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A Cough of Unknown Origin: An Often Serious, Unmet Clinical Problem

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Abstract

Coughing is a common symptom present in primary care. Results of epidemiologic surveys suggest that only a small fraction of patients with a cough seek medical care for this symptom. Typically, symptoms that have no identified cause such as the cough of unknown origin (CUO) is a serious clinical problem in internal medicine and is all too often connected to allergy backgrounds. Coughing in itself is a problem regardless of either a causative condition identified as asthma, chronic obstructive pulmonary disease (COPD), or gastroesophageal reflux, or its origin remains unknown. This article reviews our current understanding of the pathogenesis of coughing that characterizes a number of respiratory and non-respiratory diseases. A more in-depth knowledge in this field of international medicine is a condition for a more targeted clinical approach to the patient with CUO and helps contain health care costs while providing unquestionable benefits to the community. Finally, it is reported the most recent approach for the CUO's treatment.

Keywords: Asthma, Cough of unknown origin; Acid-sensing ion channels; Chronic obstructive pulmonary disease; Foreign body; Gastroesophageal reflux; Postnasal drip and sinusitis; Respiratory allergy; Transient receptor potential channels.

Introduction

Coughing is the most common symptom of whom individuals seek medical advice and one of the most demanding in terms of health care costs and resources [1,2,3]. Acute coughing is often the most prominent symptom of the common cold, which in itself is the most frequent illness in the general population. In the USA, the direct and indirect costs of the common cold have been estimated at 40 billion USD per annum [4]. Chronic coughing, as the only presenting complaint, is known to account for 10–38% of all referrals made to respiratory physicians [5,6]. Chronic coughing can be associated with significant distress and impairment in quality of life [7].

Guidelines from the European Respiratory Society (ERS) [8], as well as guidelines from the American College of Chest Physicians, provide a general consensus on the diagnosis and treatment of coughs in both adults and children [9]. However, there are cases of "cough of unknown origin" (CUO) that had no identified cause and they differ to Psychogenic cough ("habit cough" or "tic cough") that may be the cause in the absence of a physical problem [9]. The increasing demand for a more effective approach to this clinical problem is documented by the increasing number of publications on the topic "cough" in the PubMed database relative to the period 1966–2014 (Table 1).

Period	No. of publications
1966–1975	2262
1976–1985	2968
1986–1995	6564
1996–2005	10,950
2006-2014	13,966

Table1: Number of publications retrieved in the PubMed database using the keyword "cough" for the period 1966–2014 and grouped by decade.

Coughing is a troublesome symptom, sometimes disturbing, which can give light to numerous conditions, including infectious diseases that can be transmitted to other people [6]. Among the causes of a cough are a number of diseases affecting the larynx, pharynx, and sinuses, such as sinusitis, laryngitis, pharyngitis, and neoplasms; diseases affecting the trachea and bronchi, such as tracheitis, bronchitis, asthma, bronchial hypersensitivity, and cancer; diseases that affect the lungs, such as fibrosis, pneumonia, pulmonary oedema, and tumors; diseases affecting the pleura, such as pneumothorax and pleurisy; diseases affecting the mediastinum, such as tumors,

esophagitis, lymphadenitis, and aortic aneurysms; diseases affecting non-pulmonary areas, such as gastroesophageal reflux disease.

While specific therapy directed at the underlying cause of a cough is usually successful, there are no particularly effective nonspecific cough treatments. These are desperately needed for patients with CUO, for those afflicted by a cough due to pulmonary fibrosis and lung cancer, or when established treatments for asthma and chronic obstructive pulmonary disease (COPD) are ineffective. The need to obtain a rapid diagnosis in some cases is currently obstructed by the lack of consensus as to the appropriate use of instrumental tests. The adoption of reliable, shared protocols of testing and new therapeutic approach will be a much needed step towards effective cough management in patients with CUO. The objective of this review is to improve the approach to a CUO, which often presents banal symptoms and becoming a serious unmet clinical problem for many child and adult patients. Indeed, recent knowledge about treatment and management of cough in general has been revised to treat this common clinical situation better than in the past.

Regulation of cough from peripheral reflex to brain control

A cough is a reflex act in defense of the tracheobronchial tree, which frees the airway from harmful substances entering into them. Therefore, a cough is a reflex action of the respiratory tract that is used to clear the upper airways from environmental threats through an expulsive motion with a characteristic sound [10-12]. Coughing can be provoked voluntarily or induced reflexively (consciously or unconsciously), and it results from a complex interaction between the central and peripheral nervous system [10,11,13]. Different airway sensory nerves are involved in coughing, mostly originating from the vagal knot and jugular ganglia, which are located within and below the airways' epithelial tissue and are activated upon sensing the irritating signals coming into the airways. This activation process is mediated by various ion channels, and the generated action potential is conducted along nerve pathways converging at the nucleus of the tractus solitarius (nTS). Nerve signals are then integrated, resulting in efferent signals of different origin and degree [14].

