussed later in a separate chapter.

2. Bacterial Rhinosinusitis

Until relatively recently, many pediatric doctors and otolaryngologists doubted that sinusitis was a pediatric disease. It was believed that the paranasal sinuses were not developed in infants and young children and bacterial infections could not occur[18]. At around one year of age, the maxillary sinuses are sufficiently pneumatized to harbor bacterial infections[19].
Since sinusitis often occurs as a bacterial complication of viral rhinopharyngitis20, which is more common in pediatrics, and rhinosinusitis complicates rhinopharyngitis in 6 to 13% during the first 3 years of life[20,21], it can be concluded by This fact alone, that rhinosinusitis occurs more frequently in children than in adults, is an important cause of subacute/chronic/recurrent cough. Considering that children average 6 to 8 upper respiratory tract infections per year, while adults average only 2 to 4 per year. This epidemiological reason joins others of an anatomical and immunological nature.

Risk factors for Rhinosinusitis

The role that allergy plays in rhinosinusitis is still unclear. For example, it has not been proven that there are changes in the permeability of the osteomeatal complex, nor an increase in the incidence of purulent rhinosinusitis in the season of greatest pollinosis. Although it can be expected that allergy produces inflammation and edema of the nasal mucosa that obstructs the meatus and although epidemiological data show that the prevalence of rhinitis is higher in patients with rhinosinusitis, so far, the evidence is not conclusive.

Mucociliary transport at the level of the paranasal sinuses is carried out by the correct coordination of the cilia beating at a frequency of 1000 cycles per minute, moving the surface materials at a rate of 25ml per minute 3 a. An incoordination of this mucociliary apparatus, produced, for example, by thicker mucus, causes stasis that may be sufficient for subsequent infection, as demonstrated by patients with cystic fibrosis.

On the other hand, it is quite common for children to have states of relative and transient immunosuppression; up to 6% of patients had selective IgA deficiency in one study[22], which may lead to greater amount of rhinopharyngitis per year and therefore a greater amount of rhinosinusitis complicating them. its respect to infantile rhinonasal anatomy, the draining ostia are narrower and more susceptible to inflammation than in adults (whose lumen has a diameter that measures around 2mm) and a representative example of this is in the smoking women, who have a greater risk of suffering from chronic rhinosinusitis than men, suspecting that this is due to the fact that the lumen of the osteomeatal complex orifices in women could measure less and that this was a factor in producing more sinusitis in women. smokers than in smokers. This anatomical factor would become more important in children, particularly in children between 1 and 3 years of age and in relation to the presence of rhinopharyngitis[23].

Finally, children under 2 years of age whose homes use gas stoves suffer more frequently from respiratory infections, probably secondary to the action of nitrogen oxides[23].

Pathophysiology of rhinosinusitis

The pathophysiology begins first with obstruction of the sinus ostium with cessation of ventilation and hindering the secretion flow of the mucociliary system. This process is most commonly caused by mucosal edema, secondary to factors such as a viral airway infection. high temperatures or other harmful irritants such as particles from atmospheric pollution or intramurals. Or other structural alterations such as turbinate hypertrophy due to nasal allergy or a hypoplastic uncinate process. Of all of them, what most frequently causes rhinosinusitis are viral infections. These alter mucociliary clearance. During a catarrhal condition, nasal fluid containing viruses, bacteria and mediators can enter the sinus, where it produces inflammation, infection or both. Lack of ventilation promotes the absorption of oxygen within the sinus with the development of negative pressure which can cause facial discomfort, a common characteristic of many upper respiratory infections and allergies. Nasal flora can develop inside the sinus when this drainage is hindered. Once the bacteria develop more freely, they produce greater inflammation of the meatus with greater obstruction, establishing a vicious circle.

Mucosal edema→ Drain Blockage→
→Bacterial Infection →> Inflammation→
>Obstruction Perpetuation of Infection/Inflammation

Determining the bacterial etiology is not easy since taking samples from the nasal and/or nasopharyngeal surfaces does not have predictive value in rhinosinusitis[19], which is why transnasal antral puncture is used even if only for research purposes.

Microbiology of Rhinosinusitis in Children

The nasal vestibule is colonized by Staphylococcus aureus in 40% of healthy adults and the nasopharynx by Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae and Moraxella catarrhalis in children and less frequently in healthy adults[24]. Most of the published studies point out the exceptional presence of rhinosinusitis pathogens in the middle meatus and the osteomeatal complex in healthy individuals[25].
The bacteria that usually because acute rhinosinusitis is similar in type and frequency to those that cause acute otitis media in children:

	Wald ER, Reilly[26]	Till PG,Tomás BM[27]
Streptococcus pneumoniae	25 - 30%	35 - 42%
Moraxella catarrhalis	15 - 20%	21 - 28%
Haemophilus influenzae	15 - 20%	21 - 28%
Streptococcus pyogenes	2 - 5%	
Anaerobes	2 - 5%	

The bacteria that cause chronic rhinosinusitis in children[28]

Staphylococcus aureus	36%
Staphylococcus coagulase (–)	20%
Streptococcus pneumoniae	17%
Hemolytic Streptococcus β	23%

Clinical Diagnosis of Rhinosinusitis

A common condition that should make the doctor suspect rhinosinusitis is when the signs and symptoms of a common cold are persistent, resulting in nasal discharge and cough continuing beyond 10 days[29].

Cough secondary to rhinosinusitis, which is caused by posterior nasopharyngeal discharge of secretion from the sinuses, and which may or may not be associated with excessive sputum production. This secretion, especially in younger children, is usually incapable of expelling it; it can produce a wet or productive cough that can alternate with a dry cough.

Very characteristically, the cough increases when the patient is lying down (when sinus drainage is facilitated by gravity) and for this reason it is usually predominantly nocturnal but also when getting up in the morning, perhaps when the nasopharyngeal secretions accumulated during the night move.

The cough can be emetic where the characteristics of the secretion can eventually be seen (when it is not too mixed with food). Expectoration usually has the same characteristics as anterior rhinorrhea and is also similar to that which passes through the posterior pharyngeal wall. Rhinosinusitis should be considered as a diagnostic possibility under the following points:

1.- Until after a period of no less than 7 days after the onset of a viral infection of the upper respiratory tract, when this history exists, since this is how long a virus infection usually lasts[30].
2.- When the nasal secretion and/or posterior nasal discharge has a mucopurulent appearance. Sometimes it is chronic mucohyaline due to the effect of antimicrobial doses or subtherapeutic periods. Cough, which is usually the main symptom reason for consultation, can have remissions only to reappear a few weeks (or months) later and give it the recurring character that many children present. Halitosis is more common in preschoolers and if its accompanied by respiratory symptoms (in the absence of exudative pharyngitis, dental caries or nasal foreign body) it is highly suggestive of paranasal sinus infection[31].

Facial pain secondary to rhinosinusitis is not a common complaint in children, and can occur in adolescents, as can frontal headache, since the frontal sinuses become pneumatized later. Rhinosinutis usually coexists with acute otitis media, given the anatomical, physiopathogenic and etiological relationship; so, can be accompanied by ear pain.

The physical examination usually shows mucopurulent discharge in the nose (or abundant yellowish or greenish crusts attached to or obstructing the walls of the nostrils) or passing through the posterior wall of the pharynx. The presence of thick rales transmitted from large airways is common, sometimes so intense that they can be perceived by thoracic palpation, presumably a result of the passage of secretion to lower airways.

Diagnostic Imaging

The imaging approach is controversial, the study that probably details the paranasal sinuses best is nuclear magnetic resonance, followed by computed axial tomography (CT) of the paranasal sinuses, however rhinosinusitis is such a common cause of cough that the cost exceeds the benefit. Due to the characteristics of the clinical picture, the diagnosis is not problematic, and it is even less problematic to relate the type of cough produced by it. Simple radiographs can complement the study of these patients in case of doubt, perhaps with but above all to evaluate treatment results. A child diagnosed with rhinosinusitis, with recurrent symptoms, should not be considered cured until a normal x-ray of the paranasal sinuses is obtained. In children, the most important projection is the Waters radiograph (naso-mental projection) since maxillo-ethmoidal rhinosinusitis is the most common.

Chronic sinusitis (persistent symptoms for more than 3 months despite adequate treatment) and recurrent sinusitis (more than 3 episodes in 6 months) are usually the same condition treated insufficiently or with the same antimicrobial used repeatedly with loss of its effectiveness due to induced bacterial selection, which is an extremely common cause of chronic and/or recurrent cough in childhood.

There is imaging evidence (tomographic and nuclear magnetic resonance) that during the initial phases of a common catarrhal condition, the osteomeatal complex is clogged due to mucus or inflammation of the mucosa, resolving spontaneously without the need for antibiotic treatment[32]. Radiological abnormalities on tomographic images that appear in viral rhinosinusitis may result solely from inflammation or viral infection of sinus epithelial cells.

There is a prospective study of tomography of the maxillary sinuses in patients with the common cold of recent onset[33] where abnormalities are seen in 87% of patients, with improvement in 79% of patients, between 13 - 20 days even without receiving antibiotic treatment. On day 14 (the last day of the study), while their symptoms improved, 25% of patients still had complaints of cough, postnasal drip, and throat clearing. This 25% correlates to a good extent with the 21% in which the abnormalities of the tomographic image of the maxillary sinuses persist between 13 and 20 days, which suggests that a percentage of patients develop inflammation from a viral infection of the upper respiratory tract, inflammation that can in some cases perpetuate and cause chronic cough. This study was carried out in adults, it would be expected that in children, given the dimensions of the rhinosinusal drainage structures, inflammation could increase the percentages of persistence of abnormalities or, alternatively, increase the cases in which, from a common cold, develops bacterial rhinusinusitis and persistent chronic cough as observed by Wald in young children in whom approximately 5 a10% of upper respiratory tract infections were complicated by rhinosinusitis[34].

Treatment

In children with underlying causes of rhinosinus inflammation (e.g. allergic or vasomotor rhinitis) they must be managed appropriately to have more effective results (see treatment of allergic rhinitis). Rhinosinusitis in the microbiological sense, behaves to a certain extent, like abscesses in other regions, requiring the facilitation of its drainage, sometimes

pharmacologically permeabilizing the osteomeatal complex.

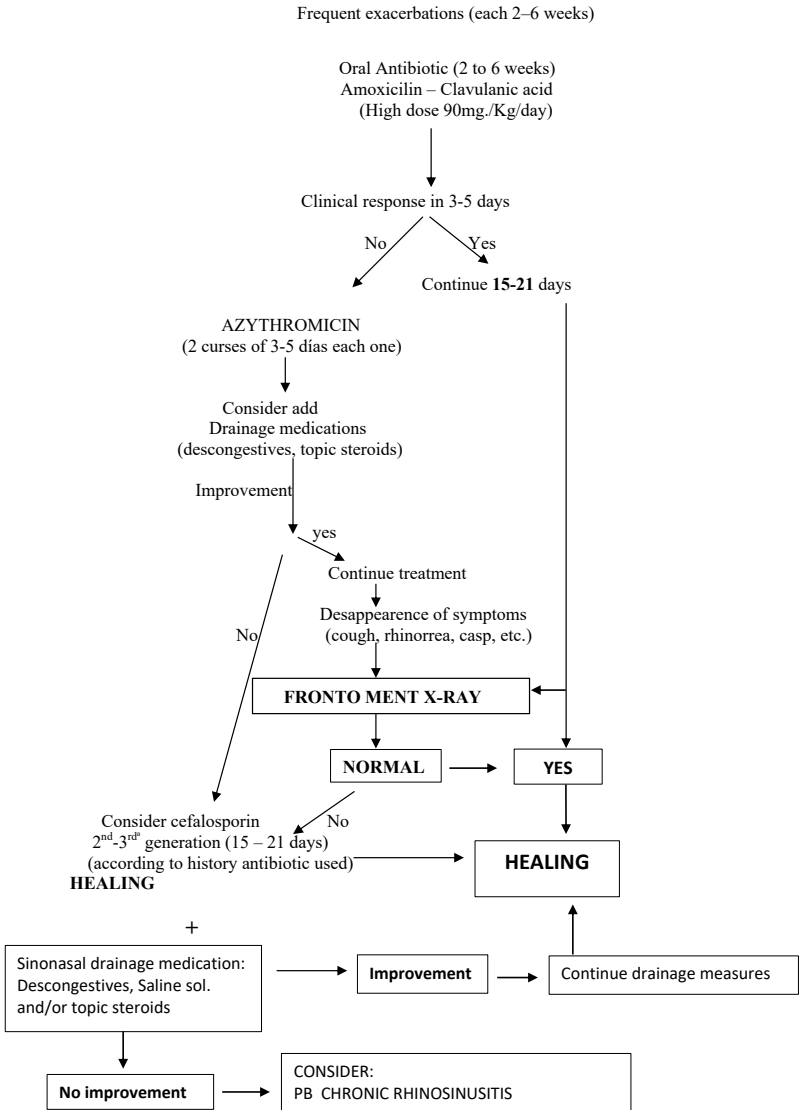
When the underlying causes are treated, the infectious aspect can be treated more effectively of antibiotics, amoxicillin is a reasonable selection. In patients who do not respond or who live in areas with a high prevalence of β-lactamase production, such as in Mexico[35], high doses should be used or clavulanic acid should be added, or use a broader spectrum antibiotic such as: acetyl-cefuroxime, cefuroxime, cefpodoxin, erythromycin or other macrolides. Duration of treatment is 10 a14 days or up to 7 days after being free of symptoms[36], however in the case of chronic rhinosinusitis, it can take 4 a6 weeks[37].

Treatment of sinonasal edema is essential in patients with chronic and recurrent rhinosinus disease. It is the experience of Parsons and Wald[38] with hundreds of patients with sinus and allergic disease that irrigation of the nose, 2 or 3 times a day with a neutral hypertonic saline solution, gives a rapid and effective cleaning of nasal debris, retraction of edematous mucosa, improving the mucociliary flow pattern. This solution has been used in children from the age of one year. There is little data on the treatment of rhinosinusitis in children. The following table shows aggressive treatment for recurrent or chronic sinusitis that has been previously multi-treated without success. It is based on knowledge about chronic rhinosinusitis, in which the response to antibiotics is variable, including those cases in which there is no antimicrobial response, for which only sinu-nasal drainage medication can be offered.

To evaluate the effectiveness of the treatment, it is not enough for the cough to subside, since recurrence is frequent, which is why the "Waters" (Fronto-ment plate) is used as a measure of treatment effectiveness, making it difficult to consider a patient cured as long as he does not have a normal x-ray of the paranasal sinuses.

For the above, computed axial tomography (which would be the ideal study) for diagnosis and follow-up has been ruled out because it requires sedation in non-cooperative children under 3 or 4 years of age and the high costs that its common use for this purpose would represent.

