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Clinical Approach to Acute Cough

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Abstract Acute cough is among the most common symptoms for which patients seek medical attention. It accounts for millions of days lost from school and work and billions of dollars spent on medical care. Acute cough is defined as cough present for 3 weeks or less. It most often is caused by a viral infection of the upper respiratory tract ("common cold") or lower respiratory tract (i.e., "acute bronchitis"). The most effective treatment for cough due to the common cold is a combination first-generation antihistamine plus decongestant. Antibiotics are not indicated for most cases of acute cough. Occasionally, acute cough can be a symptom of a life-threatening condition.

Keywords Cough · Diagnosis · Management

Introduction

The act of coughing is relatively unique. From a health point of view, cough is a vital defense mechanism that helps protect the lungs from potentially noxious and dangerous exogenous substances and simultaneously facilitates the clearance of excessive lower respiratory tract secretions. Excessive or pathologic coughing that serves no useful purpose, on the other hand, is among the most common symptoms for which patients seek medical attention. Abnormal cough can be caused by a variety of respiratory and nonrespiratory disorders. The diagnostic evaluation and treatment of cough in the United States accounts for a substantial expenditure of health-care dollars [1].

For epidemiologic purposes, cough is typically categorized based on duration: acute, defined as lasting less than 3 weeks; subacute, lasting 3–8 weeks; and chronic, lasting more than 8 weeks [2]. The primary value of this division based on duration is that it is useful in predicting the most likely etiologies of cough compared with most other characteristics [3–5].

Among the three categories, acute cough is the most common and has the greatest impact on the general public. It results in millions of lost days from school and work and billions of dollars of health care expenditures. In the United States in the year 2005, expenditures for over the counter cough (OTC) and cold remedies just for adults were estimated at 1.94 billion dollars (AC Nielson's database). Paradoxically, despite its prevalence and health and economic effects, acute cough has received relatively little attention in the medical literature compared with chronic cough.

Problems with Definition

Although using time duration to categorize cough seems easy and attractive, the presumed precision of duration to define a cough as acute, subacute, or chronic (and the differential diagnostic implied) is less precise and the issue more complex then it appears. Obviously, all cough at its beginning is acute. It is not currently possible to predict at the onset of cough in whom it will be of short duration (i.e., resolve within 3 weeks) or in whom it will become subacute or chronic. The issue is further complicated by the fact that effective therapy can abort or abbreviate the

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duration of cough, whereas failure to institute effective therapy can convert what might have been an acute cough into a subacute or chronic one. Furthermore, recurrent acute episodes of cough can be a manifestation of an undiagnosed chronic disease (e.g., asthma). Nevertheless, keeping these caveats in mind, a relatively "standard" diagnostic and therapeutic approach based on duration of cough has proved useful [4].

General Mechanism

Cough involves a complex reflex arc. It is usually initiated by the stimulation of afferent cough receptors. These receptors are present in the epithelium of the upper and lower respiratory tracts as well as in the pericardium, esophagus, diaphragm, and stomach. Cough receptors can be divided into chemical receptors sensitive to acid, heat, and capsaicin-like compounds and mechanical receptors stimulated by triggers, such as touch or displacement [6].

Impulses from cough receptors travel predominantly via afferent pathways involving the vagus nerve to a "cough center" believed to be located in the medulla. This center is under some degree of voluntary control by higher cortical centers. The cough center, when stimulated, generates efferent impulses that travel down the vagus, phrenic, and spinal motor nerves to the expiratory respiratory musculature to produce the cough. Three mechanisms have been proposed to trigger the cough reflex and are discussed below [7].

Spectrum and Frequency of Etiologies

A number of descriptive studies have been published that describe the spectrum and frequency of etiologies for chronic cough [3, 4, 8, 9]. This is not the case for acute cough. Despite its importance, there are no large, prospective studies that describe the spectrum and frequency of the causes of acute cough. It is presumed that acute cough is most commonly caused by viral respiratory tract infections. The infections that involve primarily the upper respiratory tract (URT) are designated collectively as the "common cold." Alternatively, infections that appear to involve primarily the airways of the lower respiratory tract (LRT) are termed "acute bronchitis" [10, 11]. Acute bacterial sinusitis, *Bordetella pertussis*, mycoplasma, and chlamydia infections, allergic rhinitis, environmental irritant rhinitis, and foreign body aspiration are other causes of acute cough [1]. Importantly, on occasion acute cough can be the presenting or predominant symptom of a serious or even life-threatening condition (e.g., pulmonary embolism, congestive heart failure, pneumonia) [1, 12].