However, there are different subtypes of vagal nerve fibers, exhibiting different responses to different stimulations [14]. The signal from mechanical stimulation is mainly mediated by Aδ cough receptors; these are also responsive to rapid changes in pH but not to capsaicin or bradykinin (BK) [15,16]. This is a fast conducting reflex useful to mediate immediate protection against acid or foreign body inhalation. The recognition of chemical irritants, in particular acidic stimuli, and endogenous inflammatory mediators (e.g.: PGE2; Bradkynin and Capsaicin) is mostly mediated by C-fibers [14]. C-fibers are functionally divided into two types, according to their innervation sites (bronchial vs. pulmonary). Bronchial C-fibers stimulate the upper airway, and their activity readily initiates a cough reflex. By contrast, pulmonary C-fibers stimulate the lower airways, and their activity is thought to inhibit coughing but induce apnea [14]. The paradoxical actions of two common but differently acting pathways may not be explained by peripheral levels, but may be the evolutionary adaptation to protect lower airways. These airway C-fibers exert chemosensitive functions by expression of various sensory receptors. Transient receptor potential (TRP) vanilloid 1 (TRPV1) is one of best-known nocuous receptors involved in a cough reflex, which responds to high temperatures, low pH and capsaicin [17].

TRP ankyrin 1 (TRPA1) is another recently identified cough receptor, which readily senses cold temperature and various irritants including cigarette smoke [18]. The up regulation or activation of these TRPs may be a major component in the pathogenesis of airway hypersensitivity and cough .This finding could be of particular significance because many of the chemicals that are known to activate TRPA1 are noxious respiratory irritants, moreover, a variety of TRP channels as well as acid-sensing ion channels (ASICs) are proposed to be associated with the sensation of acidic stimuli (e.g. TRPA1, TRPV1 and TRPV4). Pre-clinical and clinical evidence continues to demonstrate a role for these ion channels as potentially important targets for the treatment of cough associated with respiratory pathologies [14].

Rapidly adapting receptors and slowly adapting receptors are other sensory fibers for mechanical stimuli; however, they mainly terminate in the intrapulmonary airways, and are thought to be involved less in the cough reflex [14].

Not every cough comes as a reflex; we can also voluntarily initiate and suppress coughing. This indicates the involvement of a higher brain circuit that controls cough consciously [13].

Interestingly, Aδ fiber stimulation induces a cough reflex regard less of general anesthesia [19]; vice versa, the activity of C-fibers is maintained only when we are conscious [15]. This means that peripheral cough reflexes are variably associated with the central nervous system; the function of mechanosensitive Aδ fibers is fundamental and instinctive for airway protection, whereas the chemosensitive C-fibers are slower but more complexly related to perception by higher cortical areas. In clinical practice, many patients have an abnormal sensation or irritation in the throat that leads to "urge-to-cough" and the cough act [20]. The "urge-to-cough" sensation may be experimentally induced by C-fiber stimulation or capsaicin inhalation [21], which is a TRPV1agonist. The presence of "urge-to-cough" is clinical evidence to suggest the connection between peripheral and central cough pathways.

A role for extracellular signal regulated kinases-1 and -2 (ERK1/2) in the central processing of cough causes inputs were reported in a study by Mutolo and co-workers using microinjections of a specific inhibitor (U0126) into the caudal nucleus tractus solitarii (cNTS) in pentobarbitone anesthetized spontaneously, breathing rabbits [22]. Marked, concentration-dependent reduction or complete ablation of the cough response induced by mechanical or chemical stimulation of the tracheobronchial tree was assessed. This procedure did not affect the Breuer-Hering inflation reflex, the pulmonary chemoreflex or the sneeze reflex. This study represents the first step towards more comprehensive testing on the involvement of mitogen-activated protein kinases in the transduction of cough-related extra cellular stimulations into intracellular post-translational and transcriptional responses. These results suggest a role for ERK1/2 in the observed effects by nontranscriptional mechanisms, given the short time involved (Figure 1).