RECURRENT RHINOSINUSITIS



3. Allergic Rhinitis and PNDS

It is estimated that up to 20% of individuals suffer from allergic rhinitis39. It can be seasonal or perennial, this being the one that can be most confused with rhinosinusitis as another cause of PNDS.

Undoubtedly allergy is an important factor for coughing, however studies often do not determine the mechanism of cough that allergy promotes by itself. In fact, “allergic cough” is a poorly defined condition in both children and adults, and its relationship probably represents an overlap with asthma, nonasthmatic eosinophilic bronchitis, allergic rhinitis, and adenoid and tonsillar hypertrophy[40]. Due to its frequent association with asthma, a history of cough with wheezing is common.

The allergens that cause seasonal allergic rhinitis are more frequently found outside the home, such as certain pollens; and those of perennial rhinitis tend to be more frequently indoors such as house dust mites, cockroaches and perhaps the presence of a pet such as dogs or cats, even when their presence is in the yard and not inside the house. Or, foods that are frequently consumed such as milk or eggs.

Although not everyone who suffers from allergic rhinitis coughs, allergic rhinitis is an extremely common cause of PNDS. Presentation of other symptoms apart from cough, includes nasal obstruction (which may be continuous or predominantly nocturnal), "flashing" sneezing, that is, several sneezes which may be multiple, predominantly in the morning, nasal itching with frequent scratching through the “allergic greeting” (act of rubbing the nose with the palm of the hand moving upward), the presence of a horizontal mark near the tip of the nose (Denny's line), and hyaline rhinorrhea, which can sometimes be very abundant, particularly when there is exposure to the allergen, even when it is not identified. In addition to the above, ocular and/or otic itching.

On physical examination, a congested and shadowed appearance of the skin of the subocular region can be observed in the form of “dark circles”, whose intensity fluctuates according to changes in blood circulation presumably caused by exposure or rhinosinus disease of viral origin.

The inferior turbinates can range from moderately hypertrophic to completely obstructive, promoting oral respiration. Apparently when they are covered with abundant hyaline secretion, giving them a moist appearance, it is related to greater activity of the allergic process. The color of the turbinate mucosa is usually pale or purplish in allergic rhinitis.

Treatment for allergic rhinitis can be disappointing. A large number of topical medications such as corticosteroids, chromones, antihistamines or saline have been used, as well as systemic medication such as leukotriene inhibitors and oral antihistamines. Antihistamines appear to be very effective in treating patients with rhinitis. Perhaps the anticholinergic effect of first-generation antihistamines could play a more important role in reducing cough caused by the drip-after mechanism in allergic patients.

In the case of perennial rhinitis, it is preferable to use topical medications, among which, inhaled corticosteroids are the most effective, both for allergic and non-allergic rhinitis, [41]practically without causing side effects at the recommended doses, considering the first choice medications[42].

In children with continuous chronic cough for several months in which no major abnormality is found other than abundant hyaline rhinorrhea, having ruled out rhinosinusitis (which usually causes cough rather for long periods but recurrent and not continuous), it may be useful to take a history. Complete diet since sometimes a food can be the triggering factor for the symptoms of rhinitis that causes cough, especially if some food is abused (For example: intake of more than a liter of milk/day or daily egg consumption. Surprisingly, foods traditionally implicated in this type of reaction such as strawberries, pineapple, chocolate, etc. They are not the main ones but the most frequently ingested, such as those mentioned above, milk (up to 2.5% of children during the first year of life) and eggs (1.3% of young children)[43]. Chronic hyaline rhinorrhea may also be due to an insufficiently treated (dose or timing) nasal or rhinosinus infection.

Allergy skin testing may be useful for example, for animal dander (particularly dog and cat), house dust mites (but not testing the house dust itself), and indoor fungi for the perennial form; as well as tests on different pollens for the seasonal form. However, the presence of skin reactivity to specific allergens does not absolutely prove that said allergy is necessarily the etiology of PNDS or even that it is a contributing factor.

Controlling the environment to avoid the allergen, for example avoiding contact with the household dog, or even getting rid of it, is highly desirable when possible and of course, even more so when you are sure that it is responsible of the symptomatology.

Immunotherapy can help in the long term (not in the case of pets) but it does not help immediately and is not recommended in children under 5 years of age. If cough and other symptoms are well controlled with intranasal therapy, particularly steroids, and environmental control, allergen desensitization via immunotherapy is not necessary at any age1.

Allergy testing is often most useful when there is a seasonal component (seasonal allergic rhinitis) and/or the history strongly suggests an association with exposure to a specific allergen such as a certain pollen or animal dander. For perennial allergic rhinitis, it may be testing for house dust mites (not for house dust itself) or for indoor fungi is considered valuable.

4. Non-Allergic Perennial Rhinitis

It is divided into: vasomotor rhinitis and non-allergic eosinophilic rhinitis. Vasomotor rhinitis is characterized by excessive watery secretions, frequently in response to stimuli such as odors, changes in temperature, pressure or humidity, sometimes when eating (called gustatory rhinitis), or with the ingestion of alcohol. When old enough, patients typically describe the sudden onset

of profuse rhinorrhea and/or nasal congestion with or without the sensation of postnasal drip.

For this, an autonomic imbalance has been postulated[44,45], increase in cholinergic sensitivity or tone is suggested by the effectiveness of ipratropium bromide in controlling vasomotor symptoms. Examination of the nose may not show the turbinate hypertrophy seen in allergic rhinitis. It is considered a diagnosis of exclusion in which laboratory studies and other allergic tests are negative. It is necessary to remember that all patients with rhinitis can react to atmospheric irritants which can simulate an allergic reaction.

Non-allergic eosinophilic rhinitis is similar to vasomotor rhinitis, but itching of the nasal and ocular mucous membranes is added, as well as excessive tearing and the existence of eosinophils in nasal secretions, in the absence of positive allergic skin tests and lack of response to immunotherapy.. Perhaps the absence of these last 2 facts is insufficient to consider it "non-allergic", since allergy tests can have false negatives. In both, topical steroids are useful. Even when the etiology is uncertain, sensitivity to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs should be considered.

Treatment of Cough Secundary to PNDS

Treatment of cough secondary to SGNP should be aimed at reducing the secretion that flows through the posterior oropharyngeal wall, downward from the paranasal sinuses, nose and nasopharynx. There are general guidelines but the treatment requires continuing the diagnostic process and finding the specific cause or causes of the syndrome since each etiology requires a specific treatment, even when the cause is posterior nasal drip, try to simplify and suggest the same treatment for all causes of dripping and subsequent coughing, is undesirable. Some general guidelines are given below.

If the etiology is bacterial, it should include an antibiotic that frequently requires > 14 days of duration and possibly an initial decongestive therapy described later. The antimicrobial should be selected according to the etiological probability of sinusitis (St. Pneumoniae, H. Influenzae, staph. Aureus, M. Catarrahlis, St. Pyogenes, etc.).

If the etiology appears to be viral (acute cough), decongestive therapy with topical or systemic vasoconstrictors may be the best cough suppressants combined with a particularly first-generation antihistamine[14]. These medications are sometimes also used in the case of sinusitis to facilitate drainage, since rhinosinusitis has certain similarities with the pathogenic behavior of pyogenic abscesses in other regions, requiring drainage.

In the case of posterior drip secondary to allergic rhinitis, topical steroids such as beclomethasone, budesonide, triamcinolone or fluticasone have the best indication, to which the use of systemic anthistamines can be added in case of an increase in the intensity of symptoms, secondary to accidental or unavoidable exposure to the allergen.

Antihistamines and Decongestants

The most common cause of retronasal discharge and secondarily acute cough is due to the common cold or viral rhinopharyngitis. Cough is most often linked to the production of rhinosinusal secretion and its drainage towards the posterior oropharyngeal wall, causing pharyngeal discomfort, throat clearing and cough predominantly at night and/or in the morning. The vast majority of medications used for cough do not have sufficient evidence of their effectiveness and, given that this type of cough is self-limiting in 5 to 7 days, expectant management has been advised. This promoted the proliferation of a large number of different cough medicines, without any real use. One study estimated that more than 26% of patients presenting with upper respiratory tract infection were prescribed unnecessary medications[46].

Two-thirds of American families have between four and eight types of "over-the-counter" (non-prescription) cough and cold medications in their homes[47] which accounted for 6.2% of accidental poisonings in children under age 4 to 6 years on cough and cold medications[48].

Antihistamines, decongestants, antitussives, and expectorants offer an example of how controversial their use is despite the number of years in use. First-generation antihistamines have shown the most favorable results in relation to the common cold in adolescents and adults, particularly administered in combination with a decongestant, but there is not enough demonstrated evidence of the effectiveness of these medications in preschoolers[49]. Doxylamine succinate, clemastine fumarate, and chloropheniramine maleate significantly reduced rhinorrhea and sneezing but had no effect on other symptoms and frequently caused drowsiness. Long-acting, 2nd generation antihistamines used for allergic rhinitis have limited effectiveness, probably due to the lack of anticholinergic activity.

A meta-analysis has questioned whether the sedation effect seen with first-generation antihistamines is actually significantly greater than with newer non-sedating preparations[50]. Data on the effectiveness of both classes of antihistamines are weak and limited in adults but even weaker and more limited in children. There is a clear need for carefully designed and randomized studies that focus on clinical utility such as reduction in cough or runny nose, dose assessment, and side effects in preschoolers.

For other authors1 , cough secondary to retronasal discharge, even due to "silent" nasal discharge, will respond to an empirical course of 1st generation antihistamines plus a decongestant, which has not only therapeutic but also diagnostic implications, however the improvement reported It can be noticed within days to 2 weeks of therapy, specifically in postviral upper respiratory infection. A therapy of this type can take all that time so its activity be noticed, so the improvement is probably not due so much to its therapeutic effect, but rather to the self-limitation of the alteration that the natural history of the disease has.

The rich sympathetic innervation of the nasal vasculature offers the opportunity to decongest the swollen, turgid and hypertransudative mucosa, through the use of drugs with adrenergic activity that cause contraction of the nasal blood

vessels. However, the large pharmacological spectrum of these drugs, such as adrenaline, requires modification to produce effective nasal vasoconstriction with limited systemic effects. This vasoconstriction of the nasal mucosa consequently produces a reduction in transudation and rhinorrhea as well as a reduction in posterior nasal discharge, which could limit the cough caused by this mechanism.

Sympathomimetics such as pseudoephedrine have in the past shown a dramatic reduction in nasal symptoms in adolescents and adults, including congestion and sneezing[51,52], results that could not be reproduced in preschoolers[53]. The combinations of antihistamine, decongestant and analgesic showed a significant reduction in cough, pharyngeal discomfort and pain in two studies in children between 6 and 12 years of age[54,55].

Finally, the long action time of imidazoline derivatives, oxymetazoline, xylometazoline, etc., gives them an advantage over the previous ones, in addition to the fact that they are used as topical decongestants. They can specifically reduce coughs, often almost immediately, because they reduce rhinorrhea, but above all, they reduce retronasal discharge, the main cause of cough. They can have local and systemic side effects, the most feared being depression of the central nervous system, even leading to coma, which has been reported with naphazoline and tetrahydrozoline, but not with oxymetazoline. This has limited the use of older preparations, which has not happened with oxymetazoline, however some clinicians prefer to restrict their use exclusively to adults. Oxymetazoline can be used in children, and it is vital to avoid overdose that could lead to dangerous amounts into the systemic circulation[56].

The so-called "rebound effect", a well-known complication, is a major limitation for its chronic use, since the drug becomes less effective. The duration of vasoconstriction decreases but at the same time the return of mucosal congestion becomes more severe than before its administration. Rebound may occur in some patients after three or four days of use, while others may continue for weeks or months without this type of problem[56].

The rebound effect is more powerful with some drugs than others. A potent rebound effect has been observed with ephedrine, naphazoline, tetrahydrozoline and possibly phenylephrine. Drugs with weak or minimal rebound are oxymetazoline and xylometazoline.

Anticholinergics

They have not been used with the indication of reducing postnasal drip (and consequently reducing cough) and administered topically. It has been thought that the activation of the parasympathetic nervous system is important in the production of rhinorrhea and other symptoms of the common cold, which is why several anticholinergic compounds have been used.

Ipratropium bromide nasal spray has been shown in a randomized study to reduce nasal discharge and sneezing in the first 3 days of a cold, but some resulted in dryness and pharyngeal discomfort during the last 3 days of the illness[57]. Atropine metonitrate also produced dry nose in experimentally induced colds but with doses of 250 mcg. four times a day, considered high[58]. The rest of the cough suppressants on the market have not proven useful with the exception of codeine and morphine, which, due to their nature, are not recommended for daily use.