Common Cold

The common cold is one of the most ubiquitous infectious diseases of humankind. Adults in the United States, on average, experience two to four colds per year [13]. At least 200 viruses have been associated with the typical findings of the "common cold." They include rhinoviruses, coronaviruses, parainfluenza viruses, respiratory syncytial virus, adenoviruses, and enteroviruses [14].

The histological effects of these viral infections vary from extensive epithelial destruction of upper airway structures to the virtual absence of histological changes. In most cases these infections will cause clinical evidence of vasodilatation and hypersecretion of upper airway structures (particularly the nose, i.e., rhinitis). The resultant clinical syndrome includes nasal congestion, nasal discharge, postnasal drip (PND), throat clearing, sneezing, and cough [11].

The exact mechanisms by which viral infections associated with the "common cold" cause cough are unclear. One proposed mechanism is that the production of inflammatory mediators, such as bradykinin, prostaglandins, and tachykinins, produce excessive secretions that result in PND that mechanically stimulates the cough receptors. This is supported by a randomized, double-blind, placebo-controlled study on the common cold that demonstrated statistically significant associations among cough, throat clearing, and PND [10]. Cough improved in parallel with decreases in throat clearing and PND. Alternatively, it has been proposed that viral-induced inflammation of upper airway structures can directly irritate and activate the afferent sensory nerves in the upper airway [15]. Madison and Irwin have proposed that this increase in cough sensitivity of the upper airway during URTI may be due to an increased sensitivity of the rapidly adapting sensory receptors in the airway [16]. In recognition of the possibility that both PND and direct irritation of airway cough receptors can be factors in how upper airway cough is triggered, the term upper airway cough syndrome (UACS) was proposed in the 2006 American College of Chest Physicians (ACCP) cough guidelines to replace the term PND [1].

A third postulated, although unproven, mechanism for cough associated with the common cold is that inflammatory mediators produced at the site of upper airway infection are absorbed into the blood stream and reach the lower airways where they result in inflammation and hyperreactivity of sensory receptors [7].

Acute Bronchitis

Acute bronchitis is a common diagnosis made by primary care and emergency department physicians. It is used to

describe an acute infection of the LRT that is manifested predominantly by cough with or without phlegm production that lasts for up to 3 weeks [17]. It often is accompanied by constitutional symptoms. Several other disorders can have similar presentations. The common cold is the most difficult to distinguish from acute bronchitis because of the strong symptom overlap. Furthermore, there is no diagnostic test that can differentiate between these two disorders. According to ACCP evidence based guidelines, the diagnosis of acute bronchitis should be made only when there is no clinical or radiographic evidence of pneumonia, and the common cold, acute asthma, or an exacerbation of COPD have been ruled out as the cause of cough [18].

Various respiratory viruses appear to be the most common cause of acute bronchitis. Fewer than 10% of patients will have a bacterial infection diagnosed as the cause [18]. Viruses associated with acute bronchitis include influenza B, influenza A, parainfluenza, and respiratory syncytial virus (RSV). In addition, viruses that are predominantly associated with URT infection, including coronavirus, rhinovirus, and adenovirus have been implicated in acute bronchitis. The bacteria that have been linked to acute bronchitis include *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Bordetella pertussis*, and *Bordetella parapertussis* [18].

The mechanism of cough in uncomplicated acute bronchitis is likely multifactorial. It presumably begins with mucosal injury, epithelial cell damage, and the release of proinflammatory mediators. Transient bronchial hyperresponsiveness and even airflow obstruction can occur [18].

Approach to Management

An approach that may be useful to determine the cause and guide treatment of acute cough is shown in Fig. 1. The initial step is to differentiate between life-threatening and non-life-threatening causes. Initially, this is based on the history and physical examination. If clinical findings warrant it, diagnostic tests, typically starting with a chest roentgenogram, are obtained. In the case of suspected serious and potentially life-threatening cause (e.g., pneumonia, pulmonary embolism, and pulmonary edema), immediate diagnostic evaluation and treatment should be instituted. In the much more common circumstances of presumed non-life-threatening causes, the main conditions are respiratory tract viral infections, exacerbations of a preexisting condition, and environmental/occupational causes [19].