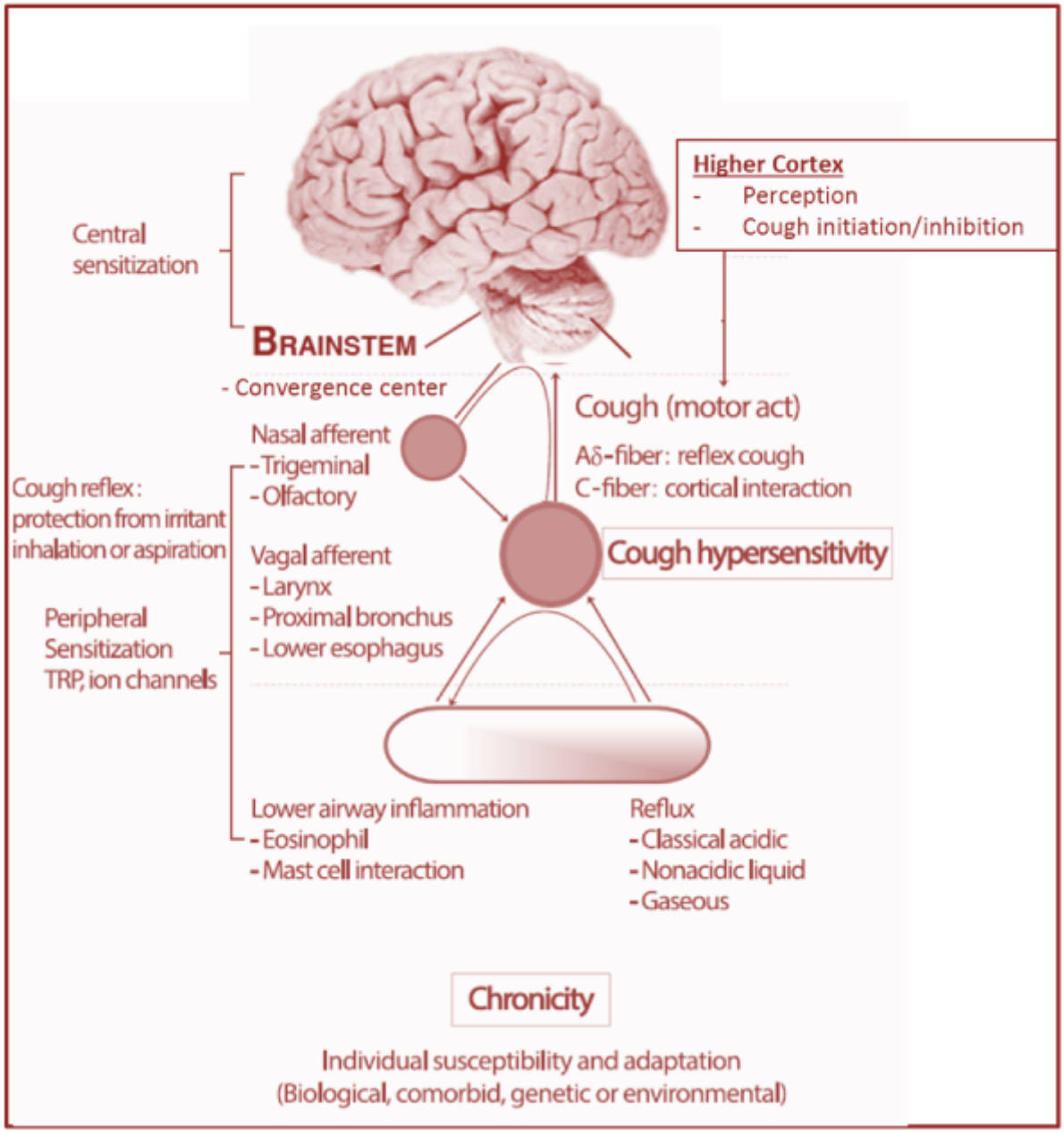

Figure 1: A key event may be the development of vagal neuronal hypersensitivity in the airways. Commonly associated diseases like rhinitis, eosinophilic airway inflammation, or classical acidic reflux may be triggers to lower thresholds for peripheral cough reflex activation. Nasal afferent stimulation may not directly initiate the cough reflex, but modulate (sensitize or desensitize) the cough reflex depending on the type of nasal stimulus. Gaseous reflux has been hypothesized to be a common factor to develop cough hypersensitivity. TRP, transient receptor potential. (Modified from Woo-Jung Song et al., Asia Pac Allergy 2014; 4: 3-13)

Many cough patients cannot suppress cough as they want. Recent capsaicin challenge studies by Hilton et al. [23] have provided evidence that chronic cough patients have potential defects in inhibitory mechanisms of cough regulation. Functional magnetic resonance imaging (MRI) studies by Mazzone et al. [13] have provided objective evidence for the presence of upper bridged pathways involved in cough regulation. The interactions between higher brain circuits and peripheral afferent fibers, present interesting implications in clinical practice and carries further clarification [10]. Insight into the neural mechanisms of cough can serve as a starting point for the conception and development of potential coughing relief drugs. Wei and Vitins studied 9th (glossopharyngeal) and 10th (vagal) cranial nerve afferents from the upper oropharynx [11]. Authors speculate that a molecule designed as an agonist with a vigorous sensory impact on the oropharyngeal surface has the potential to suppress a cough by a number of mechanisms, including: evoking pharyngeal swallowing

reflexes that are incompatible with coughing; evoking sensations that override tickling/itch in the throat; and creating gating signals in the brainstem, where the 9th and 10th nerve afferents converge. Using their particular design and screening strategy, researchers have identified multiple candidate molecules as potential cough suppressants.

Cough and bronchoconstriction

The relationship between cough and bronchoconstriction has been an area of considerable scientific inquiry for decades [24]. Ohkura and Fujimura have hypothesized that a bronchoconstriction-triggered cough could be associated with a protective effect against bronchoconstriction [25]. Testers have evaluated bronchial responsiveness and cough induction by the inhalation of methacholine in healthy volunteers. Measured recovery rates of PEF40 and FEV1 after the methacholine challenge demonstrated that a higher cough number induced protects against mild but not severe bronchoconstriction.

Zhang and colleagues offered methodological insights into the measurement of cellular and biochemical inflammatory markers that may be relevant to cough induction [11]. While in another study, the products of activated mast cells, other inflammatory cells, and resident cells can overtly stimulate nerve endings, cause long-lasting changes in neuronal excitability, increase synaptic efficacy, and also change gene expression in nerves, resulting in phenotypically altered neurons. A better understanding of these processes might lead to novel therapeutic strategies [26].