References

1. Pratter, M. R. (2006). Chronic upper airway cough syndrome secondary to rhinosinus diseases (previously referred to as postnasal drip syndrome): ACCP evidence-based clinical practice guidelines. Chest, 129(1), 63S-71S.
2. Sakchainanont, B., Ruangkanchanasetr, S., Chantarojanasiri, T., Tapasart, C., & Suwanjutha, S. (1990). Effectiveness of antihistamines in common cold.
3. McConnel, F. M., Cerenko, D., Hersh, T., & Weil, L. J. (1988). Evaluation of pharyngeal dysphagia with manofluorography. Dysphagia, 2(4), 187–195.
4. Nativ-Zeltzer, N., Kahrilas, P. J., & Logemann, J. A. (2012). Manofluorography in the evaluation of oropharyngeal dysphagia. Dysphagia, 27(2), 151–161.
5. Moreira, L. A., & Cahali, M. B. (2011). Swallowing in obstructive sleep apnea syndrome. Sleep Science, 4(2), 68-71.
6. Jäghagen, E. L., Berggren, D., & Isberg, A. (2000). Swallowing dysfunction related to snoring: a videoradiographic study. Acta oto-laryngologica, 120(3), 438-443.
7. Smyrnios, N. A., Irwin, R. S., & Curley, F. J. (1995). Chronic cough with a history of excessive sputum production: the spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. Chest, 108(4), 991-997.
8. Pratter, M. R., Bartter, T., Akers, S., & DuBois, J. (1993). An algorithmic approach to chronic cough. Annals of internal medicine, 119(10), 977-983.
9. Smith, M. B., & Feldman, W. (1993). Over-the-counter cold medications: a critical review of clinical trials between 1950 and 1991. Jama, 269(17), 2258-2263.
10. Curley, F. J., Irwin, R. S., Pratter, M. R., & Stivers, D. H. (1988). Cough and the Common Cold1-3. Am Rev Respir Dis, 138, 305-11.
11. Mandell GL, Bernett JE, Dolin R. Principles and practice of infectious diseases, 5th edition. Churchill Livingstone. 2000:651-6.
12. Mossad, S. B., Macknin, M. L., Mendendorp, S. V., & Mason, P. (1996). Zinc gluconate lozenges for treating the common cold: a randomized, double-blind, placebo-controlled study. Annals of internal Medicine, 125(2), 81-88.
13. Sperber, S. J., Hendley, J. O., Hayden, F. G., Riker, D. K., Sorrentino, J. V., & Gwaltney Jr, J. M. (1992). Effects of naproxen on experimental rhinovirus colds: a randomized, double-blind, controlled trial. Annals of internal medicine, 117(1), 37-41.
14. Mossad SB. Clinical Review. Treatment of common cold. BMJ 1998;4:33-36.
15. Hayden, F. G., Diamond, L., Wood, P. B., Korts, D. C., & Wecker, M. T. (1996). Effectiveness and safety of intranasal

ipratropium bromide in common colds: a randomized, double-blind, placebo-controlled trial. Annals of internal medicine, 125(2), 89-97.
16. Hayden, F. G., Turner, R. B., Gwaltney, J. M., Chi-Burris, K., Gersten, M., Hsyu, P., ... & Zalman, L. S. (2003). Phase II, randomized, double-blind, placebo-controlled studies of ruprintrivir nasal spray 2-percent suspension for prevention and treatment of experimentally induced rhinovirus colds in healthy volunteers. Antimicrobial agents and chemotherapy, 47(12), 3907-3916.
17. Puhakka, T., Mäkelä, M. J., Alanen, A., Kallio, T., Korsoff, L., Arstila, P., ... & Ruuskanen, O. (1998). Sinusitis in the common cold. Journal of allergy and clinical immunology, 102(3), 403-408.
18. Isaacson, G. (1996). Sinusitis in childhood. Pediatric Clinics of North America, 43(6), 1297-1318.
19. Wald, E. R., Milmoe, G. J., Bowen, A. D., Ledesma-Medina, J., Salamon, N., & Bluestone, C. D. (1981). Acute maxillary sinusitis in children. New England Journal of Medicine, 304(13), 749-754.
20. Brook, I. (1981). Bacteriologic features of chronic sinusitis in children. Jama, 246(9), 967-969.
21. Wald, E. R., Guerra, N., & Byers, C. (1991). Upper respiratory tract infections in young children: duration of and frequency of complications. Pediatrics, 87(2), 129-133.
22. Chee, L., Graham, S. M., Carothers, D. G., & Ballas, Z. K. (2001). Immune dysfunction in refractory sinusitis in a tertiary care setting. The Laryngoscope, 111(2), 233-235.
23. Karlsson, G., & Holmberg, K. (1994). Does allergic rhinitis predispose to sinusitis?. Acta Oto-Laryngologica, 114(sup515), 26-29.
24. Fokkens W, et al. European Consensus Statement on rhinosinusitis or nasal polyposis. Spanish Otolaryngologic Acta 2005;56(Suppl.2):1-93.
25. Meltzer, E. O., Hamilos, D. L., Hadley, J. A., Lanza, D. C., Marple, B. F., Nicklas, R. A., ... & Zinreich, S. J. (2004). Rhinosinusitis: establishing definitions for clinical research and patient care. Journal of allergy and clinical immunology, 114(6), 155-212.
26. Wald, E. R., Reilly, J. S., Casselbrant, M., Ledesma-Medina, J., Milmoe, G. J., Bluestone, C. D., & Chiponis, D. (1984). Treatment of acute maxillary sinusitis in childhood: a comparative study of amoxicillin and cefaclor. The Journal of pediatrics, 104(2), 297-302.
27. Til Perez, Thomas G., Barberan M.: Sinusitis. Evidence based on experience. 2006 Group ARSXXI of communication SL. Barcelona.
28. Muntz, H. R., & Lusk, R. P. (1991). Bacteriology of the ethmoid bullae in children with chronic sinusitis. Archives of otolaryngology–head & neck surgery, 117(2), 179-181.
29. Fireman, P. (1992). Diagnosis of sinusitis in children: emphasis on the history and physical examination. Journal of allergy and clinical immunology, 90(3), 433-436.
30. Shapiro GG, Rachelefsky GS. Introduction and definition of sinusitis. J Allergy Clin Immunol. 1992; 90(2):417-418.
31. Wald ER. Sinusitis in children. Pediatr Infect Dis J 1988;7(suppl)5150-5153.
32. Barberán MT, Ortega del Alamo P, Mensa Pueyo J, García Rodríguez JA, Barberán J. Rev Esp Quimioter 2008;21(1):45-59.
33. Gwaltney Jr, J. M., Phillips, C. D., Miller, R. D., & Riker, D. K. (1994). Computed tomographic study of the common cold. New England Journal of Medicine, 330(1), 25-30.
34. Wald ER, Guerra N, Byers C. Upper respiratory tract infections in young children: Duration of acute sinusitis. Ann Otol Rhinol Laringeal 1981;90(suppl 84):68-71.
35. Tomasz, A., Corso, A., PAHO/ROCKEFELLER UNIVERSITY WORKSHOP:, SEVERINA, E. P., ECHÁNIZ-AVILES, G. A. B. R. I. E. L. A., DE CUNTO BRANDILEONE, M. C., ... & DI FABIO, J. L. (1998). Molecular epidemiologic characterization of penicillin-resistant Streptococcus pneumoniae invasive pediatric isolates recovered in six Latin-American countries: an overview. Microbial Drug Resistance, 4(3), 195-207.
36. Wald ER. Sinusitis in children. N. Engl J Med 326:319-323, 1992.
37. Holinger LD. In Cotton R, Myer Ch: Practical pediatric otolaryngology 1999 Lippincott-Raven Publishers Philadelphia.
38. Parsons, D. S., & Wald, E. R. (1996). Otitis media and sinusitis: similar diseases. Otolaryngologic Clinics of North America, 29(1), 11-25.
39. Naclerio, R. M. (1991). Allergic rhinitis. New England Journal of Medicine, 325(12), 860-869.
40. Lack, G. (2001). Pediatric allergic rhinitis and comorbid disorders. Journal of allergy and clinical immunology, 108(1), S9-S15.
41. Weiner, J. M., Abramson, M. J., & Puy, R. M. (1998). Intranasal corticosteroids versus oral H1 receptor antagonists in allergic rhinitis: systematic review of randomised controlled trials. Bmj, 317(7173), 1624-1629.
42. Craig, T. J., Teetsb, S., Lehman, E. B., Chinchilli, V. M., & Zwillich, C. (1998). Nasal congestion secondary to allergic rhinitis as a cause of sleep disturbance and daytime fatigue and the response to topical nasal corticosteroids. Journal of Allergy and Clinical Immunology, 101(5), 633-637.
43. Nickel, R., Kulig, M., Forster, J., Bergmann, R., Bauer, C. P., Lau, S., ... & Wahn, U. (1997). Sensitization to hen's egg at the age of twelve months is predictive for allergic sensitization to common indoor and outdoor allergens at the age of three years. Journal of allergy and clinical immunology, 99(5), 613-617.
44. Bronsky, E. A., Druce, H., Findlay, S. R., Hampel, F. C., Kaiser, H., Ratner, P., ... & Wood, C. C. (1995). A clinical trial of ipratropium bromide nasal spray in patients with perennial nonallergic rhinitis. Journal of allergy and clinical immunology, 95(5), 1117-1122.
45. Grossman, J., Banov, C., Boggs, P., Bronsky, E. A., Dockhorn, R. J., Druce, H., ... & Wood, C. (1995). Use of ipratropium bromide nasal spray in chronic treatment of nonallergic perennial rhinitis, alone and in combination with other perennial rhinitis medications. Journal of allergy and clinical immunology, 95(5), 1123-1127.
46. English, J. A., & Bauman, K. A. (1997). Evidence-based management of upper respiratory infection in a family practice teaching clinic. Family medicine, 29(1), 38-41.

47. Maiman, L. A., Becker, M. H., & Katlic, A. W. (1986). Correlates of mothers' use of medications for their children. Social Science & Medicine, 22(1), 41-51.
48. Litovitz, T. L., Bailey, K. M., Schmitz, B. F., Holm, K. C., & Klein-Schwartz, W. (1991). 1990 annual report of the American Association of Poison Control Centers national data collection system. The American journal of emergency medicine, 9(5), 461-509.
49. Smith, M. B., & Feldman, W. (1993). Over-the-counter cold medications: a critical review of clinical trials between 1950 and 1991. Jama, 269(17), 2258-2263.
50. Bender, B. G., Berning, S., Dudden, R., Milgrom, H., & Tran, Z. V. (2003). Sedation and performance impairment of diphenhydramine and second-generation antihistamines: a meta-analysis. Journal of Allergy and Clinical Immunology, 111(4), 770-776.
51. Gwaltney Jr, J. M., Moskalski, P. B., & Hendley, J. O. (1980). Interruption of experimental rhinovirus transmission. Journal of Infectious Diseases, 142(6), 811-815.
52. Kuhn, J. J., Hendley, J. O., Adams, K. F., Clark, J. W., & Gwaltney Jr, J. M. (1982). Antitussive effect of guaifenesin in young adults with natural colds: objective and subjective assessment. Chest, 82(6), 713-718.
53. Hutton N, Wilson MH, Mellits D, et al. Effectivness of an antihistamine-descongestan combination for young children with the common cold: a randomized, controlled clinical trial. J Pediatr. 1991; 118:125-130.
54. Weippl, G. (1984). Therapeutic approaches to the common cold in children. Clinical Therapeutics, 6(4), 475-482.
55. Jaffé, G., & Grimshaw, J. J. (1983). Randomized single-blind trial in general practice comparing the efficacy and palatability of two cough linctus preparations,'Pholcolix'and 'Actifed'Compound, in children with acute cough. Current medical research and opinion, 8(8), 594-599.
56. Wilson, J. D. (1983). Asthma and allergic diseases: a clinician's guide to diagnosis and management. (No Title).
57. Borum, P., Olsen, L., Winther, B., & Mygind, N. (1981). Ipratropium nasal spray: a new treatment for rhinorrhea in the common cold. American Review of Respiratory Disease, 123(4), 418-420.
58. Gaffey, M. J., Gwaltney Jr, J. M., Dressler, W. E., Sorrentino, J. V., & Hayden, F. G. (1987). Intranasally administered atropine methonitrate treatment of experimental rhinovirus colds. American Review of Respiratory Disease, 135(1), 241-244.

Chapter - V
The Child With Recurring Colds as a Cause of Cough

Rhinorrhea caused by viruses is a very common cause of acute cough, especially in young children.

For many, colds are synonymous with hyaline rhinorrhea. For the purposes of this writing, a cold is viral rhinopharyngitis or the common cold, whose main, though not the only, etiology is rhinovirus. Given that the primary cause of cough in humans is posterior rhinorrhea (posterior nasal drip) that can accompany this condition, the analysis of this condition becomes important. The symptoms usually include antecedent rhinorrhea (runny nose), sneezing, throat discomfort (pain and/or throat clearing), sometimes cough, fever, and, to a greater or lesser extent, a decline in general well-being. The common cold affects individuals of all ages but primarily impacts infants. It can occur up to 11 times a year in infants and up to 8 times a year in preschoolers[1]. The frequency of colds increases during winter (typically during the "Viral Respiratory Season" from approximately September-October to March in the northern hemisphere). The common cold, or rhinopharyngitis, can be so common that it is difficult to discern when one episode ends, and another begins. On other occasions, the manifestations can be persistent, where the initial viral etiology may no longer be the primary cause, and rhinorrhea may change in its physical characteristics.

Nasal Discharge (Rhinorrhea)

Nasal discharge can manifest as fluid and watery, hyaline or mucohyaline, or whitish in the common cold and as an allergic manifestation. Nasal discharge that is thick, opaque, and colored (yellowish or greenish) is termed mucopurulent. Such discharge is most problematic between birth and 2 or 3 years of age and suggests a bacterial infection.

Physiopathogenesis

In healthy adults, the airways produce more than 100 ml of normal secretion daily. This secretion is transported to the pharynx, where it is swallowed unconsciously. The perception of the passage of this secretion through the posterior pharyngeal wall and its swallowing is usually associated with an increase and/or changes in physical characteristics, typically related to upper airway diseases.

To explain the above, it is necessary to review how the upper airway mucosa functions regarding the production of this secretion. The arteries in the nasal cavity differ from those in the rest of the body because they lack an internal elastic membrane, making them more porous. As a result, the tissue lining the nose is erectile, facilitating the release of blood fluids from the intravascular space[2].

Secretions that get trapped or escape from the upper airways may have a yellowish, greenish, or hyaline color. Hyaline secretions are commonly found in non-infected cases, such as allergic rhinitis, uncomplicated colds, exanthematous diseases, and in cold environments. The greenish coloration is primarily due to the oxidation of mucus by the enzyme myeloperoxidase (green peroxidase) of leukocyte origin.

Yellowish discharge results from the presence of eosinophils, cellular debris, bacteria, and the presence of fat. Therefore, not all greenish or yellowish nasal discharges are necessarily caused by bacterial or purulent infections[3].

If secretions are suppressed for extended periods (using pharmacological measures), the patient may become more susceptible to infections[2,4,5]. The neuronal control of the nasal mucosa, particularly the role of neuropeptides, is well-studied in the pathophysiology of upper airway secretions. The veins and venules of the nasal mucosa are predominantly innervated by cholinergic and adrenergic nerves. Cholinergic stimulation dilates the arterioles, increasing blood flow to the glands, mucous and serous cells, leading to the secretion of proteins and other substances (such as lactoferrin, lysozyme, secretory IgA, etc.). Neuropeptides are present in three types of nerves in the nasal mucosa: sensory C fibers, parasympathetic, and sympathetic nerves. Each of these nerves contains and releases specific neurotransmitters, with each neuropeptide playing a role in modulating nasal mucosal secretions[2,4-7].

The presence of increased nasal secretions, thus becoming noticeable in the upper respiratory tract, is due to a wide range of inflammatory and non-inflammatory stimuli. When these stimuli persist, it is almost inevitable that secondary infections will occur. Inflammatory stimuli can include viruses, bacteria, fungi, chemical agents, irritants, allergic reactions to aeroallergens or food allergens. Non-inflammatory stimuli include cold air, certain smells, certain drinks, and foods (eating very spicy chili being a quintessential example).

Chronic presence of secretions in the upper airways is attributed to the presence of bacteria, protozoa, opportunistic agents, and fungi stemming from infectious rhinitis, sinusitis, and acute or chronic adenotonsillitis. Bacterial antigenic persistence in the central region of the tonsils and adenoids can lead to inflammation and chronic hypertrophy[8,9].

