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COUGH: REVIEW OF A SYMPTOM WITH SEVERAL DIAGNOSTIC POSSIBILITIES

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Nathalia Caregnato[1], Priscila Farias da Silveira[2], Felipe Praun Simão[3] and Phelipe dos Santos Souza[4]

ABSTRACT

INTRODUCTION: Cough is a habitual reflex of the respiratory tract to an aggression, representing one of the main defense mechanisms of the respiratory tract. However, although important for the maintenance of homeostasis, the cough mechanism becomes pathological when dysregulated. OBJECTIVE: The present study aimed to clarify a path between the epidemiological issues of cough, the pathophysiological mechanisms, semiology, possible etiologies, clinical behavior and therapeutic approach to cough. METHODS: this is a narrative review of the literature, carried out in the first half of 2021, focusing on studies related to cough, its pathophysiological and etiological mechanisms, in addition to the clinical and therapeutic approach, through searches in the PubMed, SciELO, Medline/LILACS/Bireme databases, using the descriptors: cough, acute cough, subacute cough and chronic cough. RESULTS AND DISCUSSION: Cough is a frequent symptom worldwide, and is considered the most common reason for seeking medical care. The mechanism of cough is a result of the integration of the components of the neurophysiological pathways, respiratory muscles, and pulmonary mechanics and fluid mechanics. For the initial approach to cough, it is essential to extract a detailed clinical history and thorough physical examination, since the most common causes of cough are easily identifiable with a good anamnesis, being classified according to the duration of the complaint as acute, subacute and chronic. The therapeutic approach to cough, as a symptom, is vast, sometimes imprecise, and changes according to the time of onset and etiology of the condition. FINAL CONSIDERATIONS: Acute and chronic cough can aggravate and trigger different complications, but among all the possible complications, the change in lifestyle and the significant impact on the quality of life of the individual affected by cough is evident.

Keywords: Cough. Acute cough. Subacute cough. Chronic Cough.

[1] Academic
University Center of Brusque
E-mail: nathicaregnato@gmail.com/ 3789547091832093
[2] Academic
University Center of Brusque
E-mail: priifsilveira@gmail.com/5965428755573090
[3] Academic
University of Vale do Itajaí
E-mail: felipepraunsimao@gmail.com/3610200466110752
[4] Allergist and Immunologist
University of Vale do Itajaí
Email: phelipe.alergia@gmail.com/7466031030776321

INTRODUCTION

A topic forgotten by many but with a fundamental importance, cough is a physiological process that plays a defensive role and is considered a warning symptom for numerous diseases. Currently, it is considered the most common reason for seeking medical care (PATRICK, 1995; SATIA et al., 2016. PORTO, 2017).

Cough is a habitual reflex of the respiratory tract to a chemical, physical, biological or immunological aggression, representing one of the main defense mechanisms of the respiratory tract, helping the ciliary beat to remove particles. On the other hand, it is an important disseminator of droplets to the environment, causing the transmission of numerous diseases, in addition to being considered a potential reverser or trigger of cardiac arrhythmias. In the United States of America (USA), chronic cough represents up to 38% of the cases referred to the pulmonologist, and, although in Brazil there is not all precise data on the prevalence of this symptom, clinical practice reveals that cough is quite prevalent, leading patients to seek various medical services and undergo numerous tests for cough solution (LIN; AUGUSTO, 2010).

For the initial approach to cough, it is essential to extract a detailed clinical history and thorough physical examination, since the most common causes of cough are easily identifiable with a good anamnesis. The type and pattern of cough should be characterized in order to try to limit the diagnostic approach, and it is important to ask about the presence of sputum and its characteristics (color, volume, odor, appearance), relief and aggravating factors, time of recurrence, outlining the occurrence of concomitant symptoms, such as dyspnea, wheezing, fever, dyspepsia, gastroesophageal reflux, rhinorrhea, nasal congestion, and the presence of comorbidities such as systemic arterial hypertension, atopy and medications in use. During the anamnesis, it is essential to establish the duration of the complaint, between up to three weeks (acute), more than three and less than eight weeks (subacute) and more than eight weeks (chronic), since with this characterization it is possible to try to establish a diagnostic investigation for the main causes associated with the time of evolution of the cough and also a correlation of prognosis and complications, since chronic cough can trigger insomnia, syncope, urinary incontinence, subconjunctival hemorrhage, gastroesophageal reflux, inguinal hernia, pneumothorax, rib fracture and, above all, lifestyle changes (LIN; AUGUSTO, 2010).

This narrative review will clarify a path between the epidemiological issues of cough, the pathophysiological mechanisms involved, semiology and possible etiologies, and behavior in relation to time and the respective therapeutic approach.

METHODOLOGY

The present study is a narrative review of the literature, carried out in the first half of 2021, focusing on studies related to cough, its pathophysiological and etiological mechanisms, in addition to the clinical and therapeutic approach, through searches in the PubMed, SciELO, Medline/LILACS/ Bireme databases, using the descriptors: cough, acute cough, subacute cough and chronic cough.