Different causes of cough

Postnasal drip and sinusitis (UACS: upper airway cough syndrome): A diagnosis of CUO can also be made after a trial of therapy. CUO that is not caused by sinusitis usually responds to a combination of a decongestant and first-generation histamine H1 receptor antagonist [27]. The non- sedating antihistamines are not as effective if the UACS is not mediated by histamine (e.g. in non-allergic rhinitis) [9]. A patient in that CUO is suspected and who does not respond to therapy should undergo sinus imaging [27]. Radiography is 84% sensitive and 77% specific (positive likelihood ratio [LR]=3.6, negative LR=0.21). Plain radiography may be used as a screening modality; computed tomography (CAT) is used to confirm and determine the phase of chronic inflammatory diseases of the sinuses [28].

Initial therapy for most UACS should include an antihistamine-decongestant combination (Table 2). First-generation antihistamines, such as dexbrompheniramine maleate or azatadine maleate, have been demonstrated to be superior to second-generation drugs, due to their additional anticholinergic activity. If drowsiness is problematic, therapy may be initiated with bedtime dosing before starting twice-daily dosing. Second-generation antihistamines are useful primarily in allergic rhinitis syndromes. The role of bacteria in perpetuating chronic sinusitis is controversial, and treatment regimens are not well defined. Except for chronic sinusitis, in most patients symptoms respond within 1 week. Long-term use of topical decongestants should be discouraged to avoid rebound nasal congestion (rhinitis medicinal). The treatment of GERD as an integral component of the diagnostic/therapeutic algorithm for the management of chronic cough in case of UACS, because GERD is generally considered among the most common etiologies of chronic cough (Table 2) [29].

Syndrome	Treatment	Examples	Comments
Post-infection	First-generation antihistamine plus decongestant combination	Dexbrompheniramine maleate 6 mg plus pseudoephedrine 120 mg twice a day	Nasal corticosteroids are useful for maintenance therapy Ipratropium nasal MDI is also effective
Allergic rhinitis	Second-generation antihistamine	Loratadine 10 mg/day	Cromolyn, azelastine, leukotriene inhibitors are also useful
	Nasal corticosteroid	Beclomethasone nasal 42 mcg each nostril four times a day	Consider allergy testing
	Allergen avoidance		
Non-allergic rhinopathy (vasomotor rhinitis)	Anticholinergic nasal spray	Ipratropium 0.06% 2 snuffs/ nostril 4-6 times/day	Intranasal glucocorticoids and/or intranasal antihistamine only if congestionand sneezing are present
Chronic sinusitis	First-generation antihistamine plus decongestant (3 wks)	Dexbrompheniramine	Use antibiotic active against Haemophilus influenza, Streptococcus pneumoniae, oral anaerobes
	Nasal decongestant (5 days)	Pseudoephedrine as above	Nasal corticosteroids after cough resolves
	Appropriate antibiotics (3 wks)	Oxymetazoline 2 sprays twice a day	
GERD	diet, antacids, prokinetics , PPIs (4 weeks)	.Sucralfate1 g q.d.s Cisapride5 mg twice a day, Esemeprazole/ Pantoprazole 40 mg twice a day	Some time it needs the antireflux surgery in improving or curing reflux cough syndrome*

Table 2: Treatment for UACS and GERD

Asthma: Asthma is the next most common cause of chronic cough in adults [30]. Spirometry is required to diagnose asthma and can be reliably used to demonstrate airflow obstruction and assess reversibility of the condition in patients older than the age of 4 [31]. Coughing is the most commonly reported symptom in patients with chronic asthma, and is the only proof shown in up to 57% (i.e., cough-variant asthma) [32].

Cough-variant asthma should be considered when a persistent cough gets worse by cold, exercise, and at night. In patients suspected of having cough-variant asthma but who have no diagnostic physical examination and spirometry, a methacholine inhalation challenge testing may be performed to confirm asthma [32]. The methacholine challenge test (MCT) is highly sensitive, and a negative test virtually excludes the diagnosis of asthma. Furthermore,H1 receptors are involved in bronchoconstriction related to coughing, it is reported that oxatomide (OXA), a histamine H1 receptor antagonist, mast cell stabilizers, so called antiallergic drugs, that also have blocking effects on receptors for chemical mediators (e.g. anti-H1 and anti-PAF), is effective in the treatment of patients with allergic rhinitis and bronchial asthma [33]. Because the diagnosis of asthma is only established after the recognition of a cough with specific asthma therapy, a trial of inhaled bronchodilators or corticosteroids is an alternative diagnosis [27].

Gastroesophageal reflux disease (GERD): GERD is the third leading cause of chronic coughs in adults [29]. Acid reflux can stimulate the afferent limb of the cough reflex by irritating the upper respiratory tract without aspiration or by irritating the lower respiratory tract through aspiration. GERD can also cause chronic cough by stimulating an oesophageal-bronchial cough reflex [34]. Through this neural reflex mechanism, reflux into the distal oesophagus alone, is thought to cause cough. Daily heartburn and regurgitation suggest a GERD-induced chronic cough. These symptoms may be absent in "silent" GERD [27]. Although GERD treatment is not universally beneficial for coughs associated with the disease, an empiric trial of a proton pump inhibitor is recommended [29,35] (Table 2). A definitive diagnosis of GERD-related cough requires that the cough disappears nearly or completely with treatment. The most sensitive and specific test for acid-induced GERD is 24-hour esophageal pH monitoring; this test may be performed if therapeutic trials are ineffective. Indeed, cough management guidelines published by numerous respiratory societies worldwide recommend evaluation and treatment of GERD as an integral component of the diagnostic/therapeutic algorithm for the management of chronic cough. However, a significant number of patients with chronic cough presumed due to GERD do not report improvement despite aggressive acid-suppressive therapy. Some of these refractory cases may be due to the recently appreciated entity of non-acid or weakly acidic reflux (Table 2) [29,35].