In children, the relationship between the size of the sinus drainage orifice and the size of the sinus itself is greater than in adults, leading to differences in the signs and symptoms of sinusitis between these age groups. Children produce and eliminate more secretions, mainly through the nose, which can lead to posterior nasal discharge.

Differential Diagnosis

Purulent nasal discharge can indicate an inflammatory disorder, an immunological problem, or an intranasal structural abnormality. Inflammatory disorders can be divided into infectious disorders and those resulting from allergies. When assessing purulent nasal discharge, it is important to gather specific information about the onset and duration of the discharge, severity (e.g., impact on appetite, sleep, or activity), quality, color (serous, mucoid, purulent, white, yellow, green), precipitating factors (e.g., apparent viral upper respiratory tract infections, allergens like

new pets, climatic changes), complaints of malodorous breath, associated periorbital edema, and previous histories of nasal discharge and previous therapeutic interventions (including whether they were partially successful or effective for a certain period).

In many children with purulent nasal discharge, the history and physical examination lead to a probable diagnosis of upper respiratory tract viral infection. In this group, symptomatic therapy with normal saline drops (to humidify nasal crusts and facilitate nasal aspiration) or humidification of inspired air may be beneficial.

In cases where a child has purulent nasal discharge that persists for more than 10 days without signs of improvement, the diagnosis of rhinosinusitis is likely. It's worth noting that the presence of Haemophilus influenzae, Streptococcus pneumoniae, Streptococcus pyogenes, or Staphylococcus aureus in nasal flora is rare. Their presence may suggest infections like infectious rhinitis, rhinosinusitis, and/or adenoiditis. Some authors propose that healthy asymptomatic children may harbor these bacteria in the nasopharynx without necessarily indicating an infection.
Viral infection typically presents with an acute onset of clear nasal discharge. In some cases, this discharge may become thick, opaque, and colorful (white, yellow, or greenish). When the discharge is also posterior, it leads to the typical nocturnal and/or morning cough associated with rhinopharyngitis. This nasal discharge usually resolves without specific therapy, as does the cough.

Sinusitis, on the other hand, presents with slimy, thick, yellowish, or greenish nasal discharge that persists for more than 10 days. This is often accompanied by worsening of a productive cough during the day, particularly at night or in the morning, as well as halitosis[10].

Radiological Studies of the Paranasal Sinuses

Radiological studies are essential for diagnosing sinusitis. A diffuse opacity, mucosa thickening of more than 4mm, and an air-fluid level seen on a simple X-ray (occipito-mental position) can indicate sinusitis. However, the definitive diagnostic method is computed tomography (CT) of the paranasal sinuses, which offers higher resolution than a simple X-ray. CT has become the preferred diagnostic method due to its accuracy, although it may show abnormalities in up to 40% of asymptomatic individuals. CT scans are recommended for complicated cases, while simple X-rays are employed for diagnosis or post-treatment monitoring.

Sinus X-rays can be conducted in children aged approximately one year and older. When these X-rays are markedly abnormal and correlate with suggestive symptoms and signs, the diagnosis is relatively straightforward[11]. The appearance of diffuse opacification in the absence of respiratory inflammation symptoms can be due to an infection with potential subsequent manifestations.

Although some argue that obtaining sinus X-rays does not influence the initial treatment, it helps establish the diagnosis, refine the treatment duration to prevent recurrences, and verify the effectiveness of a treatment during follow-up.

Adenoiditis is another potential cause of nasal discharge[12]. The pathophysiology of this infection is not fully understood. However, in some children with purulent nasal discharge not associated with a foreign body, group A streptococcal infection, or sinusitis, an enlarged adenoid may be evident on lateral neck radiography. Many of these children seem to respond to antimicrobial therapy aimed at common respiratory pathogens that cause otitis media and rhinosinusitis. Allergic rhinitis is less common in younger infants but may manifest from the age of 2 or 3. Both perennial and seasonal allergic rhinitis can cause mucosal swelling and obstruction of the ostium, predisposing the individual to bacterial sinusitis and resulting in persistent mucohyaline or purulent nasal discharge. Several studies have demonstrated that rhinoviruses promote infection by binding to mucosal cells during the antigen-IgE reaction, explaining the higher frequency of viral infections in allergic patients.

Treatment of the Common Cold

Acute respiratory infections are the second most common diagnosis made in doctors' offices[13] and the most common discharge diagnosis from emergency department[14]. One review shows that almost a quarter of American adults had taken cough medications with or without sedating antihistamines in the preceding week[15].

Acute respiratory infections represent the second most common diagnosis in medical offices and the most frequent discharge diagnosis from emergency departments. Nearly a quarter of American adults have taken cough medications (with or without sedating antihistamines) in the past week. The use of cough and cold medications was prevalent in young children, as well. In 1991, a study by the Center for Disease Control (CDC) revealed that two-thirds of children under 3 years of age had taken cough or cold medicine in the preceding 30 days[16].

Recommendations for treatment vary considerably. Only two investigations have been systematically assessed. One study, involving children over 2 months of age with non-hyaline nasal discharge, compared those who received antimicrobials and antihistamine-decongestant for five days with those given a placebo. There was no significant difference[17]. Another study observed children with nasal discharge and categorized them based on discharge quality (clear or mucopurulent). These groups received no specific intervention, and the study found no difference in terms of illness duration and complications between the two groups[18].

In children under 2 years of age with purulent nasal discharge lasting more than 10 days, the gold standard treatment is amoxicillin-clavulanate. This suggests a diagnosis of acute bacterial rhinosinusitis[19]. Regarding the treatment of general symptoms, over-the-counter (OTC) pharmaceutical products differ depending on the specific symptom. For cough, there is a lack of strong evidence supporting the effectiveness of any OTC product in reducing the frequency and severity of cough in both

children and adults[20]. The American College of Chest Physicians does not recommend central suppressant medications for cough associated with lower respiratory tract infections[21]. A few studies suggest a modest beneficial effect of dextromethorphan and antihistamine-decongestant combinations for cough, but the outcomes may be outweighed by adverse effects[22]. Conversely, non-sedating antihistamines have not been shown to effectively reduce cough in children with viral rhinopharyngitis.

Antihistamines are popular treatments for nasal congestion and rhinorrhea, although their effectiveness in the context of the common cold differs from that of allergies. In general, antihistamines alone are not recommended for children[12,23] and should be used with caution in adults. Antihistamines and decongestants have not been shown to provide significant benefits to young children[24].

Ipratropium bromide may be beneficial for rhinorrhea caused by perennial rhinitis and the common cold[25]. For managing children with colds, several treatments have been suggested, including the use of saline solution[26] multiple times a day, which is theorized to act as a mild decongestant and improve mucociliary transport, among other effects.

Various other treatments have been proposed for the "flu" and colds, but there is no universally accepted treatment of choice, and results with these treatments are generally partial. Therefore, the market offers a wide variety of medications to address this confusion.

When examining the nose and observing pale or purplish hypertrophic or hyperemic and moist conchae with hyaline bridges, it suggests allergy, especially if the patient has a compatible history after ruling out ongoing viral rhinopharyngitis. If a patient treated for acute sinusitis continues to experience nasal symptoms for more than 10 to 14 days after antimicrobial therapy and has hyaline nasal discharge, allergy may be a likely underlying cause. In such cases, topical steroids may help modify nasal symptoms, suggesting allergic inflammation. If this treatment fails, an evaluation of potential perennial exposures is warranted.

Treatment of General Symptoms

For general discomfort, arthralgia, headache, fever, or low-grade fever, which is often accompanied by irritability or intolerance, paracetamol (acetaminophen) is the preferred treatment. Non-steroidal anti-inflammatories such as ibuprofen and naproxen are also used. The use of acetylsalicylic acid is avoided due to the risk of Reye's syndrome[27]. Some medications include antivirals like amantadine in their formulas, although its effectiveness, even in influenza cases, is questionable. Antihistamines are also added, but their use is contraindicated in children under 2 years of age.

References

1. Grüber, C., Keil, T., Kulig, M., Roll, S., Wahn, U., Wahn, V., & MAS-90 Study Group. (2008). History of respiratory infections in the first 12 yr among children from a birth cohort. Pediatric allergy and immunology, 19(6), 505-512.

2. Raphael, G. D., Jeney, E. V., Baraniuk, J. N., Kim, I., Meredith, S. D., & Kaliner, M. A. (1989). Pathophysiology of rhinitis. Lactoferrin and lysozyme in nasal secretions. The Journal of clinical investigation, 84(5), 1528-1535.

3. Ziment, I. (1982). Physiopathology and pharmacology of escarro. In Ziment I. Pharmacology and respiratory therapy, Cap 2, Inter-American Ed, 41.

4. Lundgren, J. D., & Shelhamer, J. H. (1990). Pathogenesis of airway mucus hypersecretion. Journal of allergy and clinical immunology, 85(2), 399-417.

5. Raphael, G. D., Baraniuk, J. N., & Kaliner, M. A. (1991). How and why the nose runs. Journal of allergy and clinical immunology, 87(2), 457-467.

6. Casale, T. B. (1988). Airway neuropeptides. Am J Rhinol, 2:121-125.

7. Meltzer, E. O., Schatz, M., & Zeiger, R. S. (1988). Allergic and nonallergic rhinitis. In Allergy: principles and practice (pp. 1253-1289). CV Mosby Co St. Louis.

8. Brodsky, L. (1990). Tonsillitis/adenoiditis: the clinical work-up. J Respir Dis, 11, 19-28.

9. Demain, J. G., & Goetz, D. W. (1995). Pediatric adenoidal hypertrophy and nasal airway obstruction: reduction with aqueous nasal beclomethasone. Pediatrics, 95(3), 355-364.

10. Wald, E. R. (1988). Acute sinusitis in children. Adv Otolaryngolog Head Neck Surg, 2:165-88.

11. WALD, E. R. (1991). Purulent nasal discharge. The Pediatric infectious disease journal, 10(4), 329-333.

12. Schroeder, K., & Fahey, T. (2001). Over-the-counter medications for acute cough in children and adults in ambulatory settings. The Cochrane Database of Systematic Reviews, (3), CD001831-CD001831.

13. Woodwell, D. A., & Cherry, D. K. (2004). National ambulatory medical care survey: 2002 summary.

14. McCaig, L. F., Burt, C. W. (2004). National hospital ambulatory medical care survey: 2002 emergency department summary. Adv Data, 340, 287:1-34.

15. Dw, K. (2002). Recent patterns of medication use in the ambulatory adult population of the United States: the Slone Survey. JAMA, 287, 337-344.

16. MD, K. (1994). Over-the-counter medication use among US preschool-age children. JAMA, 272, 1025-1030.

17. TODD, J. K., TODD, N., DAMATO, J., & TODD, W. A. (1984). Bacteriology and treatment of purulent nasopharyngitis: a double blind, placebo-controlled evaluation. The Pediatric Infectious Disease Journal, 3(3), 226-232.

18. Steinweg, K. K. (1983). Natural history and prognostic significance of purulent rhinitis. The Journal of family practice, 17(1), 61-64.

19. Brook, I. (2012). Amoxicillin–clavulante as the gold standard empirical therapy of acute bacteria rhinosinusitis. Expert Review of Anti-infective Therapy, 10(12), 1367-1369.

20. Schroeder, K., & Fahey, T. (2002). Systematic review of randomised controlled trials of over the counter cough medicines for acute cough in adults. Bmj, 324(7333), 329.

21. Irwin, R. S., Bauman, M. H., Bolser, D. C., Boulet, L. P., Braman, S. S., et al. (2006). American College of Chest Physicians. Diagnosis and management of cough executive

summary: ACCP evidence-based clinical practice guidelines. Chest 129 (1suppl):1S-23S.
22. Pavesi, L., Subburaj, S., & Porter-Shaw, K. (2001). Application and validation of a computerized cough acquisition system for objective monitoring of acute cough: a meta-analysis. Chest, 120(4), 1121-1128.
23. Paul, I. M., Yoder, K. E., Crowell, K. R., Shaffer, M. L., McMillan, H. S., Carlson, L. C., ... & Berlin Jr, C. M. (2004). Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. Pediatrics, 114(1), e85-e90.
24. De Sutter, A. I., Lemiengre, M., Campbell, H., & Cochrane Acute Respiratory Infections Group. (1996). Antihistamines for the common cold. Cochrane Database of Systematic Reviews, 2009(3).
25. Hayden, F. G., Diamond, L., Wood, P. B., Korts, D. C., & Wecker, M. T. (1996). Effectiveness and safety of intranasal ipratropium bromide in common colds: a randomized, double-blind, placebo-controlled trial. Annals of internal medicine, 125(2), 89-97.
26. Naspitz, C. K., & Tinkelman, D. G. (1990). Childhood rhinitis and sinusitis: pathophysiology and treatment. (No Title).
27. Beutler, A. I., Chesnut, G. T., Mattingly, J. C., & Jamieson, B. (2009). Aspirin use in children for fever or viral syndromes.

Chapter - VI

Post-Viral Cough - Viral (Residual Post-Viral, Post-Infectious Cough)

Introduction

The common cold, or viral rhinopharyngitis, is one of the most prevalent infectious diseases in humans[1]. Adults typically experience 2 to 4 colds per year, a number that rises to 3.8 to 5 infections per year in children under 5, particularly those attending daycare, who are especially susceptible. Although there are no prospective studies pinpointing the causes of acute cough, it has long been believed that the common cold is the most frequent reason for acute cough in both children and adults.

The exact mechanisms by which viral infections trigger cough are not entirely clear, but they are attributed to a clinical syndrome shared among these infections. This syndrome includes nasal congestion, postnasal drip, pharyngeal clearing (sore throat), eventually leading to cough.

A study demonstrated a significant association between cough, pharyngeal clearing, and posterior nasal drip[2], suggesting that postnasal drip induced by viruses, of which there are at least 200 identified types capable of causing the common cold[3], is the primary mechanism responsible for cough.

Frequent or consecutive viral infections, which are especially common in the winter months, can often be misdiagnosed as chronic cough[4]. Regarding chronic cough, many parents of children who suffer from it associate the onset of the cough with a previous viral upper respiratory tract syndrome, which may have occurred several weeks or even months before (even after the viral infection has resolved). In these cases, the diagnosis of post-viral cough[3], also known as residual or post-infectious cough, is typically given. This type of cough persists as a consequence of a viral infection, primarily in the upper airways but sometimes affecting the lower airways as well.

However, assigning the diagnosis of post-viral cough to children is not particularly helpful, as it does not suggest a specific treatment. It's essential to continue with the diagnostic process to determine the specific sequelae produced by the virus, which perpetuate the acute cough. A viral infection can lead to persistent or chronic cough in children through various mechanisms, not just due to postnasal drip, as often observed in acute cough. This chapter explores these mechanisms, the outcomes, or sequelae of a previous viral infection.