Articles in Portuguese and English were included, which adequately addressed the proposed theme, without restriction on the time of publication, but which were made available in full, considering among the types of study reviews, original articles, essays, guidelines and also government publications on this theme. The exclusion criteria were: duplicate articles, available in the form of abstracts, and those that did not directly address the proposal studied.

After the selection criteria, thirty-five documents remained that were submitted to thorough reading to collect information on the topic under study. The results were presented in a descriptive way, divided into thematic categories contemplating cough, acute cough and chronic cough.

RESULTS AND DISCUSSION

COUGH

Cough is a physiological process characterized by a sudden and explosive force of air, constituting a defense mechanism of the airways, through the removal, for example, of infectious microorganisms and foreign bodies. (PATRICK, 1995; DALAL; GERACI, 2011; WEINBERGER; HURVITZ, 2020). However, although important for the maintenance of homeostasis, the cough mechanism becomes pathological when dysregulated (PAVORD; CHUNG, 2008; SIAS; AMARAL, 2001; DALAL; GERACI, 2011). Thus, in addition to being very common, cough is a warning symptom for numerous diseases, and is often capable of making the patient seek medical help (BALBANI, 2012; KANG et. al, 2020; PAVORD; CHUNG, 2008).

In this sense, coughing as a mechanical process can be divided into three stages: the inspiratory phase - characterized by a rapid and deep inspiration, the opening of the glottis and the fixation of the lower ribs; the compressive phase - defined by an expiratory effort against the closed glottis and by the contraction of the muscles of the larynx, thorax, diaphragm, abdomen and pelvic floor; and the expiratory phase - where there is a sudden opening of the glottis due to the high intrathoracic pressure, which generates explosive release of air and, consequently, the characteristic cough sound (SIAS; AMARAL, 2001; PAVORD; CHUNG, 2008).

EPIDEMIOLOGY

A frequent symptom worldwide, cough is considered the most common reason for seeking medical care (SATIA et. al, 2016; NUNES et. al, 2010). Both in outpatient consultations, in the number of 2.7 million per year, and in emergency departments, in more than 4 million annual visits, the different types of cough are responsible for a significant part of the work of a health professional (KINKADE; LONG, 2016).

Sources of medical research on outpatient care reveal an even more worrying scenario, in which cough is responsible for 27 million, or about 3.1% of outpatient medical practice visits in the USA, and that the surprising amount of 3.6 billion US dollars are collected annually from the sale of cough medicines, demonstrating the dimension of this problem (ALTMAN; IRWIN 2011; NUNES et. al, 2010; CASH et. al, 2015).

To make matters worse, the lack of adequate antitussives ends up making cough one of the main unmet clinical needs, as it ends up greatly impairing the patient's quality of life. On the other hand, an example of a tool used to estimate the well-being of patients with cough is the Cough Quality of Life Questionnaire, which uses 28 questions about the symptom and its effects, taking into account both physical and psychosocial complaints (SATIA et al., 2016; ALTMAN; IRWIN 2011; FRENCH et al, 2002), seeking to understand the impacts of cough on the individual, which can help in a better therapeutic conduction.

PATHOPHYSIOLOGY

The cough mechanism, according to Sias and Amaral (2001), is a result of the harmonious integration of three components: the neurophysiological pathways, the

respiratory muscles, and the pulmonary mechanics and fluid mechanics. Thus, although it can be controlled voluntarily, cough is, most of the time, a consequence of a reflex arc that has afferent, central and efferent components.

Thus, the onset of the cough reflex occurs when some stimulus activates the numerous receptor sites, activated either by chemical or mechanical stimuli, distributed throughout the respiratory epithelium — nasopharynx, trachea, carina, branches of the large airways and distal portion of the small airways — and beyond, being present in structures such as the diaphragm, the pericardium, the peritoneum and the esophagus (RODRIGUES; GALVÃO, 2017; BALBANI, 2012). Regarding the nature of the stimulus, which, as mentioned above, can be chemical or mechanical, there will be two subtypes of afferent nerve fibers, mainly vagal: C fibers, where chemoreceptors are located, and Aδ (delta A) fibers, characterized by the presence of mechanoreceptors (SATIA et al., 2016).

In this sense, C fibers are non-myelinated nerve fibers sensitive to acidity, heat, and especially capsaicin and capsaicin-like compounds. Chemoreceptors are found in them, such as the vanilloid-type transient potential receptor 1 (TRPV1) and the ankyrin-type transient potential receptor (TRPA1), both nociceptive ion channels (SATIA et al., 2016; RODRIGUES; GALVÃO, 2017). While TRPV1 can be activated by capsaicin and other vanilloid compounds, arachidonic acid metabolites, bradykinin and other inflammatory mediators, hydrogen ions (low pH) and high temperatures (above 43°C), TRPA1 is related to lower temperatures and numerous other harmful substances, such as cigarette smoke (SATIA et. al 2016; RODRIGUES; GALVÃO, 2017; PAVORD; CHUNG, 2008; BALBANI, 2012).