ACE inhibitors: A causal association with cough has also been reported for angiotensin converting enzyme inhibitors (ACEI), which have been frequently used as drugs in the registration of clinical trials of angiotensin receptor blockers (ARBs). ACE inhibitors cause a non-productive cough in 5% to 20% of patients, affecting women more often than men [36]. This effect is not dose related, and a cough may begin one week to six months after therapy has started. A cough should spontaneously resolve itself after a few days to several weeks when the ACE inhibitor is discontinued; therefore, a four-week trial of withdrawal is usually sufficient to determine whether the medication has caused the cough [36]. An ARB may be substituted for the ACE inhibitor. Although coughing is listed as an aggressive drug reaction (ADR) on the labels of ARB, this view has been recently proven contrary by a study based on the use of comparators with well-known ADRs [37].

Non asthmatic eosinophil bronchitis (NAEB): Nonasthmatic eosinophil bronchitis has been increasingly identified in patients presenting to pulmonary medicine clinics [38-40]. Its prevalence in primary care patients with chronic cough is unknown, but probably lower. It is defined as a chronic cough in patients with a normal hypersensitive airway, eosinophil sputum, and no symptoms or evidence of variable airflow obstruction. The presence and activity of eosinophil and metachromatic cells in the sputum differentiate NAEB from classic chronic bronchitis. The lack of bronchial hypersensitivity in NAEB differentiates it from asthma, because asthma also may result in the presence of reactive cells, e.g. eosinophil in the sputum. Patients with NAEB have normal spirometry and respond to inhaled and systemic corticosteroids. This condition usually can be ruled out if induced sputum contains insufficient eosinophil (less than 3%) or if corticosteroid therapy does not improve the cough. The condition may be transient, episodic, or persistent unless treated [41]. Rarely, patients may require long-term treatment with prednisone.

Post infection Cough: Post infection cough is common in primary care, but has no proven effective treatments. Post infection cough is self-limited and will resolve itself spontaneously, although it may persist for three or more months. Reassurance is a good approach in otherwise healthy patients. Oral or inhaled corticosteroids, ipratropium, or cough suppressants may be prescribed to help sleep [27].Cysteinyl leukotrienes are involved in the pathogenesis of post-infection cough and whooping cough, but the effectiveness of montelukast, a cysteinyl leukotriene receptor antagonist in the treatment of post-infection cough is not shown [41].

Chemical irritants: Chronic bronchitis caused by exposure to cigarette smoke or other irritants is an important cause of chronic cough. Cigarette smoking is the most common risk factor for COPD [42]. Although chronic bronchitis is a relatively common cause of chronic cough, it accounts for only 5% of patients who present for evaluation and treatment [6]. The initial treatment is eliminating the patient's exposure to irritants.

Psychogenic or habitual cough: A habitual cough is a diagnosis of exclusion [6]. Many patients with this condition do not cough during sleep, are not awakened by cough, and generally do not cough during the day. Failure to cough during sleep is not a specific sign of this condition. Common signs include changes in environmental temperature; taking a deep breath; laughing; talking on the telephone for more than a few minutes; exposure to cigarette smoke, aerosol sprays, or perfumes; or eating crumbly, dry food [3,9].

Patients with abnormal chest radiography: If chest radiography reveals abnormalities (Table 3), further tests may be required to establish a diagnosis. Possible studies include high-resolution computed tomography (CAT) of the chest, pulmonary function testing, barium esophagography, cardiac studies, and bronchoscopy. Referral to a pulmonologist or cardiothoracic surgeon may be required to obtain a determinative diagnosis for detected lesions [27].

Normal Chest Radiography	Abnormal Chest Radiography
UACS (Upper Airway Cough Syndrome)	Bronchiectasis
Asthma and Nonasthmatic eosinophilbronchitis	Bronchogenic Carcinoma
ACE Inhibitors	Tuberculosis
Gastroesophageal reflux disease	Sarcoidosis
Post-infection Cough	Mediastinal Lymphadenopathy
Chemical Irritants	Genetic disease (e.g., cystic fibrosis, primary ciliary dyskinesia, α1-antitrypsin deficiency)
Psychogenic or Habitual Cough	

Table 3: Listed are the most common causes of chronic cough, grouped by normal or abnormal chest radiography.

Bronchiectasis: Coughing is associated with excessive overproduction and reduced clearance of airway secretions [6]. Bronchiectasis can be associated with CUO, asthma, GERD, and chronic bronchitis. Chest radiography may demonstrate increased thickening of the bronchial wall. Etiologies of bronchiectasis include post-infectious and idiopathic causes; genetic disease (e.g. cystic fibrosis, primary ciliary dyskinesia, α1-antitrypsin deficiency); inhalation or GERD; immune deficiency; rheumatoid arthritis; ulcerative colitis; and allergic bronchopulmonary aspergillosis [43].