There are Certain Elements that Characterize Post-Viral Cough:
The cough typically does not last more than 8 weeks.
Chest x-rays show no abnormalities.
Cough usually resolves spontaneously.
The histological effects of a viral infection can range from epithelial destruction to no histological changes at all. All of these can cause vasodilation, inflammation, hypersecretion, and cough.

Bronchoscopy with biopsy in adult patients with uncomplicated type A influenza reveals significant desquamation of epithelial cells down to the basement membrane[5], showing lymphocytic bronchitis (as opposed to the eosinophilic characteristic of asthma). This contrasts with the predominant lesion of bronchiolitis due to the respiratory syncytial virus, where, although the alterations are similar, neutrophils are the predominant cell type, similar to bronchiolitis caused by rhinovirus[6].

Even though the pathogenesis is not entirely understood, it has been proposed that viral infections can disrupt epithelial integrity and lead to persistent inflammation. This disruption can cause several effects, including:
-The induction or exacerbation of existing bronchial hyperreactivity.
-Hypersecretion of the bronchial mucosa and the upper airway.
-Inflammation that can extend to the lower airways.
-Reduced effectiveness of mucociliary clearance in the respiratory epithelium.
-Increased sensitivity of cough receptors.
-Any of these processes, independently or in combination, can produce chronic cough in children, often initiated by a viral infection in the upper respiratory tract.

Regarding increased cough receptor sensitivity, studies have shown that during the acute phase of upper respiratory tract infections with an unidentified cause that leads to persistent cough, there is increased sensitivity to capsaicin challenge. About four weeks later, during convalescence, this sensitivity returns to baseline[7].

In addition to this, inflammation of the nasal mucosa and paranasal sinuses can produce secretions that drain into the hypopharynx and stimulate cough receptors, leading to a postnasal drip syndrome with similar results (for more details, see the chapter on Postnasal Drip Syndrome). Another factor to consider is that cough, due to increased intra-abdominal pressure, can cause pathological gastroesophageal reflux events, which, in turn, worsen the cough, perpetuating it. Lastly, a rarely mentioned phenomenon is that cough itself can, through mechanical trauma, worsen inflammation[8]. Thus, it becomes another process that can prolong cough.

All the above-mentioned mechanisms exemplify the various ways in which these processes can be established after a viral infection. They create a cascade of events that feed on each other, establishing one or more vicious cycles that continue the cough. However, it's important to remember that when chest x-rays show no abnormalities, the evaluation of post-viral cough should be extended to consider the three most common causes of chronic cough: asthma or transient bronchial hyperreactivity, hypersecretion of mucus with poor mucociliary clearance from the lower respiratory tract, hypersecretion of mucus from the rhinosinusal passage promoting postnasal drip syndrome, or gastroesophageal reflux disease. Additionally, there's always the

possibility of a foreign body in children.

The Following is an Analysis of Some of these Causes:

Transient Bronchial Hyperreactivity (Early Wheezer)

A viral respiratory tract infection can induce transient bronchial hyperreactivity and cough, which can persist for up to 8 weeks, even in non-asthmatic children[8,9]. After the viral infection has resolved, a slow-resolving bronchial inflammatory process can persist, affecting the symptomatology and airway function to varying degrees.

Cough due to bronchospasm, whether due to asthma or early wheezing, responds to medication that includes inhaled beta-2 adrenergic agonists, sometimes with a dramatic effect. However it is important to remember that cough may be the only manifestation of asthma[10]. This type of response is valuable for diagnosing the direct cause of the cough, bronchospasm.

Cough produced by bronchial hyperreactivity, as a consequence of a viral process, is more common in children who had bronchiolitis or were born prematurely, requiring mechanical ventilation, and developed bronchopulmonary dysplasia. In these two scenarios, bronchial inflammation causes smooth muscle dysfunction, bronchospasm, and hypersecretion of mucus (as explained in the next section). Therefore, the recommended treatment includes inhaled steroidal anti-inflammatories for long-term well-being.

Mucus Hypersecretion

Mucus hypersecretion, whether or not associated with bronchial hyperreactivity (excluding posterior nasal drip syndrome), can occur as a result of airway inflammation. This hypersecretion can also impair mucociliary clearance[11], leading to cough.

Mucus hypersecretion can contribute to cough in the lower respiratory tract through mechanical and irritant effects on cough receptors. It can also be associated with reduced mucociliary clearance and bacterial superinfections. The buildup of thick mucus can lead to persistent cough, especially in patients with comorbidities like bronchopulmonary dysplasia and bronchiectasis.

Various types of medications have been used to treat mucus hypersecretion. Although mucolytic agents have no proven clinical value in this regard, some patients may experience improvement with their use. Bronchodilators are commonly used not only to alleviate bronchospasm but also to enhance mucociliary clearance[12], along with corticosteroids, which indirectly inhibit mucus secretion. Antibiotics are only indicated when there is evidence of bacterial superinfection, which is not uncommon in these patients.

In the case of the upper respiratory tract, secretion from the paranasal sinuses and rhino-sinus passages can lead to postnasal drip cough syndrome, which is the most common cause of persistent (or recurrent) cough in children and adults. Postnasal drip syndrome can lead to cough, dyspnea, and wheezing due to the drainage of secretions into the hypopharynx and even lower regions.

Patients with postnasal drip often experience retropharyngeal discharge, nasal discharge, and the frequent need to clear the pharynx, known as "throat clearing." Examination of the nasopharynx may reveal mucous or mucopurulent secretions and a cobblestone appearance of the mucosa of the posterior pharyngeal wall.

In cases with a strong clinical or radiological suspicion of rhinosinusitis (e.g., mucopurulent nasal discharge), antibiotics are indicated for treating cough due to posterior nasal drip syndrome, typically for a minimum of 10 days. Topical and/or systemic decongestants can facilitate sinus drainage and enhance the effectiveness of antibiotic treatment.

Gastroesophageal Reflux Disease (GERD)

Gastroesophageal reflux has been mentioned as an important factor associated with chronic cough in children, affecting up to 32.5% of patients in some cases[13]. While viral infections don't directly cause GERD, the severe cough produced by these infections can exacerbate GERD and lead to cough[12,14].

Reflux should be suspected when there is frequent regurgitation or vomiting, or in children when there are complaints of heartburn, a sour taste, or the sensation of food coming up, particularly when these symptoms are accompanied by postprandial cough. These symptoms alone allow a diagnosis of GERD without further testing. However, in the evaluation of cough, an esophagogastric series with barium and/or 24-hour monitoring of esophageal pH are reserved for identifying "silent" reflux, which produces cough without gastrointestinal symptoms and is common in children.

Treatment of cough due to GERD in the context of post-viral cough may require addressing other contributors to cough first, beginning with the high intra-abdominal pressures generated during coughing, which can exacerbate reflux.

Significant improvement from maximal medical therapy for reflux is often slow, sometimes taking up to 6 months to be fully effective. It's essential to determine whether cough is the primary factor causing gastroesophageal reflux or if gastroesophageal reflux is the main factor causing cough. In the former case, resolving the cough may subsequently resolve the reflux, as a partially effective lower esophageal sphincter may be the cause.

If gastroesophageal reflux is determined to be the primary cause of the cough, antireflux treatment includes a high-protein, low-fat antireflux diet, acid suppression with H2 antagonists or proton pump inhibitors, a prokinetic agent, and potentially other components, such as treating obstructive sleep apnea and discontinuing medications that exacerbate GERD when possible.

Pertussis

When evaluating post-viral cough that persists for 3 to 8 weeks, it's important to consider Bordetella pertussis[12,15]. In cases where

upper respiratory symptoms improve but the cough worsens, pertussis should be considered. Pertussis should be suspected in children with uncontrollable, emetic cough syndrome and characteristic stridor. Additionally, look for similar symptoms or severe cough in recent contacts. Erythromycin is used to treat pertussis and as prophylaxis for exposed individuals. For problematic persistent cough during the chronic phase of infection, it may be reasonable to consider corticosteroid treatment.

Conclusions

Viral respiratory infections are the most common cause of acute cough and can initiate subacute and chronic cough. While the exact pathogenesis of post-infectious cough remains unclear, it is believed to result from varying degrees of disruption of epithelial integrity and the extent of inflammation in both the upper and lower airways[16].

The specific infection responsible for post-infectious cough in children remains unidentified in most cases. Respiratory viruses, especially respiratory syncytial virus, influenza, parainfluenza, and adenovirus, are often considered as potential causes, which is why it is commonly referred to as post-viral cough. However, other agents, such as Mycoplasma pneumoniae, Chlamydophila pneumoniae, and Bordetella pertussis, have also been implicated.

Transient inflammation of the lower airways appears to be crucial in the pathogenesis of post-viral cough in some patients. Recurrent and consecutive viral infections, which are particularly common in winter and in daycare centers, can frequently lead to chronic cough.

The diagnosis of post-viral cough is of limited utility. Instead, physicians should expand the diagnosis by considering all pathways through which post-viral inflammation can promote cough. Typically, specific therapy for common or frequent causes of chronic cough (such as asthma, NPGS, and GERD) rapidly and completely resolves the symptoms.

Literature suggests that dry cough, isolated from other symptoms and lacking specific diagnostic indicators, relatively common[17]. It seems that we have yet to develop a system to identify these indicators. Consequently, cough classified as non-specific due to a lack of other manifestations or indicators is a rare occurrence.

Therefore, over-the-counter cough suppressants typically address cough in a non-specific manner, which contrasts with the principles outlined in this book. These medications have limited, if any, effectiveness, with very few exceptions. The main reason for this is the potency of the cough stimuli, which often outweighs the central or peripheral antitussive effects of the medications. Morphine is an exception, as it exhibits a strong antitussive effect; however, the potential risks of its use often outweigh the benefits in the majority of cases.

Furthermore, cough is an incredibly effective protective mechanism against lung infections. This fact has been overlooked in a market driven by different priorities. This may be an expression of the frustration that cough has caused throughout human history. To the extent that the specific causes of cough are identified, nonspecific therapies aiming to suppress cough become unnecessary.

References

1. Irwin, R. S., French, C. T., & Fletcher, K. E. (2002). Quality of life in coughers. Pulmonary pharmacology & therapeutics, 15(3), 283-286.
2. Hoffstein, V. (1994). Persistent cough in nonsmokers. Canadian Respiratory Journal, 1, 40-47.
3. Poe, R. H., Israel, R. H., Utell, M. J., & Hall, W. J. (1982). Chronic cough: bronchoscopy or pulmonary function testing?. American Review of Respiratory Disease, 126(1), 160-162.
4. Kamei, R. K. (1991). Chronic cough in children. Pediatric Clinics of North America, 38(3), 593-605.
5. WALSH, J. J., DIETLEIN, L. F., LOW, F. N., BURCH, G. E., & MOGABGAB, W. J. (1961). Bronchotracheal response in human influenza: type A, Asian strain, as studied by light and electron microscopic examination of bronchoscopic biopsies. Archives of internal medicine, 108(3), 376-388.
6. Taussig, L. M., & Landau, L. I. (2008). Pediatric Respiratory Medicine E-Book. Elsevier Health Sciences.
7. O'connell, F., Thomas, V. E., Studham, J. M., Pride, N. B., & Fuller, R. W. (1996). Capsaicin cough sensitivity increases during upper respiratory infection. Respiratory medicine, 90(5), 279-286.
8. Empey, D. W., Laitinen, L. A., Jacobs, L., Gold, W. M., & Nadel, J. A. (1976). Mechanisms of bronchial hyperreactivity in normal subjects after upper respiratory tract infection. American Review of Respiratory Disease, 113(2), 131-139.
9. Little, J. W., Hall, W. J., Douglas Jr, R. G., Mudholkar, G. S., Speers, D. M., & Patel, K. (1978). Airway hyperreactivity and peripheral airway dysfunction in influenza A infection. American Review of Respiratory Disease, 118(2), 295-303.
10. Corrao, W. M., Braman, S. S., & Irwin, R. S. (1979). Chronic cough as the sole presenting manifestation of bronchial asthma. New England Journal of Medicine, 300(12), 633-637.
11. Del Donno, M., Bittesnich, D., Chetta, A., Olivieri, D., & Lopez-Vidriero, M. T. (2000). The effect of inflammation on mucociliary clearance in asthma: an overview. Chest, 118(4), 1142-1149.
12. Irwin, R. S., Boulet, L. P., Cloutier, M. M., Fuller, R., Gold, P. M., Hoffstein, V., ... & Rubin, B. K. (1998). Managing cough as a defense mechanism and as a symptom: a consensus panel report of the American College of Chest Physicians. Chest, 114(2), 133S-181S.
13. Khoshoo, V., Edell, D., Mohnot, S., Haydel Jr, R., Saturno, E., & Kobernick, A. (2009). Associated factors in children with chronic cough. Chest, 136(3), 811-815.
14. Irwin, R. S., & French, C. T. (2001). Cough and gastroesophageal reflux: identifying cough and assessing the efficacy of cough-modifying agents. The American journal of medicine, 111(8), 45-50.
15. Senzilet, L. D., Halperin, S. A., Spika, J. S., Alagaratnam,

M., Morris, A., & Smith, B. the Sentinel Health Unit Surveillance System Pertussis Working Group 2001 Pertussis is a frequent cause of prolonged cough illness in adults and adolescents. Clin. Infect. Dis, 32, 1691-1697.
16. Braman, S. S. (2006). Postinfectious cough: ACCP evidence-based clinical practice guidelines. Chest, 129(1), 138S-146S.
17. Shields, M. D., & Doherty, G. M. (2013). Chronic cough in children. Paediatric respiratory reviews, 14(2), 100-106.

Chapter - VII

Persistent Cough in Children, Related to Hyperreactivity of the Upper and Lower Airway

From an epidemiological perspective, sinusitis can be a significant factor that destabilizes patients with bronchial asthma and precipitates exacerbations by stimulating neural receptors in the nose or paranasal sinuses, leading to the activation of the bronchoconstriction reflex[1-4]. In this context, these patients may experience cough due to posterior nasal drip syndrome, primarily due to rhinosinusitis-induced secretions. Additionally, they may cough due to reflex bronchial hyperreactivity[5-7].

It is well-established that diseases such as rhinitis, pharyngitis, laryngitis, and rhinosinusitis can manifest as hyperreactivity in the extrathoracic airway, which pertains to the upper airways. These conditions can generate symptoms akin to those seen in asthma. Furthermore, these diseases can co-occur with asthma and influence lower airway function, leading to the production of cough and wheezing[5,7]. Based on the above, it is evident that cough and other asthma-related symptoms may not solely stem from intrathoracic airway dysfunction. They can, in many instances, be attributed to the extrathoracic airway as well.