On the other hand, myelinated and subepithelial Aδ fibers, and their RARs and SARs, respectively fast-adapting receptors and slow-adapting stretch receptors, are located in regions such as the stomach, pericardium, pleura, proximal airways, eardrums, and the external acoustic meatus. Because they do not have the ion channels TPRV1 and TRPA1, they are considered insensitive to stimulation by capsaicin and inflammatory mediators, being activated by touch, by any eventual distension, by changes in osmolarity and pH, and by other stimuli such as mucus secretion, bronchospasm, bronchoconstriction, pulmonary congestion, atelectasis, and reduction in lung volume (SATIA et al., 2016; RODRIGUES; GALVÃO, 2017; BALBANI, 2012; PAVORD; CHUNG, 2008).

It is precisely the activation of these two types of receptors that leads the afferents to travel their path through the trigeminal nerve (V cranial nerve), glossopharyngeal nerve (VIII cranial nerve) and vagus nerve (X cranial nerve), from the periphery, through the spinal cord, until they reach the brainstem, in a place close to the respiratory center, more specifically in the nuclei of the solitary tract (NTS) and paratrigeminal tract of the brainstem, where they synapse (SIAS; AMARAL, 2001; SATIA et. al 2016; RODRIGUES; GALVÃO, 2017; PAVORD; CHUNG, 2008). Then, the activation of a large number of complex neural networks occurs with the propagation of the signal to cortical and subcortical areas. Thus, the most important structure to participate in is the cough center, responsible for regulating the cough response, located in the upper portion of the brainstem and controlled by cortical centers (SATIA et. al 2016; RODRIGUES; GALVÃO, 2017). Some of the other neural projections that depart from the nuclei go to the reticular formation, nucleus ambiguus, periaqueductal gray matter, and dorsal raphe nucleus (BALBANI, 2012).

Finally, after all this process, the brainstem will emit efferents via the vagus nerve, phrenic nerve and spinal motor nerves (C3-S2) to the muscles participating in the cough mechanism, which will generate the 3 phases of cough mentioned above (diaphragm, intercostal muscles, laryngeal muscles, abdominal wall muscles and pelvic floor muscles) (RODRIGUES; GALVÃO, 2017; SATIA et. al 2016; BALBANI, 2012; SIAS; AMARAL, 2001).

COUGH SEMIOLOGY AND POSSIBLE ETIOLOGIES

In general, cough, as a sign, has several important semiological aspects, which, added to possible complementary tests, can lead to the diagnosis (SIAS, 2001).

In the anamnesis, the complaints associated with cough are varied, something consistent with the fact that cough has numerous diagnostic possibilities. There may be dyspnea, chest pain, tiredness, fever, chills, among many others. One should be aware of numerous characteristics of cough, such as the onset, duration, type or character, frequency, period in which it predominates, tone and timbre, relationship with decubitus, intensity and the presence or absence of other associated signs and symptoms. Regarding duration, as will be discussed later, cough can be chronic, acute or subacute. Regarding the character of the cough, the presence or absence of expectoration stands out, which characterizes it as productive, dry or wet. In the case of a productive cough,

it is important to evaluate the volume, color, odor, transparency, and consistency of the sputum, since these characteristics depend on its composition. Thus, sputum can be serous, mucoid, purulent and hemoptoic (SIAS, 2001; NUNES et. al, 2010; PORTO, 2017; YOSHIKAWA; CASTRO, 2015).

On the other hand, as for frequency, coughing can be rare or frequent. Regarding the period in which it predominates, it can be classified as episodic, morning, nocturnal, and whether or not it is associated with meals. Regarding tonality and timbre, cough can be bitonal, hoarse, shrill (also known as metallic) or aphonic. As for intensity, the cough is classified as weak, medium or strong. Finally, the topics related to the relationship with the decubitus position and the presence of other associated signs and symptoms are extremely important in the search for a diagnosis (SIAS, 2001; NUNES et. al, 2010; PORTO, 2017; YOSHIKAWA; CASTRO, 2015).

Likewise, the patient's use of antihistamines, bronchodilators, antimicrobials, and corticosteroids that were able to relieve the symptom should be taken into account. It is also essential to search, in family history and in previous morbid history, for diseases such as tuberculosis, pneumonia and pertussis, recurrent acute respiratory infections, immunodeficiencies, environmental exposure to allergens such as house dust and smoke, and smoking habits (SIAS, 2001; NUNES et. al, 2010).

In line with the above, the physical examination is now followed. The general physical examination should begin and pay attention to details such as fever and chills, weight loss, clubbing, capillary perfusion, evaluation of mucous membranes, evaluation of secretions, edema and vital signs. It is very important to perform the respiratory physical examination, looking for changes in the shape of the chest, respiratory rhythm and respiratory rate. On auscultation, the presence of wheezing and stridors is highlighted. Finally, it is interesting to perform the cardiac physical examination, looking for signs of jugular turgidity on inspection and, on palpation, for an increased ictus cordis (PORTO, 2017).