Bronchogenic carcinoma: Computed tomography (CAT) should be done if chest radiography findings suggest malignancy. Sputum samples can be examined for the presence of cancer cells. A patient with persistent symptoms despite having normal chest radiography and a negative evaluation of common causes of cough should also be evaluated with computed tomography (CAT) or bronchoscopy. Lung cancer is a heterogeneous, complex, and challenging disease to treat. With the arrival of genotyping and genomic profiling, our simple binary division of lung cancer into non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) is no longer acceptable. In the past decade and with the oncoming of personalized medicine, multiple advances have been made in understanding, underlying biology and molecular mechanisms of lung cancer. Lung cancer is no longer considered a single disease entity and is now being subdivided into molecular subtypes with dedicated targeted and chemotherapeutic strategies. The concept of using information from a patient's tumor to make therapeutic and treatment decisions has revolutionized the whole view for cancer care and research in general. Management of non-small-cell lung cancer, in particular, has seen several of these medical progresses, with the understanding of activating mutations in EGFR, fusion genes involving ALK, rearrangements in ROS-1, and ongoing research in targeted therapies for K-RAS and MET genes. The next era of personalized treatment for lung cancer will involve a comprehensive genomic picture of adenocarcinoma, squamous-cell carcinoma, and small-cell carcinoma into various subtypes [44].

Tuberculosis: Tuberculosis should be considered in patients with chronic cough who have sputum production, hemoptysis, fever, or weight loss and who live in areas with a high prevalence of the disease, and in those at high risk (e.g. human immunodeficiency virus–seropositive people who use injected drugs) [45]. These patients may have normal physical examination and chest radiography findings, so additional testing (e.g. skin testing, sputum culture) may be needed to make the diagnosis.

Sarcoidosis: Sarcoidosis is another less common cause of chronic cough. Patients with sarcoidosis typically have chest radiography results suggestive of the diagnosis (i.e., mediastinal widening caused by bilateral hilar adenopathy and reticular opacities) [46]. Before sarcoidosis is determined to be the sole cause of cough, other more common disorders such as COPD and GERD should be excluded as primary or contributing causes. The clinical manifestations depend on several factors such as ethnicity, site and extent of organ involvement and on the activity of granulomatous process. Although, the classification of thoracic sarcoidosis is based on the findings of the chest radiogram and relies on the lung parenchyma and hilar nodes abnormalities, recently,flexible bronchoscopy has revolutionized the evaluation of patients with suspected sarcoidosis and the treatment of sarcoid patients with significant endobronchial disease [47].

Chronic cough in children: In children, a cough lasting longer than four weeks is considered chronic. The most common causes of chronic cough in children are asthma, respiratory tract infections, and GERD [48]. The differential diagnosis for chronic isolated cough without associated wheezing in an otherwise healthy child includes recurrent viral bronchitis, post infection cough, whooping cough-like illness, cough-variant asthma, CUO, psychogenic cough, and GERD. Signs suggesting serious underlying lung disease include neonatal onset of cough, chronic moist or purulent cough, a cough starting and persisting after a choking episode, a cough occurring during or after feeding, or associated with growth reduction [49]. Well-established causes of chronic cough, such as asthma, are likely to be well known, whereas more recently identified etiologies, such as protracted bacterial bronchitis, needs to be looked into with more detail. The differential value of flexible and rigid bronchoscopy and bronchial flushing to aid in the differential diagnosis is included for those entities where their use is essential [50].The pathway recommended for testing chronic cough in adults is not suitable for children younger than 15 [29]. Children with a chronic cough should undergo chest radiography and spirometry, at minimum [46,48,51-53]. Foreign body inhalation should be considered in young children if the characteristic of this cough is the whooping-like-cough. Human bocavirus (HBoV), a proposed member of the family Parvoviridae, is one of the most recently described respiratory viruses. Initial reports indicate that HBoV is a common cause of respiratory tract infection in children. HBoV DNA is commonly present in children with upper and lower respiratory tract infections. The presence of a whooping-like cough and diarrhea in association with HBoV infection deserves looking further into [54].

Congenital conditions, cystic fibrosis, and immune disorders are possible diagnoses in children with chronic cough and recurrent infections. Congenital abnormalities, although rare, can include

vascular rings, tracheoesophageal fistulas, and primary ciliary dyskinesia [50,55].

Current treatments of coughing

There are different types of coughs, each demanding a different therapeutic approach. In particular, acute coughs (attacks of coughing) and chronic coughs are treated differently. An acute cough may cause considerable distress for patients with upper airway infections and is a symptom commonly presented to doctors. The main evidence for pharmacological treatment of this condition suggests that there is limited evidence to support the use of antibiotics in acute bronchitis. Antibiotics may have a modest beneficial effect on some patients such as frail, elderly people who may not have been included in trials to date. However, the magnitude of this benefit needs to be considered in a broader context of potential side effects, a self-limited medical condition, increased resistance to respiratory pathogens and the cost of antibiotic treatment [56,57].

Although chronic cough may be successfully treated when associated with the common causes such as asthma and eosinophil bronchitis, GERD and UACS, increasingly, idiopathic cough or CUO cause is recognized. Doctors should always work towards a clear diagnosis, considering common and rare illnesses. In some patients no cause is identified, leading to the diagnosis of psychogenic cough [57].