Further observations have shed light on the significance of extrathoracic airway hyperreactivity in generating lower airway symptoms:
1. In bronchial challenge tests using methacholine, a considerable number of patients develop symptoms such as dysphonia, tracheal cough (seal-like cough), and stridor. This signifies the presence of extrathoracic hyperreactivity, as indicated by a reduction in maximum inspiratory flow, in approximately 60% of patients with asthma[8]. It is noteworthy that in about 30% of these patients, this extrathoracic hyperreactivity represents the sole functional abnormality, with no substantial variations in FEV1 (forced expiratory volume in 1 second). This indicates that methacholine affects the lower airways in some individuals but not others[8].
2. A significant percentage of children who experience recurrent laryngotracheitis or croup eventually develop bronchial hyperreactivity. This suggests that hyperreactivity may originate in the upper airway, manifesting as croup during initial episodes, and subsequently descending into the lower airway, presenting as asthma[9,10].

In a study[7], postnasal drip was found to be associated with an increased likelihood of coughing, both as an isolated symptom and when combined with other lower airway symptoms like dyspnea and wheezing. The same author previously reported that bronchial hyperreactivity in rhinosinusitis is related to extrathoracic airway hyperreactivity, and that both forms of hyperreactivity can be reversed with treatment involving antibiotics and nasal steroids[11]. In cases of children diagnosed with cough-variant asthma, those who exhibit cough without wheezing but experience substantial improvement with bronchodilators have raised questions about whether viral infections can cause a temporary increase in bronchial reactivity. This has significant diagnostic and therapeutic implications, as extrathoracic hyperresponsiveness (ETHR) can produce asthma-like symptoms, necessitating the treatment of upper airway diseases underlying the symptoms.
Additionally, Dr. Bucca's study[11] revealed that patients who solely had chronic cough (without wheezing or dyspnea) had the highest probability of exhibiting extrathoracic hyperreactivity. Although the study was not designed to assess the effects of medications, it is worth noting that among the 71 patients with postnasal drip syndrome, treatment with intranasal steroids, decongestants, antibiotics, or antihistamines (as necessary for rhinosinusitis and rhinitis) led to a considerable reduction in symptoms indicative of asthma. This treatment regimen alleviated extrathoracic hyperreactivity and improved bronchial hyperreactivity. This improvement indicates that ETHR plays an etiological role in lower airway disease rather than just being an underlying factor.

It's important to consider that children tend to experience more frequent rhino pharyngitis episodes than adults, which, in combination with their greater susceptibility to complications due to epidemiological and anatomical factors, makes them theoretically more prone to extrathoracic airway hyperreactivity and subsequently, bronchial hyperreactivity. This may also impact the number of early wheezers and potentially even the number of children who develop asthma. Particularly if upper airway stimuli persist and other factors such as passive smoking and atopy come into play.

Studies conducted in animal models of sinusitis[12] indicate that reflexes originating from the upper airway and affecting the lower airway are initiated by pharyngeal receptors, rather than nasal or sinus receptors. This aligns with observations that patients experiencing sinusitis exacerbations show a swift and significant reduction in maximum inspiratory flow upon histamine inhalation challenge, indicative of a constrictive response at the pharyngeal-laryngeal level. In severe cases, this is followed by bronchial narrowing. These findings suggest that a critical threshold of extrathoracic dysfunction is needed to trigger bronchoconstriction. Remarkably, this extrathoracic dysfunction was mitigated with nasal steroids and antibiotics[13].

The same researchers also showed a strong association between rhinosinusitis and HRET, which was confirmed through nasopharyngeal biopsies. Biopsy findings included epithelial membrane thinning, a significant increase in eosinophils (even in non-atopic individuals), and submucosal nerve fiber proliferation[11].

It's important to note that non-asthmatic patients with rhinosinusitis have frequently reported cough as the most common

symptom of sinusitis exacerbations, followed by wheezing and rhinorrhea. This suggests that damage to the pharyngeal mucosa in non-asthmatic patients with rhinosinusitis contributes to airway dysfunction both upper and lower by exposing sensitive nerve endings to irritants and activating constrictive reflexes at various levels[14]. Pathological studies of chronic sinusitis have shown that eosinophils, along with polymorphonuclear cells, are the predominant infiltrating cells in sinus mucosa, regardless of allergic status[15]. These cells, through inflammatory mediators and cytotoxic products, cause damage to sinus epithelium[16]. This damage can also extend to the pharyngeal and hypopharyngeal mucosa due to the drainage of these cells, mediators, and cytotoxic products into the posterior nasal drip originating from infected paranasal sinuses.

It is in line with this observation that postnasal drip is the most common cause of persistent cough in non-asthmatic individuals[17]. It arises due to the continuous stimulation of pharyngeal and hypopharyngeal receptors as a result of local inflammatory changes. In other studies, nasal steroids were found to significantly improve bronchial hyperreactivity in patients with seasonal allergic rhinitis[18], with similar results reported by Dr. Bucca in patients with sinusitis[19]. Long-term studies involving non-asthmatic patients with sinusitis are necessary to confirm whether a sequence of events—beginning with pharyngitis leading to extrathoracic dysfunction, subsequently causing bronchial dysfunction—indeed takes place. In such cases, early treatment of rhinosinusitis may prevent the development of bronchial asthma preemptively.

References

1. McFadden Jr, E. R. (1980). Nasal-sinus-pulmonary reflexes and asthma. J. Allergy Clin. Immunol., 78, 1-3.
2. Slavin, R. G. (1982). Relationship of nasal disease and sinusitis to bronchial asthma. Annals of allergy, 49(2), 76-79.
3. Rachelefsky, G. S., Katz, R. M., & Siegel, S. C. (1984). Chronic sinus disease with associated reactive airway disease in children. Pediatrics, 73(4), 526-529.
4. Adinoff, A. D., & Irvin, C. G. (1987, April). Upper respiratory tract disease and asthma. In Seminars in Respiratory Medicine (Vol. 8, No. 04, pp. 308-314).
5. Borson, D. B., Brokaw, J. J., Sekizawa, K., McDonald, D. M., & Nadel, J. A. (1989). Neutral endopeptidase and neurogenic inflammation in rats with respiratory infections. Journal of Applied Physiology, 66(6), 2653-2658.
6. Bucca, C., Rolla, G., Scappaticci, E., Baldi, S., Caria, E., & Oliva, A. (1991). Histamine hyperresponsiveness of the extrathoracic airway in patients with asthmatic symptoms. Allergy, 46(2), 147-153.
7. Bucca, C., Rolla, G., Brussino, L., De Rose, V., & Bugiani, M. (1995). Are asthma-like symptoms due to bronchial or extrathoracic airway dysfunction?. The Lancet, 346(8978), 791-795.
8. Turktas, I., Dalgic, N., Bostanci, I., & Cengizlier, R. (2002). Extrathoracic airway responsiveness in children with asthma-like symptoms, including chronic persistent cough. Pediatric pulmonology, 34(3), 172-180.
9. Çetinkaya, F., & Turgut, S. (2001). The relation between recurrent acute subglottic laryngitis and asthma in children. International journal of pediatric otorhinolaryngology, 57(1), 41-43.
10. Castro-Rodrıguez, J. A., Holberg, C. J., Morgan, W. J., Wright, A. L., Halonen, M., Taussig, L. M., & Martinez, F. D. (2001). Relation of two different subtypes of croup before age three to wheezing, atopy, and pulmonary function during childhood: a prospective study. Pediatrics, 107(3), 512-518.
11. Bucca, C., Rolla, G., Pinna, G., Oliva, A., & Bugiani, M. (1990). Hyperresponsiveness of the Extrathoracic Airway in Patients with Captopril-lnduced Cough. Chest, 98(5), 1133-1137.
12. Irvin, C. G. (1992). Sinusitis and asthma: an animal model. Journal of allergy and clinical immunology, 90(3), 521-533.
13. Rolla, G., Colagrande, P., Scappaticci, E., Bottomicca, F., Magnano, M., Brussino, L., ... & Bucca, C. (1997). Damage of the pharyngeal mucosa and hyperresponsiveness of airway in sinusitis. Journal of allergy and clinical immunology, 100(1), 52-57.
14. Vanhoutte, P. M. (1989). Epithelium-derived relaxing factor (s) and bronchial reactivity. Journal of Allergy and clinical Immunology, 83(5), 855-861.
15. Demoly, P., Crampette, L., Mondain, M., Campbell, A. M., Lequeuxc, N., Enander, I., ... & Bousquet, J. (1994). Assessment of inflammation in noninfectious chronic maxillary sinusitis. Journal of allergy and clinical immunology, 94(1), 95-108.
16. Harlin, S. L., Ansel, D. G., Lane, S. R., Myers, J., Kephart, G. M., & Gleich, G. J. (1988). A clinical and pathologic study of chronic sinusitis: the role of the eosinophil. Journal of Allergy and Clinical Immunology, 81(5), 867-875.
17. Irwin, R. S., Corrao, W. M., & Pratter, M. R. (1981). Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. American Review of Respiratory Disease, 123(4), 413-417.
18. Foresi, A., Pelucchi, A., Gherson, G., Mastropasqua, B., Chiapparino, A., & Testi, R. (1996). Once daily intranasal fluticasone propionate (200 µg) reduces nasal symptoms and inflammation but also attenuates the increase in bronchial responsiveness during the pollen season in allergic rhinitis. Journal of allergy and clinical immunology, 98(2), 274-282.
19. Bucca, C., Rolla, G., Scappaticci, E., Chiampo, F., Bugiani, M., Magnano, M., & D'Alberto, M. (1995). Extrathoracic and intrathoracic airway responsiveness in sinusitis. Journal of Allergy and Clinical Immunology, 95(1), 52-59.

Chapter - VIII

Considerations about some International Guidelines for the Evaluation and Management of Chronic Cough In Children

There are efforts in various parts of the world to evaluate and treat cough in children, to which several countries have made interesting contributions.
The problems we face when conducting them is a lack of double-blind studies to obtain properly supported conclusions.

Below, three guides that represent some of these efforts from the United Kingdom, the United States and Japan are analyzed in a panoramic manner to give an idea of the different perspectives from which cough has been approached. "All published guidelines agree on the current lack of good quality evidence with which to make evidence-based statements for the diagnosis, investigation and treatment of cough in children"

Malcolm Brodlie

Great North Children's Hospital UK. At the end of each guide presentation, reflections are made about
their approach.

Recommendations for the Evaluation and Management of Cough in Children

British Thoracic Society Guidelines[1].

Introduction

Cough and cold medications are among the most commonly used in Western societies and possibly throughout the world, despite evidence suggesting the medication's ineffectiveness in treating cough as a symptom. The etiology of cough in children is covered by a broad spectrum of respiratory disorders and treating the underlying cause is important.

The need for the British Chest Society recommendations for Cough: Cough is a very common problem that generates anxiety, has numerous causes and is frequently misdiagnosed as well as inappropriately treated.

Methodology for the Generation of the Guides

Most investigations of cough characteristics have not been formally evaluated for their predictive value in the diagnosis of a specific disease as there is currently a lack of evidence in relation to cough to make evidence-based statements for diagnosis. Therefore, most of the guidelines have been made through consensus on the known literature.

Terms used in these Guides

Chronic Cough: one that lasts more than 8 weeks
Acute Cough: One that lasts less than 3 weeks
Prolonged Acute Cough: Between 3 and 8 weeks
Since cough due to infection will resolve within no more than 8 weeks:
Recurrent Cough: Two or more cough episodes in a year other than those associated with colds
Postviral Cough: One that begins with a viral infection and lasts more than 3 weeks
Specific Cough: A cause is clearly identified
Non-specific "isolated" cough: Child with a dry cough without other symptoms or signs of another disease.

Summary

Most children with an acute cough have a viral upper respiratory infection. Most children with a cough due to a simple upper respiratory tract infection will not need further investigation.

All published guidelines agree on current lack of good quality evidence-based statements for diagnosis, investigation and treatment of cough in children.

Recurrent Cough

Cough episodes are considered recurrent when they are more than 2 in a year and are not accompanied by rhinopharyngitis and last more than 7-14 days apart from cough episodes associated with colds. If the remission periods are short, it may be difficult to distinguish from chronic or persistent cough.

Chronic Cough

In otherwise healthy children with isolated dry cough without indicators of specific disease, a course of treatment:
- Anti-asthma
- Anti-allergic rhinitis or
- Anti-gastroesophageal reflux

They are unlikely to be beneficial and are generally not recommended.

However, it may be difficult to rule out asthma as a cause of cough in young children, so a course of anti-asthma therapy (typically with inhaled steroids) may be used.

A defined period of time should be established (e.g. 8 – 12 weeks) after which the course of anti-asthma medication should be discontinued. It is important that children with simple bronchitis recurrent viral do not complete a long-term course of high-dose inhaled steroids.

Alerts in case of the following characteristics:

- Onset at birth
- Cough when eating
- Sudden onset cough
- Chronic cough with production of phlegm
- Continuous cough, without remission or that gets worse
- Signs of chronic lung disease

Natural history of cough: 25% of children with acute cough still cough at 2 weeks and 10% at 3-4 weeks[2]. Most children with a

cough due to a simple upper respiratory tract infection will not need any investigation.

The absence of fever, tachypnea and chest signs seems to be the most useful to rule out future complications in children with cough at first contact. Treatments: If croup, bronchiolitis, pneumonia or asthma is diagnosed, each of these conditions requires specific treatment.

Antihistamines and intranasal steroids are beneficial in children with allergic rhinitis in the pollen season, with steroids having an advantage in efficacy in relation to antihistamines.

Chronic Cough in Children

Most coughs in children are related to temporary infections. An observation period of 3-8 weeks is necessary to determine what investigations will be required.
Most children with chronic cough have recurrent viral bronchitis (recurrent cough) or postviral syndromes (subacute cough) and are otherwise healthy.

Generally cough in children can be put into one of three overlapping categories:

1.- Normal Child

He averages 11 coughs a day with some experiencing up to 30 coughs a day. Experience is required to be sure when a child is normal[3-4].

2.- Specific Cough

Look for indicators that suggest a specific diagnosis

3.- Isolated, Non-Specific Cough

There is probably a specific but not yet identified cause. However, a precise diagnosis is not at hand.
Some of these children may have elevated cough receptor sensitivity; the role of gastroesophageal reflux disease (GER) as a cause of an isolated cough in a healthy child is unclear. GER is a common finding in infants but is only sometimes associated with cough.