Finally, the complementary exams will depend a lot on the situation. However, some examples are the use of imaging tests such as chest and paranasal sinus X-rays and the request for laboratory tests such as blood count, total immunoglobulin measurement and tuberculin skin test (PPD) (SIAS, 2001).

Also, semiologically, the main etiological manifestations of cough are divided into infectious and non-infectious causes. In the first group, several etiological agents stand

out. One of them is the viruses (influenza, coronavirus, adenovirus, among others), which are responsible for the flu and the common cold. The cough characteristic of a respiratory virus is dry and frequent. Another, bacteria (Mycobacterium tuberculosis, Streptococcus pneumoniae, Mycoplasma pneumoniae, Bordetella pertussis, among others), which are associated with tuberculosis, in which cough is commonly associated with hemoptoic expectoration, pneumonia, where a dry cough with a stabbing pain in the hemithorax stands out, and pertussis, the latter characterized by a quintose cough (BALBANI, 2012; PORTO, 2017).

Parasites (Ascaris lumbricoides, Schistosoma mansoni, among others), related to parasitic pulmonary eosinophilia and chronic pulmonary schistosomiasis, protozoa (Leishmania chagasi), responsible for visceral leishmaniasis, and fungi (Aspergillus spp, Histoplasma capsulatum, Paracoccidioides brasiliensis), which cause, respectively, aspergillosis, histoplasmosis, and paracoccidioidomycosis, are also present (BALBANI, 2012).

As for the second group, that of non-infectious causes, some more factors are exposed. One of them is the use of medications, such as captopril, an Angiotensin-Converting Enzyme (ACE) inhibitor, in which coughing is characterized as dry and frequent. There is also a relationship with cardiovascular diseases, such as congestive heart failure, which manifests itself as a nocturnal cough accompanied by orthopnea. On auscultation, it is possible to perceive wheezing. In addition, there is gastroesophageal reflux, which has as its main characteristic that it occurs in access when the patient lies down, in addition to mainly nocturnal. In addition, neoplasms are associated with cough with hemoptoic expectoration. Asthma, on the other hand, is characterized by a cough accompanied by wheezing; while in tracheal obstruction, cough is associated with stridors. Also, classic in cases of smoking, there is morning cough with scarce expectoration. Finally, the typical cough of laryngitis has a metallic and bitonal timbre and is accompanied by dysphonia. (BALBANI, 2012; PORTO, 2017; YOSHIKAWA; CASTRO, 2015).

SNEAKERS AGUDA

Acute cough is a condition lasting less than 3 weeks often associated with viral infections of the upper and lower respiratory tract. This group of infections includes the common cold, acute tracheobronchitis, acute sinusitis, influenza, rhinitis, laryngitis,

tracheitis, and pharyngitis. In addition, the exacerbation of chronic diseases such as asthma, chronic obstructive pulmonary disease and rhinosinusopathy. Also included are exposure to allergens or irritants and drugs (ACE inhibitors and B-blockers) (II BRAZILIAN GUIDELINES ON THE MANAGEMENT OF CHRONIC COUGH, 2006).

Acute cough is often associated with other acute symptoms of syndromes or infections. In these conditions, in addition to acute cough, the patient may have fever, other airway symptoms and myalgia. An assessment is necessary to exclude the risk of more serious conditions such as neoplasms, tuberculosis, pneumonia, severe asthma attacks or chronic obstructive pulmonary disease, pulmonary embolism, pulmonary edema due to left ventricular failure, interstitial lung disease, and foreign body inhalation (II DIRETRIZES BRASILEIRAS NO GESTÃO DA TORRSE CRÔNICA, 2006; MARSHALL; WHITE; LOVERIDGE, 2020).

The risk group for these severe conditions includes smokers, former smokers, and immunosuppressed patients, thus requiring an in-depth evaluation of these pathologies. In the case of suspected inhalation of a foreign body, a referral to a specialist occurs. If the patient does not have severe symptoms and inhalation of a foreign body, there is a high chance that it is a viral infection, usually self-limiting within 3 weeks with relief from cough and other associated symptoms (MARSHALL; WHITE; LOVERIDGE, 2020).

The main factors for evaluating a patient with acute cough are to investigate exposure to allergic, environmental or occupational factors that have a temporal relationship with the onset or worsening of cough (II BRAZILIAN GUIDELINES ON THE MANAGEMENT OF CHRONIC COUGH, 2006). It is worth remembering that acute cough is the main cause of pediatric consultations, but its prevalence in adults is estimated at 28% among men and 30% among women (LAMAS, 2014; SHIELDS, 2007).