Such cases will be dealt with a clinical approach that limits the use of instrumental and therapeutic modalities in order to maintain a reasonable balance of management costs and benefits to the patient, in terms of health gain and maintenance, in particular in normal immune adults (Figure 2) [58].

Coughing remains a serious unmet clinical problem, both as a symptom of a range of other conditions such as asthma, COPD, GERD, and as a problem in its own right in patients with chronic CUO. We have summarized our current understanding about the pathogenesis of coughing and the hyper-coughing state characterizing a number of diseases and review here in the evidence of the different levels of cough relief medicine currently in clinical use. On the whole, the review also discusses a number of major medicinal categories often used to treat coughs but that are not generally classified as cough relief drugs. We have also reviewed a number of drug categories in various phases of development as cough relieving drugs. Surprisingly, maybe because coughing is a common symptom, there is an insufficient amount of well-controlled clinical studies documenting evidence of the use of many of the medicinal categories in use today, particularly those available over the counter. There is no available information demonstrating suppression of the urge-to-cough in humans with chronic coughs using cough relief medicine as yet. In normal subjects, codeine (30 and 60 mg) did not alter cough sensitivity, electromyograms of abdominal muscles, airflows, or sensations associated with capsaicin-induced cough [59]. Cough is stopped if the urge-to-cough is satisfied; if the urge has not been satisfied then the urge-to-cough will continue to motivate the central nervous system. The central component within this cough motivation system is the intrinsic brain mechanism which can be activated to start the cycle for motivating a cough, the urge-to-cough, in humans awaits specific studies that use effective cough suppressants [60].

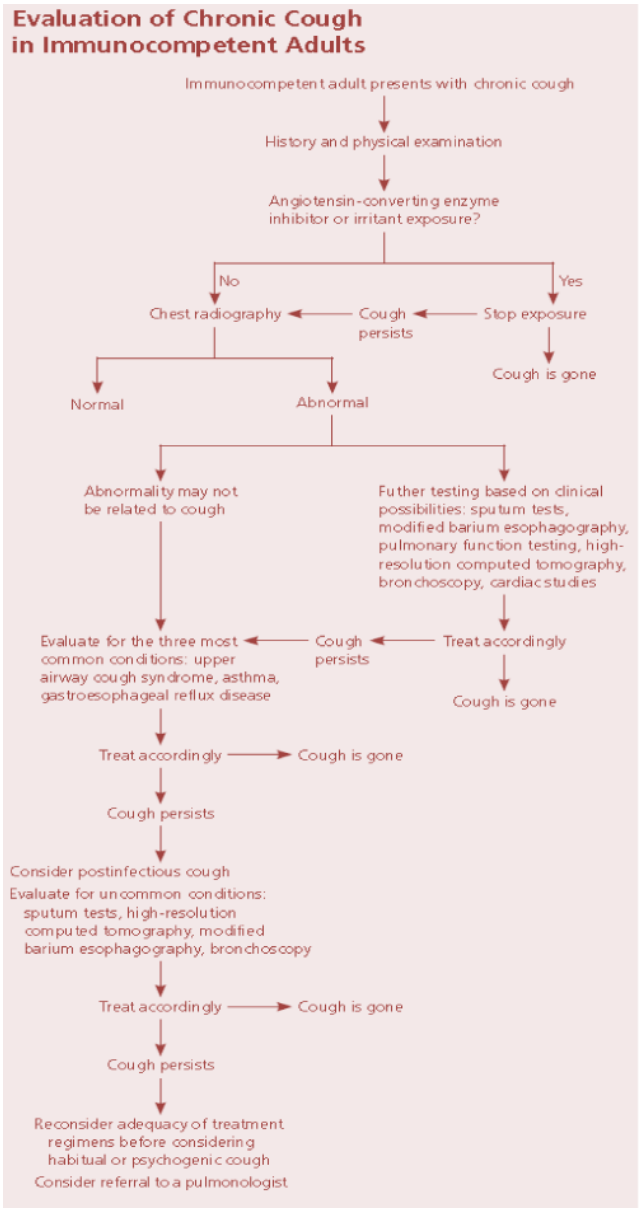

Figure 2: Algorithm for the evaluation of chronic cough in immunocompetent adults. Adapted from Irwin RS, Boulet LP, Cloutier MM, et al. Managing cough as a defense mechanism and as a symptom. A consensus panel report of the American College of Chest Physicians. Chest. 1998;114(2 suppl managing):166S.

Nonetheless, there has been a considerable increase in our understanding of the cough reflex over the last decade that has led to a number of promising new targets of cough relief medicine being identified and thus giving some hope of new drugs being available in the not too distant future for the treatment of this often debilitating symptom.

Although in most patients chronic cough can be diagnosed and treated successfully, a substantial minority continues to have persistent cough. These unexplained or unsolved cases have been termed habit cough, psychogenic cough, tic cough, idiopathic cough, neuropathic

cough, irritable larynx, and unexplained cough [61,62]. CUO remains a diagnosis of exclusion. A list of recommendation is reported by a modified Algorithm (Figure 2).