A detailed history will need to be taken

Traditional search:

- Starting age
- Dry or wet,
- Quality (seal, staccato, paroxysmal),
- Continuous, nocturnal, when getting up;
- Factors that trigger it
- Factors that alleviate it
- Presence of associated symptoms (wheezing, dyspnea) or cough
isolated
- There is a family history of atopy
- What medication have you taken and what effect has it had?

Determining whether the cough is wet and productive or dry is discussed as important and in young children it is possible to describe the characteristics of the secretion if they vomit it.

Determine if the cough is metallic, croupy or like the honking of an old horn (strident), the latter characteristic of the usual or psychogenic cough but also of the child who has had a tracheo-esophageal or tracheo-malacia fistula repaired.

The croupy, metallic or seal cough characteristic of croup/ laryngotracheobronchitis.

Determine if Cough is an Isolated Symptom

The diagnoses that are taken into account: asthma, obliterative bronchiolitis, foreign body, tracheomalacia, cardiac malformation.

Determine what Triggers the Cough

Determine family history: Asthma, tuberculosis, cystic fibrosis, etc.
Record medication administered, dose, period and effect

Research

Complete systematic clinical examination
Chest TV
Spirometry
Observation of cough and collection of sputum sample
Allergy tests as they support asthma

Treatment

The algorithms used in adults are not useful for children: In a study[5] it was considered that the 3 common problems that cause cough in adults (postnasal drip, asthma and gastroesophageal reflux) explained only 10% of cough in children[6]. Avoid exposure to tobacco treat cough with a specific diagnosis trreatment of extended bacterial bronchitis is with antibiotics for 4 to 6 weeks.

Treatment of isolated cough in an otherwise healthy child (postviral cough or recurrent viral bronchitis) does not appear to be effective. Cough usually self-limits over time. A period of observation without treatment is indicated.

An anti-asthma course can be used to diagnose whether the cough is due to asthma. In order to clearly confirm or exclude the diagnosis of asthma, inhaled steroids are required. Alternatively, a short course of systemic steroids can be used. If you use anti-asthma treatment and treat asthma you should see a reduction in cough in 8 to 12 weeks.

Children with extended or elongated bacterial bronchitis should have other diagnostic possibilities excluded and a prior sputum culture performed. When a specific study of cough in a child is not possible to carry out as part of a management plan (that is, when cough is a completely isolated symptom) it should be self-limiting over a certain period of time. A subsequent review is advisable to ensure that the cough is resolved and has not developed specific indicators.

Giving anti-asthma, anti-reflux or anti-rhinitis treatments in children with non-specific cough has not been helpful, so they are not generally recommended.

Analysis

These guidelines suggest that there are enough differences in the

cough of children and adults to separate the guidelines for the evaluation and management of cough and that the main causes of cough in adults[7]: Asthma, postnasal drip, and gastroesophageal reflux, "not necessarily" are valid for children.

It is clear that in adults it is more It is difficult to suspect a foreign body if the patient does not mention it, or viral bronchiolitis or cystic fibrosis, but in the case of reflux, postnasal drip and asthma (or transient wheezing) they still cause cough in children of any age and these diagnoses should be considered. in the presence of a child with cough and a normal chest x-ray.

It is not always justified to separate the diseases of children and adults, this can lead to confusion. Many diseases are first described in adults, treated in them and later the treatments are adapted in children; This is the case of: Pneumonia, tuberculosis, AIDS, surgical techniques, and a very long etcetera.

Of course, there are variations that are sometimes very important, not only in terms of etiologies and treatment of diseases but even in nosological entities that are very specific to children or others to adults and that are therefore not shared between them, even and when The substrate (mucosa, bronchi, alveoli, etc.) could be similar.

In the case of cough, we could not think of some pediatric causes in an older adult, such as bronchopulmonary dysplasia. However, in the not too distant future, it will be possible to characterize how older adults who developed bronchodysplasia at birth behave.

This is not the case with the very common causes of acute and chronic cough (greater than 3 weeks) that is accompanied by a normal chest x-ray. In these cases of frequent causes, it can be included in the causes described in adolescents and adults, which are:

- Postnasal drip syndrome
- Asthma (or temporary wheezing from other causes)
- Gastroesophageal reflux disease

In children there are reasons, perhaps very compelling, for these 3 conditions to occur:

1.- Posterior nasal drip syndrome

As a producer of cough in children, at birth the height of the epiglottis with respect to the nasopharynx causes the child to breathe only through the nose during the first 6 months of life, which causes secretions from the nasopharynx, if increase due to some infection, they can move to the hypopharynx and larynx and cause cough. Even more, eventually a common cold can represent a major obstacle to breathing.

As the child grows, the epiglottis gradually lowers and allows oral breathing to occur (approximately 6 months). The high position of the epiglottis, gradually lowering as the first months of life pass, and opening the oral passage for breathing is a difficult step in the development of the infants. It is the process of joining two pathways, nasal and oral (air and digestive), previously functionally separated, now reunited requiring new coordination for swallowing and breathing (see: Cough mechanisms).

The above could be the reason for less effective management of posterior nasal secretions than in older children, which would explain both a greater susceptibility to lower respiratory tract infections and the sensation of a thrill (produced by secretions) that mothers frequently report. by applying the palm of your hands on the chest of your infants when they have an upper respiratory tract infection.

2.- Bronchospasm (with or without wheezing)

Children have a greater propensity to develop bronchospasm than adults even without being asthmatic, that is, the mucosa of their airways tends to become inflamed more easily for different reasons, including viral infections that, by the way, children suffer more frequently, especially. First years of life.

3.- Gastroesophageal reflux disease

The lower esophageal sphincter is a tributary, like most organs and systems of the body, to maturation. In fact, nearly 100% of newborns regurgitate milk as a manifestation of gastroesophageal reflux and immaturity of said sphincter.

At approximately 2 years of age, the majority have overcome it, however, at least during these first 2 years it proportionally exceeds the rate of adults with reflux and therefore the probability of cough from this cause.

Due to the above reasoning, it is not only difficult, but also risky, to separate the common causes of cough in adults and children.

It is possible that when diagnosing cough in children, even in the youngest ones, one can start, as in adults, from considering these 3 causes as the main and most frequent ones, taking the precautions that arise when handling children, especially all the smallest ones.

On the other hand, these guidelines do not give importance to rhinopharyngitis and colds as a cause of acute cough or as a trigger for some causes of chronic cough.

Chronic cough is taken as one that lasts more than 8 weeks. If it is true that a cough that occurs daily for 8 weeks, without failing to occur on a single day, requires a more in-depth study due to the possibility of representing a delicate illness. Now, considering that in children who are otherwise asymptomatic, waiting 8 weeks for the cough to self-limit is not the healthiest thing.

Much of the literature defines chronic cough in children as one that lasts 3 weeks or more, since this period contains the vast majority of causes of acute cough or as a sequel to an acute process. Apparently, considering it this way does not leave much room for a cough to become a severe problem in which the solution is facilitated by acting earlier.

The natural history of cough in children has been studied and it turns out that 25% of children who start coughing continue coughing at 2 weeks and only 10% continue doing so at 3 weeks[2]. So, the majority of Patients with cough secondary to upper respiratory tract infection will not require any investigation. Since cough is a very common symptom, that 10% implies a large number of children with an ongoing process, which can be considered chronic and which should be investigated and treated. Cough should ideally be diagnosed and treated as soon as it appears, even more so if it has been going on for 3 weeks or more.

If it is true that there are "banal coughs", the cough usually represents an abnormality. Some authors point out that it is normal for a child to cough up to 30 times a day and that experience is required to determine when a child's cough exceeds normality[3,4]. I do not believe that experience is required to say which cough is abnormal, it is enough for the parents to consider it abnormal enough to consult, for the doctor to make efforts to reduce or suppress it, acting on its cause.

Recurrent Cough

Cough episodes are considered recurrent when they are more than 2 in a year and are not accompanied by rhinopharyngitis and last more than 7-14 days apart from cough episodes associated with colds. If remission periods are short it may be difficult to distinguish from chronic or persistent cough in which remissions are only partial and not completely free of cough.

Isolated Nonspecific Cough

Cough is divided into specific and isolated nonspecific, the first has elements to connect it with a specific cause or disease. Nonspecific is considered common in otherwise healthy children, in which there is probably a specific but so far unidentified cause and therefore a precise diagnosis is not available.

A non-specific cough that is not accompanied by any indicator of underlying disease is mentioned as common when in reality this is very rare, and most of the time, this type of cough shows a trait, a characteristic, no matter how subtle, which may be related to some cause or causes that make it more specific to a certain cough production mechanism.

Treatment with inhaled steroids is suggested for all types of cough (or non-specific cough) to see a response in a few weeks. Through treatment based on a bronchodilator, the response can be observed practically immediately.

The test can give noticeable but only partial results, in case of:

- A very intense bronchospasm causing cough
- Severe airway inflammation
- Presence of concomitant infection, which may not necessarily be bronchial, but also (or only) upper airway.

If you have confirmed using a bronchodilator (with the decrease or disappearance of cough) that a bronchospasm (sometimes subclinical) is the cause of the cough, then you should start an inhaled steroid.

Precipiting Factors

Determine what Triggers the Cough

Sometimes it is different, which disease generated the cough initially, and what factors trigger the coughing spells some time later. Sometimes these are very different events. Thus, rhinopharyngitis can trigger asthmatic coughing in an asthmatic. Once the cough has already occurred, the attacks can be triggered by running or by cold air, which would hardly trigger the cough in the same asthmatic child if there had not been rhinopharyngitis.

In fact, many times rhinopharyngitis is no longer symptomatic (it may subside in no more than 7 a10 days) and the cough continues due to bronchial hyperreactivity as a sequel to rhinopharyngitis. Some factors can help determine the cause of cough, that is, they can be almost exclusive to certain causes, other factors can cause different types of cough and help little in their diagnostic differentiation. Finally, there are factors that cause all types of cough and finding them does not help us elucidate its cause.

Factors That Suggest one or 2 Causes:

Cold air and exercise	Bronchospasm
During the meal	Swallowing disorder
Cold (acute cough)	Post nasal drip
Sequence of a cold	Rhinosinusitis and/or bronchospasm
At bedtime (or at night)	Post nasal drip
When getting up	Post nasal drip or Bronchiectasis (with abundant expectoration)

Some factors reduce cough partially or completely. In the case of cough due to posterior nasal discharge, typically at night, moving from the supine position to the sitting position can reduce the cough somewhat (sometimes enough to be able to fall asleep). If the cough is due to bronchospasm, there is usually no better antitussive than the effect of a bronchodilator.

Chronic Cough in Children

Most coughs in children are related to temporary infections. An observation period of 3 to 8 weeks is recommended to see if they require further investigation, that is, a comprehensive review. Many children with chronic cough have recurrent viral bronchitis or post-viral syndromes and are otherwise healthy.

Most children with a cough due to a simple upper respiratory tract infection will not need any investigation. Which does not include the very large 10% in whom the cough persists for more than 10 days. Indeed, cough that lasts more than 10 days should alert the clinician that a complication has arisen and it is possible that the virus that initially caused the cough is no longer the cause.

One study almost completely excludes the existence of the 3 important causes of cough in children (bronchospasm, postnasal drip, and gastroesophageal reflux) with a normal chest x-ray. The algorithms used in adults are not useful for children. The 3 common problems that cause cough in adults, they explained only 10% of cough in children. And then the now famous disease

exclusive to children, bacterial bronchitis, occurs. prolonged, which would explain around the 30% of the causes of chronic cough (defined as greater than 8 weeks), based on a study in which bronchoscopy was performed as part of the protocol and in which, at this same percentage, bacterial growth was detected in the samples obtained[5-7].

In this regard, possibly many of the children studied had infectious bronchitis as demonstrated by bronchoscopy; however, given the long period of more than 8 weeks with cough, there is the possibility of having started an upper respiratory tract infection which, through the mechanism of posterior nasal drip eventually developed extension of the infection to lower levels, which could explain not only the positivity of the cultures in these samples but also the chronicity of the cough.

Possibly the diagnosis of infectious bronchitis (which cannot be called chronic and that is why they call it "prolonged") is a The most frequent diagnosis is when the cough has been present for more than 8 weeks, which would not rule out rhinosinusitis[7] as an underlying or accompanying disease, or even more so, a triggering disease for said bronchitis.

The cough described as "throat clearing" in these guidelines suggests allergic inflammation versus postnasal drip from any cause, even though allergic rhinitis is not fully accepted as a cause of cough. Another type of cough mechanism is suggested as more probable in the case of allergic rhinitis, which is the extension of nasal inflammation to the trachea and bronchi[8].

Regarding that, a defined period of time should be established that should be no longer than 8 – 12 weeks, after which the course of anti-asthma medication with inhaled steroid should be suspended. The logical alternative is the use of beta-2-agonists (instead of inhaled steroid) and observe response during the first hours or days. With the inhaled steroid, the expected response, in the case of cough due to bronchospasm, is more gradual and therefore less noticeable.

If we observe a cough for a period of no more than 7 days (and not 8 a12 weeks) under treatment with a bronchodilator, and the cough does not disappear or at least decreases noticeably, it is reasonable that the suspected diagnosis may be erroneous or there is another added cause of cough, which has not been considered.

Guidelines for Evaluating Chronic Cough in Pediatrics American College of Chest Physicians (ACCP) Guidelines Based on Evidence from Clinical Practice[9]

Summary

There are international guidelines specifically for children regarding common respiratory diseases such as community-acquired pneumonia and asthma, differentiating them from those of adults. Therefore, there must be guidelines for the evaluation and management of cough, exclusively pediatric.

There is a relative lack of pediatric research compared to adult research, so child health clinicians are alert to the limitations and potential adversity of extrapolating data from adults to children. Data are lacking regarding the specificity and sensitivity of individual symptoms when evaluating cough in children (and adults as well). There is also little data about the validity of other characteristics of the cough and the clinical examination.

Unlike data in adults, the relationship between cough and upper airway disorders, asthma and gastroesophageal reflux are less convincing in children[10-12]. In general, the management of specific cough should be based on etiology, but the management of specific cough in children involves the entire spectrum of pediatric pulmonology which explains the lack of data in pediatrics, readers are referred to medical guidelines of adults, but extrapolation must be accepted with caution.

The physiology of the respiratory system in children is similar to that of adults in many ways, however, there are also differences, especially between young children and adults, including differences in maturation of the respiratory system: Airways, respiratory muscles, rib cage structure, sleep-related characteristics, respiratory reflexes and control[13-14], as well as protective aspiration reflexes.

Children have between 5 and 8 respiratory infections a year but a more recent study indicates that there could be between 3.8 to 5 annual events[7,15].

Pediatric cough can be classified in several ways:
- Etiology
- Temporality
- Characteristic (dry or wet)
- Specific or nonspecific

A systematic review showed that cough related to upper respiratory tract infection in children resolved within one and 3 weeks and that 10% continued to cough afterwards[2].