Clinical and therapeutic approach to acute cough

Symptomatic medications are often used in cases of acute cough, in many cases without a medical prescription. In the context of empirical therapy with products and/or herbal medicines, bee honey and Ananas comosus extract products have good results in relieving acute cough and improving children's sleep (PEIXOTO, et.al, 2016). This is due to its antiviral, anti-inflammatory, and antibacterial effect (LAM, et al., 2021). It is

safe for use in children and has a low rate of allergies (BALBANI, 2012), ideally above two years of age.

Chart 1 lists the main drugs used for the treatment of Acute Cough and their respective mechanisms of action:

Drug	**Mechanism of action**
Dextromethorphan	It is a drug whose mechanism of action is to suppress the reception of cough in the central nervous system. (LAM, et al., 2021).
Fendizoato de cloperastina	It acts as a cough sedative and has a peripheral action, causing desensitization of the tracheobronchial vagal afferents. (BALBANI, 2012).
Dropropizine	It is an antitussive with a mechanism of action of bronchial muscle relaxation, which reduces the excitability of tracheobronchial receptors (PAULA, 2016).
Codeine	Codeine is a weak opioid with action on the central nervous system that leads to cough suppression. (KINKADE; LONG, 2016).
Benzonatato	An oral anesthetic that suppresses cough by inhibiting pulmonary stretch receptors by peripheral action (KINKADE; LONG, 2016).
Inalated corticosteroids.	They suppress cough by inhibiting inflammation and hyperreactivity of the airways. (LAM, et al., 2021).
Promethazine	Antihistamine, which carries out its mechanism of action through peripheral histamine receptors and central histamine and dopamine receptors. (LAM, et al., 2021).
Guaifenesina	It is the resin of the Guajacum officinale L. plant, called guaiacol. It has an antitussive effect in cases of URTI, but its mechanism of action is not clarified (BALBANI, 2012)
Vasicin	It is isolated from Adhatoda vasica leaves and has an expectorant action (BALBANI, 2012).
Bromexina Chloridrate	It is a synthetic derivative of Vasiciin. Its active metabolite, ambroxol mucolytic hydrochloride, has anti-rust, anti-inflammatory, surfactant and local anesthetic actions (BALBANI, 2012).

The American College of Chest Physicians does not recommend the use of codeine in the treatment of respiratory tract infections and the European Medicines Agency has published that people under the age of 12 should not use codeine medications. There was also a publication by the Food and Drug Administration (FDA) on the contraindication of the use of codeine in children under 12 years of age, and it also discourages people between 12 and 18 years of age with risk factors for respiratory depression from using it (LAM, et. al, 2021).

With regard to Benzonatate, its symptoms of overdose include restlessness, tremors, seizures, and coma, occurring between 15 and 20 minutes after administration and can lead to death within hours. The FDA has made an announcement about the risk of accidental death in children under the age of 10 (LAM, et al., 2021).

SNEAKERS SUBAGUDA

In 2006, based on the North American Cough Consensus, a new classification for cough lasting 3 to 8 weeks was proposed, which is called subacute cough. According to this guideline, one of the main causes of the newly classified acute cough is post-infectious cough (II BRAZILIAN GUIDELINES ON THE MANAGEMENT OF CHRONIC COUGH, 2006).

Post-infectious cough is a diagnosis of exclusion, with three aspects: cough lasting between 3 and 8 weeks, clinical evaluation without identification of the cause, and history of airway infection in less than 3 weeks. The etiology of post-infectious cough includes B. pertussis, M. pneumoniae and C. pneumoniae, with inflammation and epithelial injury to the respiratory tract, with or without transient hyperresponsiveness. There is no specific treatment for post-infectious cough. Inhaled ipratropium bromide and corticosteroids can be used, in addition to prednisone or prednisolone at 30 to 40 mg per day for five to seven days in more severe cases. The use of antibiotics is done in cases such as mycoplasma tracheobronchitis, due to the high chance of bacterial infection (II BRAZILIAN GUIDELINES ON THE MANAGEMENT OF CHRONIC COUGH, 2006).

In addition to post-infectious cough, subacute cough can occur due to asthma, rhinosinusitis, gastroesophageal reflux disease, eosinophilic bronchitis, and bronchopulmonary diseases. Once the post-infectious etiology is ruled out, the management will be the same as for chronic cough (II BRAZILIAN GUIDELINES ON THE MANAGEMENT OF CHRONIC COUGH, 2006).

CHRONIC COUGH

Chronic cough, a condition that affects 12% of the general population (SATIA, 2016), is defined as a persistent or recurrent disease. However, research reports that chronic cough should persist for a period of 3 weeks - the most accepted concept - but others use it as a duration of more than 8 weeks (RIBEIRO, 2020; NETO, 2011).

Chronic cough is the main physiological mechanism responsible for the secretion of the airways, but repetitive coughs induce some complications such as changes in lifestyle, feelings of exhaustion, insomnia, hoarseness, headache, muscle pain, excessive sweating, urinary disorders and even syncope (JACOMELLI, 2003; MICHAUDET, 2017; RIBEIRO, 2020). Patients usually complain of a strong urge to cough associated with a sensation of irritation in the throat, which is a dry cough (SATIA, 2016).