Hypersensitivity may be an important component in these patients. Referral to specialists in cough clinics is recommended [62]. An evaluation of past therapies with emphasis on adherence to guideline recommendations, patient adherence, and adequacy of treatment is warranted. In addition, less common thoracic pathologic abnormalities are sought. For example, bronchoscopy may reveal endobronchial sarcoidosis, and high-resolution CT of the chest may show bronchiectasis, mucus plugging, bronchial wall thickening, endobronchial lesions, and interstitial lung disease. Symptomatic relief is a challenge because over-the-counter preparations, such as guaifenesin and dextromethorphan, are not effective in chronic cough [62]. Speech pathology therapy and behavioral desensitization with refocusing are not pharmacological options [63]. Aside from the use of nebulized lidocaine [64], amitriptyline [65], and gabapentin [66], the main emphasisis on avoiding potential everyday use of narcotic-based cough suppressants.

Finally, the bronchial endoscopy is suggested to resolve in some cases acute cough by foreign body inhalation during emergency in pediatric as well as in adult medicine [67]. Even with current treatment protocols, a subset of patients will continue to have chronic cough without a diagnosis. As understanding of the pathophysiology of chronic cough evolves particularly around the concept of cough reflex hypersensitivity, future research should lead to new diagnostic and therapeutic modalities for this challenging problem [68].

General recommendations for treatment of coughs

Inhaled corticosteroids are generally required to optimize therapy for most patients with coughs associated with asthma. Using a pressurized metered-dose inhaler (MDI) can aggravate cough which may be alleviated by the addition of a spacer. Mast cell stabilizers, such as cromolyn sodium, are also effective. Few patients require oral corticosteroids for symptom control. Zafirlukast, a leukotriene inhibitor, has been shown to have a cough relief effect on patients with a condition termed cough-variant asthma (CVA). CVA accounts for 6.5% to 57% of all asthmatic patients [5,69].

The presence of bronchial hypersensitivity should be demonstrated by stimulation testing or evaluating the patient health record before initiating oral steroids. Caution is suggested with interpreting the results of empirical therapeutic success with asthma therapy; NAEB is a recognized cause of chronic cough, accounting for up to a third of cases in some series, and post-infection coughs might respond similarly. For this reason, we recommend at least one attempt to diminish therapy gradually. Steroids should also be diminished in patients whose methacholine test was obtained in the setting of a post-infection cough.

Cough suppression

Nonspecific cough suppression becomes necessary when the symptom impacts the quality of life significantly or when it is due to a disease process without effective treatment (e.g. idiopathic pulmonary fibrosis). Narcotics (morphine, codeine and dextromethorphan) have traditionally been used for cough suppression but have well known and prohibitive side effects with habitual use. Benzonatate is a valuable option for cough suppression; however, the side-effect profile includes seizures and cardiac arrhythmias. Effective pharmacological therapy for cough suppression remains an unknown necessity. Recent introduction of central cough suppressants such as cloperastin [70] and peripheral cough suppressants such as levodropropizine [71] and moguisteine [72] have been welcome additions but are available only in the Euro zone.

The anti-immunoglobulin (Ig) E monoclonal antibody omalizumab has been proposed as an innovative pharmacological tool in the treatment of poorly controlled moderate to severe allergic asthma, which is characterized by frequent exacerbations, functional instability, and the need forhigh-dosed, inhaled corticosteroids, systemic corticosteroids, or both [73,74], as well as in chronic eosinophilic pneumonia (CEP), an idiopathic eosinophilic pulmonary disease characterized by an abnormal and marked accumulation of eosinophils in the lung. When these patients have a cough with high total IgE levels and a positive skin prick test result, the reported response to omalizumab is satisfactory [75]. Recently, various study results about the effect of new biochemical treatment according to the inflammatory phenotype of asthma like omalizumab, also for Mepolizumab (anti-IL 5 Ab), and Lebrikizumab (anti-IL 13 Ab) have been published [76,77].

Recent additions in the treatment of chronic cough have been significant as they consider coughing to have a unifying diagnosis of cough hypersensitivity with or without the presence of a neuropathic basis. Primarily, effective treatments for chronic cough target these areas and include behavioural treatment such as speech pathology and pharmaceutical treatment with neuromodulating medications such as gabapentin [78].

The discovery of upper regulated TRP nociceptors in patients with cough reflex hypersensitivity may lead to the development ofnew peripherally active agents (TRP receptor antagonists) in the treatment of persistant coughs [79], raising hope for improved control of this symptom that quite often is associated with hard-to-manage diseases.

Conclusion

In current practice, it is forever more common to come into contact with CUO. The treatment protocols for chronic cough should be well known, and need to be implemented to avoid that this symptom remains without “a disease”. Many reports show that it is possible to reach an accurate diagnosis in the vast majority of cases in patients with persistent CUO, provided the clinical diagnosis is supported by the clinician’s experience and an appropriate method of testing. Foreign body inhalation has to be suspected with unsolved cases of acute cough, as well as, however seldom in some cases of chronic coughs in adults.

As an understanding of the pathophysiology of chronic cough evolves particularly around the concept of cough reflex hypersensitivity, future research should lead to new diagnostic and therapeutic modalities for this challenging problem, including the development of overall new categories of agents such as TRP receptor antagonists. It is fundamental to maintain reasonable use of newly received knowledge to avoid a wrong diagnosis of CUO and inappropriate treatment of this common symptom.

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