Cough should be recognized in 3 themes:
- Normal or "expected".
- Non-specific or isolated (Nocturnal cough whose parental reports are not reproducible)
- Cough subject to a period of time where the placebo effect stands out.

Gastroesophageal Reflux Disease

Reflux can be the reason for a persistent cough[16-17] and cough can cause reflux episodes in adults[18-19]. As cough is very common in children and respiratory symptoms can exacerbate reflux, it is difficult to differentiate cause from effect[20].

Considerations

With respect to cough, there are differences but also clinical and physiological similarities in children and adults and thus, some definitions in adults (e.g., chronic bronchitis and chronic obstructive pulmonary disease) are not applicable to children, and other entities in children (e.g., dysplasia). bronchopulmonary and viral bronchiolitis) are not usually diagnosed entities in adults. Others can be shared even when there is a clear

predominance of some (example: Foreign body in children) over others (example: cough due to angiotensin-converting enzyme inhibitors in adults).

Excluding a certain number of diseases; Children and adults share a wide variety of disorders due to which they cough, especially the most common disorders, which in both are due to transient infections of the upper airways with posterior nasal drip.

3.5 to 8 upper airway episodes are taken as normal in children when other studies indicate up to 11 episodes per year in infants, 8 episodes per year in preschoolers and 4 episodes in schoolchildren[2].
These guidelines are also focused on non-specific cough, that is, dry cough in the absence of other symptoms that facilitate the search for its origin, and this is the least common since most of the time there is combined data that facilitates the search for its origin.

Clinical History, Examination and Investigations

There is generally a lack of data on the specificity and sensitivity of individual symptoms when evaluating cough in children, and there is little data validating other characteristics of cough and physical examination. This is confusing. There is a series of clinical data about cough itself that guides the clinician in a relatively easy way about the anatomical and physiopathogenic origin of cough.

Etiological associations

Analyzing the concept: "Unlike the data in adults, the relationship between cough and upper respiratory tract diseases, asthma and gastroesophageal reflux, is less convincing in children." It is possible that the lack of conviction is due to the research strategy used: The studies reviewed related key words to cough or chronic cough in children (Ex: Chronic cough + Beta-2-agonists) and what agonists) and what turned out was that, indeed, the use of beta-2-agonists was not useful for treating all types of cough.

If stratified, in the group of children with cough due to asthma, the beta-2-agonist is highly effective.

"In general, the management of specific cough should be based on its etiology, so the management of specific cough in children covers the entire spectrum of pediatric pulmonology."

In relation to the previous paragraph, we start from a principle accepted as true to land on a principle that leaves confusion, which arises as follows:
First, we start from an undoubted concept:
“Cough, the most common symptom in pediatric respiratory diseases, can be caused by almost all pediatric pulmonary diseases.” However, if we stratify into, for example, frequent causes of subacute cough (more than 3 weeks) in children, we will not begin our etiological search with a bronchial mucosa biopsy to rule out or confirm ciliary dyskinesis syndrome, (a rare disease that appears in all textbooks within the great spectrum of diseases of pediatric pulmonology), but we will begin our investigation by asking, for example, if the cough is more when running (suggestive of bronchospasm), or if it has been accompanied by rhinorrhea, the production of which very frequently produces cough due to posterior nasal discharge.
“Viruses are associated with common colds in adults, and in children they can cause serious respiratory diseases such as bronchiolitis and croup in previously healthy people.” This is undoubtedly true, however, in these diseases the cough is accompanied by certain characteristics that guide the diagnoses, wheezing and increased of respiratory effort in the case of bronchiolitis, and the cough is seal-like and can accompany stridor and/or dyspnea in the case of laryngotracheobronchitis (croup).

Also for this reason, it is important that expectant behavior should not be adopted with any type of cough, especially in children. On the other hand, in adults a cold can cause bronchial hyperreactivity and cause respiratory difficulty. That is, in both cases it must be diagnosed and treated.

Therefore, these guidelines point out that cough in children is very nonspecific and there is great difficulty in treating it, that most coughs are self-limiting and that the placebo effect plays an important role. That the vast majority of coughs with a time period of 3 to 8 weeks will disappear.

What this book is about is exactly the opposite, that different diseases cause different coughs either because of the cough itself or the clinical characteristics that accompany or trigger it. That we cannot differentiate cough only as dry or wet, only because it presents with characteristics that we have not been able to evaluate and currently remain undefined in terms of both their sensitivity and specificity.

Cough in specific populations (pediatric patients, elderly patients and patients with underlying diseases) Guidelines for the management of cough from the Committee for Japaneses Respiratory Society[22]

Summary

Most coughs in children are caused by upper respiratory tract infections with nasal congestion and throat clearing, including the common cold. However, some children have sinusitis or lower respiratory tract infections.

Although rarer in adults, children can have congenital malformations and foreign body aspiration. Characteristics of cough in pediatric patients and considerations in its evaluation:

1.- The causes vary with age (typical disorders for each age)
2.- Coughs due to outbreaks of infection are common
3.- Some diseases with rapid worsening require urgent diagnosis and treatment.

Typical Disorders in Each Age Group

Cough is evaluated according to age groups and it is mentioned that some causes of cough are more or less frequent according to the different ages, even so, some conditions that cause cough are common to all pediatric ages

Thus, in newborns and young infants, congenital anomalies and viral respiratory infections should be considered more than at other ages.

Lower respiratory tract infections (acute nasopharyngitis, acute pharyngitis and common cold), secondary bacterial infection including otitis media and rhinosinusitis are common. Postnasal drip is characteristic of many young children; it itself causes coughing, persistent wheezing and other adventitious sounds (wet rales), so care should be taken not to misdiagnose bronchitis or asthma.

In many cases, suctioning nasal secretions dramatically improves cough due to postnasal drip. When many children vomit, they stop coughing (as if the vomit "cleansed" the hypopharynx of the secretion produced by the cough).
In 1 a 6-year-old children, rhinosinusitis can easily occur.

A good number of factors predispose young children to have respiratory infections, to be more persistent and to suffer secondarily rhinosinusitis. These factors include, among others, the following:

- narrow airways
- Immune immaturity
- Immaturity of mucociliary function
- Difficulty blowing your nose
- Inability to expectorate
- Phase of rapid development of lymphatic tissue areas of tonsils palatine and adenoids.

Cough can be associated with an asthma attack or as a complication of allergic rhinitis or rhinosinusitis.

Asthmatic bronchitis is a diagnosis that is frequently made in infants and young children with cough and wheezing. The clinical presentation ranges from an acute upper respiratory infection with a runny nose following an asthma attack. Care is required in making a
accurate diagnosis. In children with recurrent episodes, a specialist should be consulted.

In schoolchildren and adolescents, psychogenic cough is added to the previous causes of cough. Characteristic coughs such as croup and whooping cough and a history of allergies suggestive of an atopic disorder are described. he importance of the health status of other family members and the history of atopic disorders is highlighted.

Finally, a table is made with a treatment for each age of the child who coughs, according to the highest frequency of causes:

Cause	**Specific Treatment**
All age groups	
Common cold	**Non-specific (symptomatic treatment)**
Bronchitis/Pneumonia	**Antibiotics as needed**
Newborn/Infants	
Aspiration	**Food instructions, treat GER,** **Consider hospitalization**
Bronchiolitis	**Supplemental oxygen** **Consider hospitalization**
Chlamydia pneumonia	**Macrolide antibiotic** **Consider hospitalization**
Pertussis	**Antibiotics** **Consider hospitalization**
Congenital (e.g. tracheal fistula) **esophageal)**	**Surgery**

Small children	
Rhinosinusitis	**Antibiotics, reference to ENT**
Bronchial asthma	**Antiasthmatic medications**
Croup (Laryngotracheobronchitis)	**Inhaled epinephrine, steroids** **Consider hospitalization**
Acute epiglottitis	**Hospitalization,** **emergencies/resuscitation**
Foreign body in the airway	**Foreign body removal**
Schoolchildren and adults	
Asthma	**Antiasthmatic medications**
Rhinosinusitis	**Antibiotics. Refer to ENT**
Allergic rhinitis	**Anti-allergy medications**
Psychogenic Cough	**Psychosomatic approach**
Tuberculosis	**Anti-tuberculosis medications**
Bronchiectasis	**Antibiotics**

GER: "This guides are the first to provide a stratification of cough causes according to pediatric age groups, to types of cough, to modes of presentation and causes. Furthermor, they offer a treatment suggestion according the last. Undoubtedly a great contribution".

References

1. Shields MD, Bush A, Everard ML, McKenzie S,Primhak R, on behalf of the British Thoracic Society Cough Guideline Group Recommendations for the assessment and management of cough in children. Thorax 2008;63(Suppl. III):III1-III15.
2. Hay A.D. Wilson. The natural history of acute cough in children aged 0 to 4 years in primary care: a systematic review. British J Gen Practice 2002;52: 401-409
3. Munyard P, Bush A. How much coughing is normal? Arch Dis Child 1996;74:531-534.
4. Shann F. How often do children cough? Lancet 1996;348:699:699-700.
5. Marchant JM, Masters IB, Taylor SM, Cox NC, Seymour GJ, Chang AB. Evaluation and oucome of young children with chronic cough. Chest 2006;129:1132-1141.
6. Chang AB. Cough : are children really different to adults? Cough 2005;1:7.
7. Chang AB, Phelan PD, Sawyer SM et al. Cough sensitivity in children with asthma, recurrent cough and cystic fibrosis. Arch Dis Child 1997;77: 331-4
8. Campanella SG, Asher MI Current controversy: Sinus disease and the lower airways. Pediatr Pulmonol 2001;31:65-72
9. Diagnosis and Management of cough: American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines. Chest 129(1S) January 2006. Chang AB; Guidelines for Evaluating Chronic cough in Pediatrics
10. Tatli MM, San I, Karaoglanoglu M. Paranasal sinus computed tomographic findings of children with chronic cough. Int J Pediatr Otorhinolaringol 2001; 60: 213-217.
11. Chang AB, Phelan PD, Carlin J. Et al. Randomised controlled trial of inhaled salbutamol and beclometahasone in children with recurrent cough. Arch Dis Child 1998; 79: 6-11.
12. Chang AB, Gaffney J,Connor FC,et al. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults. Cochrane Database Syst Rev (Database online). Issue 2; 2005.
13. Polgar G, Weng T. Functional development of the respiratory system from the period of gestation to adulthood. Am Rev Resp Dis 1979: 120:625-695.
14. Thach BT. Maturation and transformation of reflexes that protect the laryngeal airway from liquid aspiration from

fetal to adult life. Am J Med 2001;111 (suppl):69S-77S.
15. Monto AS. Studies of the community and family: acute respiratory illness and infection. Epidemiol Rev 1994;16:351-373
16. Cucchiara S, Santamaria F, Minella R et al. Simultaneous prolonged recordings of proximal and distal intraesophageal pH in children with gastroesophageal reflux disease and respiratory symptoms. Am J Gastroenterol 1995; 90:1791-1796.
17. Orenstein SR,Orenstein DM. Gastroesophageal reflux and respiratory disease in children. J pPediatr 1988;112:847-858.
18. Gastal OL, Castell JA,Castell DO Frequency and site of gastroesophageal reflux in patients with chest symptoms: studies using proximal and distal pH monitorin. Chest 1994; 106:1793-1796.
19. Johnston BT, Gideon RM, Castell DO. Excluding gastroesophageal disease as the cause of chronic cough (Editorial). J Clin Gastroenterol 1996;22:168-169.
20. Gilger MA. Pediatric otolaryngologic manifestation of gastroesophageal reflux disease. Curr Gastroenterol Rep 2003;5:247-252.
21. Grüber C, Keil T, Kulig M, RollS, Whan U, Whan V,; MAS-90 Study Group. History of respiratory infections in the first 12 years among children from a birth cohort. Pediatr Allergy Immunol 2008 19(6):505-512.
22. Cough in specific populations (paediatric, elderly patients and patients with underlying disease) The committee for the Japanese Respiratory Society guidelines for management of cough. Respirology (2006) 11 (Suppl. 4): S175-S186.

Acknowledgment

To my parents from whom I obtained the encouragement to carry out my professional studies and encouragement for the development of the project and whom I had the honor of accompanying very closely during their last days. I would like to thank my wife and daughters: Diliana, Ana Paula and Carolina for the harmony and tranquility they have brought to my life, necessary to be able to focus my attention on the reflection about cough, captured in this book.

I thank my nephews, Al Nacson+ and Angelina de la Hoz for their advice and push to restart the project that I had put aside. To Dr. Claudia Garrido, Master of Science, for her guidance with ideas and in the development of the research protocol for the development of new cough therapies.

To Dr. Carlos Aboitiz, Ms. Anaissa Galicia, Lizbeth Barajas, Lic. Magaly Hernández and Edda Denver for their technical support Finally, to all my colleagues at the National Institute of Respiratory Diseases, friends and rest of family, from whom I have received encouragement every day.

By publishing your work with us, you are guaranteed a high level of service and impeccable standards. You can also be assured that stringent practices are followed in terms of peer review and digital infrastructure.

Choose the right home for your research across our journals and find the resources to help you submit, publish and promote your work:

Journals List

Clinical

1. Journal of Chronic Diseases and Illness
2. Virology: Research & Reviews
3. Journal of Clinical, Medical & Pharma, and Diagnostic Research
4. General Surgery and Clinical Medicine
5. BioMedical & Pharma Science and Clinical Research
6. Video Journal of Research and Education
7. Archives of Clinical and Medical & Pharma Microbiology
8. Journal of Neuro and Spine
9. Journal of ENT Surgery Research
10. Dermatology Journal of Cosmetic and Laser Therapy
11. Journal of Pathology and Laboratory Medicine
12. Journal of Surgery Care
13. International Journal of Clinical and Medical & Pharma Education Research
14. Journal of Ophthalmology & Clinical Research
15. International Journal of Alzheimer's Disease Research
16. Stem Cell Research International
17. Journal of Oral & Dental Health
18. Journal of Gastroenterology & Digestive Systems
19. Journal of Clinical Review & Case Reports
20. Journal of Clinical & Experimental Immunology
21. International Journal of Women's Health Care
22. International Journal of Orthopaedics Research
23. Advancements in Journal of Urology and Nephrology
24. International Journal of Cancer Research & Therapy
25. Advances in Neurology and Neuroscience
26. Advances in Hematology and Oncology Research
27. New Advances in Brain & Critical Care
28. Journal of Clinical Rheumatology Research
29. International Journal of Endocrinology Research and Reviews
30. Autism Spectrum Disorders: Open Access