Hypersensitivity syndrome is a term suggested in consensus that can be used to describe patients with chronic cough (SATIA, 2016). In otorhinolaryngology, chronic cough is a nonspecific symptom, while it can help in the differential diagnosis, in the evaluation of lesion involvement, and even in the prognosis. Because it is present in a variety of diseases, the main one being postnasal drip and laryngitis due to gastroesophageal reflux. In addition, there are 3 groups of causes that represent 95%: Otorhinolaryngology, lung diseases and psychogenics (NETO, 2011).

It is worth noting that chronic smokers or former smokers have a three times higher rate of having chronic cough compared to people who have never smoked. In addition, children exposed to tobacco smoke have a higher risk factor for chronic cough (CHUNG, 2008).

The prevalence of chronic cough ranges from 14% to 23% for nonsmoking adults, ranking fifth in the most common cause of seeking medical care in the world. In children, it is one of the main reasons for a visit to the pediatrician (PATRICK, 1995; JACOMELLI, 2003; CASH, 2015).

In Europe and the USA the prevalence of cough ranges from 9-33%, including young people and children. However, patients with chronic cough represent 10-39% of respiratory outpatient clinics in the USA, and a small part of the population only seeks medical help or advice on symptoms (CHUNG, 2008; BALBANI, 2012).

A cross-sectional, quantitative study, carried out at home. It states that women are more affected by chronic cough than men, thus causing a greater impact on their quality of life (ROSA, 2017).

The most common causes of seeking medical attention for chronic cough are: hoarseness; fear of cancer, acquired immunodeficiency syndrome (AIDS) and tuberculosis. The main causes of chronic cough are composed of a triad that represents

90 to 95% of the times that a patient has chronic cough: Postnasal drip, asthma and gastroesophageal reflux (PATRICK, 1995; JACOMELLI, 2003).

Studies in pediatric populations, with chronic cough as the main symptom, have identified as the main causes: infections (sinusitis, upper respiratory tract infection), airway hypertrophy (asthma) and gastroesophageal reflux disease. In addition, other causes were included, such as: laryngomalacia, allergic rhinitis, and coughing habits. If initial ENT treatment fails, chest X-ray and early pulmonary consultation are recommended (CASH, 2015).

Postnasal drip has been the most frequent cause of chronic cough since the 1980s. The main etiologies related to this are seasonal or perennial allergic rhinitis, vasomotor rhinitis, post-viral rhinitis, rhinitis medicamentosa and sinusitis. The main symptoms are: feeling of "something running down the throat", nasal congestion or rhinorrhea. A minority of patients have no symptoms. On physical examination, some alterations in the nasal mucosa (enanthema, congestion or areas of pallor) and pharynx may be highlighted, with or without secretion. However, these findings are insufficient to determine the disease, and it is therefore necessary to complement it through radiological and endoscopic examination, as well as an evaluation of the response to the therapy instituted. Treatment should be instituted according to the clinical presentation, symptoms and complementary tests (JACOMELLI, 2003).

Asthma represents the second most common cause of chronic cough. The clinical history (wheezing, dyspnea and chest tightness, worsening with the use of beta blockers) in association with the therapeutic response to the β2-agonist, is a determining factor in the diagnosis (JACOMELLI, 2003).

Chronic cough as an isolated symptom occurs in 6.5 to 57% of the cases, and this presentation is also known as "cough variant of asthma". The difference is that, in addition to having the cough alone, the patient does not present signs of bronchoobstruction in the clinical history or physical examination, but presents symptom relief with β2-agonist (JACOMELLI, 2003).

Eosinophilic bronchitis may present with chronic cough, increased eosinophil count, and metachromatic cells in the sputum, similar to what occurs in asthma. However, what allows its differentiation from asthma is the absence of variable airflow obstruction, airway hyperresponsiveness, and mast cell infiltrate in airway smooth muscle (JACOMELLI, 2003).

Gastroesophageal reflux is the third most frequent cause of chronic cough. Its pathophysiological mechanism is not completely understood. However, the patient has no dyspeptic symptoms in 50-75% of cases, already symptoms of hoarseness. Choking, spasms, pain or burning in the pharynx, frequent throat clearing, and globus pharyngeal have been reported. Tests that may be requested to identify gastroesophageal reflux are: Endoscopy of the esophagus, when normal, does not exclude the disease. Ambulatory 24-hour esophageal pH monitoring has high sensitivity and specificity, which can lead to false-negatives. Direct laryngoscopy allows the detection and grading of acute or chronic inflammatory changes. However, it is worth remembering that in patients with chronic cough, even in the face of a positive result of reflux by any of these methods, the symptomatic improvement compared to anti-reflux treatment is what establishes the causal diagnosis (JACOMELLI, 2003).

In addition to the triad of upper airway disorders, there are other diseases that cause chronic cough, which are bronchiectasis, chronic bronchitis, and post-infectious cough (II DIRETRIZES BRASILEIRAS NO MANEJO DA TORROSIS CRÔNICA, 2006).

CLINICAL AND THERAPEUTIC APPROACH

Initially, an appropriate and targeted anamnesis should be taken in order to identify potential triggers such as environmental exposures. Next, you should rule out warning signs (fever, weight loss, hemoptysis, hoarseness, excessive dyspnea or expectoration, smoking history) that suggest the cause of the cough (MICHAUDET, 2017; MALESKER, 2020).

One of the first steps is to know if it is an acute or chronic cough, as it is extremely important for the physician to establish a diagnostic reasoning (JACOMELLI, 2003). One should pay attention to every detail of the patient's description of the cough and explore each detail (character, time, presence or absence of sputum production) (MALESKE, 2020). In the previous and psychosocial history of the anamnesis, there should be a greater focus on COPD, asthma, bronchitis, gastroesophageal reflux, workplace, and smoke exposure (MALESKE, 2020).

On physical examination, when it is normal and there is no severe signaling, computed tomography is not necessary, nor is bronchoscopy. If there is a signal in the physical examination, these tests should be ordered for diagnostic purposes (MALESKE, 2020).

To reach the final diagnosis, the most common causes in adults must first be considered: High airway cough syndrome, gastroesophageal or laryngopharyngeal reflux disease, asthma, and non-asthmatic eosinophilic bronchitis. In children from six to 14 years of age, it is necessary to initially think about asthma, prolonged bacterial bronchitis, and upper airway cough syndrome (MICHAUDET, 2017).

After evaluation and empirical management of these etiologies, less common causes should be considered (MALESKE, 2020). In adults: angiotensin conversion, enzyme inhibitor use, environmental triggers, tobacco use, and chronic pulmonary obstruction disease. In patients with refractory chronic cough - cases of cough that persist to medical treatment (RIBEIRO, 2021) - referral to a pulmonologist or otorhinolaryngologist should be considered (MICHAUDET, 2017).

Currently, there are questionnaires to assess the quality of life of patients with cough: the Cough Quality-of-Life Questionnaire, developed by French et al, and the Leicester Cough Questionnaire (LCQ), developed and validated by Birring et al.

The main objective of these questionnaires is to assess the impact on the health status of patients with chronic cough. The main one for chronic cough is the LCQ, which is a self-explanatory questionnaire and requires less than five minutes to complete, consisting of 19 items and subdivided into three domains (physical, psychological and social), and can also be used in the temporal assessment of the evolution of cough and in the follow-up of the response to treatment. As it is an instrument originally developed in English, the LCQ must be translated and adapted to the social and cultural circumstances of the place where it is intended to be used, Therefore, its translation and cultural adaptation to the Portuguese language was carried out by Felisbino et al (FELISBINO, 2014 ; ROSA, 2017)

TREATMENT

Treatment is done through combinations of pharmacological agents. Starting with a long-acting, decongestant oral antihistamine, if there is no improvement in the first week, start inhaler nasal corticosteroids in the second week. (PATRICK, 1995)

It is assumed that half of the patients with chronic cough have a degree of vocal fold motor dysfunction (BPPV). Thus, speech therapy has been shown to be a potentially efficient intervention in the management of chronic cough, benefiting patients who use pharmacological treatment. Respiratory laryngeal dystonia (RLD) is

characterized by spasms of the adductor muscles of the vocal folds during the inhalation phase of respiration, in which there is involuntary paradoxical supply of BPPV. It can be triggered by: inhalation of irritants, low temperature or extreme humidity of the air, motor acts that involve the respiratory muscles or stress. In this case, cough is refractory to pharmacological treatment with cough suppressants, antihistamines, and proton pump inhibitors (BALBANI, 2012 ; RIBEIRO, 2020; Lebl, 2003).

The treatment of chronic cough in children is through environmental control, hot steam, homemade syrup, honey that gives an anti-oxidant effect and potential antimicrobial effects, increasing the release of cytokines (II DIRETRIZES BRASILEIRAS NO MANEJO DA TORRSE CRÔNICA, 2006).

Patients with asthma or eosinophilic bronchitis tend to have a satisfactory response to corticosteroid therapy. Rhinitis, sinusitis and postnasal drip require treatment based on topical corticosteroids, however, in more aggravating cases, topical ipratropium bromide 40 µg twice and daily oral antihistamine are used (PAVORD, 2008). However, patients with chronic cough without asthma and who have sputum without eosinophilia do not respond to the treatment mentioned above, but rather to the removal of exposure (II DIRETRIZES BRASILEIRAS NO GESTÃO DA TORRSE CRÔNICA, 2006).

In cases of rhinitis, the drugs used would be antihistamines, oral and topical vasoconstrictors, ipratropium bromide, disodium cromoglycate, nedocromil sodium, and oral and topical corticosteroids. They can be used alone or in combination (II BRAZILIAN GUIDELINES ON THE MANAGEMENT OF CHRONIC COUGH, 2006).

Randomized controlled trials associated with the treatment of gastroesophageal reflux with acid suppression therapy have been disappointing, and for this reason there is still no reliable treatment. Use of cough suppressant in chronic cough, these agents usually suppress rather than cure cough, however we do not have a study that brings certainty about the safety of using these drugs over a long period. In a clinical trial, patients with chronic cough who administered lidocaine by aerosol or nebulizer had good evidence of efficacy, but without clarity regarding safety (PAVORD, 2008).

Nasal decongestant is used in cases of rhinosinusitis and common colds, however they should be used for a maximum of 5 days, as they can bring side effects such as cardiac arrhythmias, development of high blood pressure and psychological dependence. In addition, they are contraindicated for hypertensive, diabetic, prostatic

hyperplasia patients. However, an alternative that can be adopted to replace this medication is the use of saline solution associated or not with the use of nasal corticosteroids. (REGIONAL COUNCIL OF PHARMACY OF THE STATE OF SÃO PAULO)

Antibiotics should not be routinely used for the treatment of chronic cough in the absence of infections, as their effects have not been systematically evaluated. Prolonged use of this class of drug can produce undesirable side effects, such as digestive problems, fungal infections, drug interactions, photosensitivity (II BRAZILIAN GUIDELINES ON THE MANAGEMENT OF CHRONIC COUGH, 2006;)

It is worth remembering that each patient must be treated according to their symptom and need, it is up to the doctor to evaluate and see what is the best form of treatment. Chart 2 lists the main classes of medications, their respective mechanisms of action, and the indication for use in the treatment of chronic cough.

Class	Mechanism of Action	Use
Corticosteroid	It has anti-inflammatory action that acts through the interaction with the glucocorticoid receptors that are in the cytoplasm of the cells and that after activation migrate to the cell nucleus where they intervene with the transcription machinery along with the DNA making acetylation and remodeling of the chromatin	Maintenance and prophylaxis.
Histamine	It acts on the smooth muscle of the bronchi and blood vessels, is responsible for many of the symptoms of the allergic reaction, playing a fundamental role in allergic reactions and immediate hypersensitivity	Frequent nasal itching and sneezing
Nasal Decongestant - Gout/Aerosols	It acts on the nasal mucosa, where they will act as sympathomimetic agents that act on adrenergic receptors, inducing vasoconstriction. They shrink the swollen mucosa and improve ventilation. Systemic absorption is little or none	Use no more than 5 days for rhinosinusitis and common cold
Anticholinergics - Ipratropium bromide	A bronchodilator that reduces intrinsic cholinergic tone of the airways. It is slow acting and inferior to that of b²-agonists and its use is limited in long-term management	Treatment of choice for beta-blocker-induced bronchospasm

Adapted from: Revista do farmacêutico, 2005; PAVORD; CHUNG, 2008; II BRAZILIAN GUIDELINES, 2006; III BRAZILIAN CONSENSUS ON ASTHMA MANAGEMENT. (Lam et al. 2021)
Adapted from: Revista do farmacêutico, 2005; PAVORD; CHUNG, 2008; II BRAZILIAN GUIDELINES, 2006; III BRAZILIAN CONSENSUS ON ASTHMA MANAGEMENT. (Lam et al. 2021)

COMPLICATIONS

Chronic cough can have a negative impact on the individual and on the most different organs and systems in various ways, such as cardiovascular complications: subconjunctival hemorrhage, syncope, hypotension, and arrhythmias; neuropsychiatric: seizures, dizziness, radiculopathies, insomnia, and anxiety; gastrointestinal: rupture of the spleen, gastroesophageal reflux, rupture of the rectus abdominis, inguinal hernia; genitourinary: urinary incontinence and bladder injury; and most commonly to the respiratory tract, with: pneumomediastinum, asthma exacerbation, laryngeal trauma, pneumothorax, and rib fracture. Among all the possible complications, the change in lifestyle and the significant impact on the quality of life of individuals affected by chronic cough (LIN; AUGUSTO, 2010).

CONCLUSION

The complex pathophysiology of cough reveals a vast etiopathogenesis that can transform this physiological and protective symptom of the airways into a pathological process capable of spreading diseases.

Clinical examination, with well-constructed anamnesis and well-performed physical examination, continues to be the main diagnostic tool for acute, subacute, and chronic coughs, since the characteristics and behavior of cough help in the identification of infectious agents and non-infectious etiologies of cough.

Cough continues to be one of the most frequent symptoms reported by patients seeking medical help, generating a significant socioeconomic impact, aggravated by the exuberant behavior of self-medication to relieve the symptom by the general population.

The therapeutic approach to cough, as a symptom, is vast, sometimes imprecise, and changes according to the time of onset and etiology of the condition, which should always be clarified in the best way to optimize the choice of medication.

Acute and chronic coughs can aggravate and trigger different complications, but among all the possible complications, the change in lifestyle and the significant impact on the quality of life of the individual affected by cough is evident.

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