For acute cough related to the common cold, the combination of a first-generation antihistamine (brompheniramine) plus a decongestant (pseudoephedrine) has been shown in a double-blind, placebo-controlled study to hasten resolution of both cough and postnasal drip [10]. In contrast, the newer, so-called second-generation "nonsedating" antihistamines have been shown to be ineffective in treating the symptoms of the common cold [20]. The efficacy of a combined first-generation antihistamine plus decongestant preparation is postulated to be related to the anticholinergic properties of the antihistamine and vasoconstricting property of the decongestant [21]. Another double-blind, placebo-controlled study showed that the

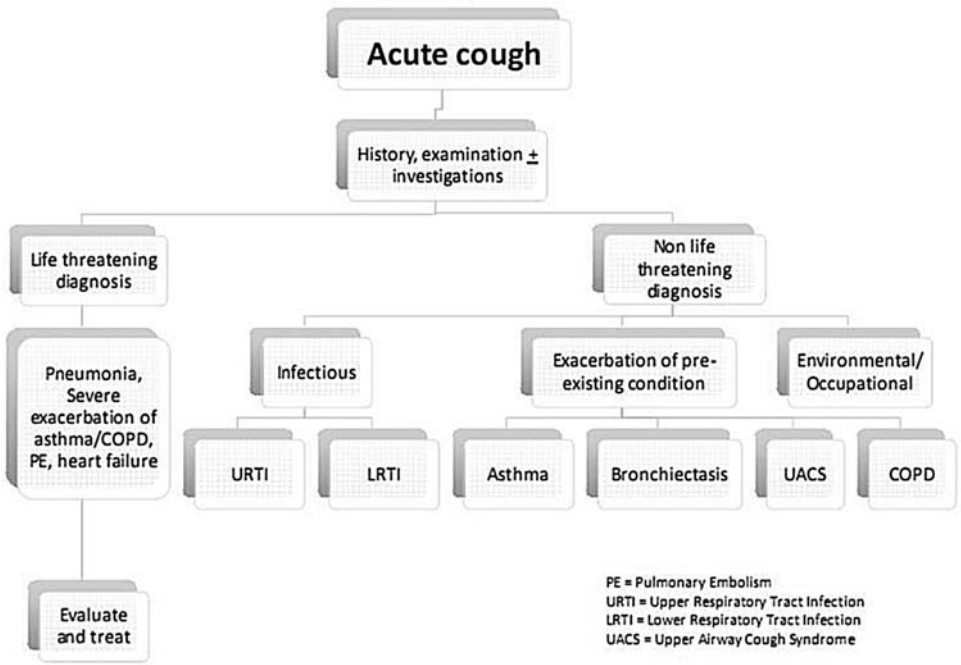

Fig. 1 A practical approach to this common problem. It is important not to miss a serious condition. Outlined is guidance for how to approach the vast majority of patients with common and mundane causes of acute cough, such as viral URTI

nonsteroidal anti-inflammatory drug, naproxen, favorably affects the cough of the common cold [22].

A number of other treatments are commonly used to treat the common cold. Topical α-adrenergic therapy can be used in the short term (e.g., 3–5 days), although no prospective data showing its efficacy are available. Prolonged use is not advised because of the risk of rhinitis medicamentosa. Zinc-containing lozenges abbreviated the symptoms of the common cold, including cough in one prospective study [23]. Two other studies and a meta-analysis, however, did not support the purported benefit of zinc in treating the common cold [24]. Because zinc-containing therapy is associated with a significant incidence of side effects, its use cannot be recommended [25]. Topical anticholinergic therapy has been shown in one prospective study to decrease rhinorrhea and sneezing in the common cold, but its efficacy on decreasing cough was not evaluated [26]. Interferon may decrease symptoms of the common cold, but only if used prophylactically. Further limiting interferon's value is the significant potential for side effects. [27]. Specific antiviral therapies for the common cold have shown some promise, but their efficacy is limited by the myriad of potential viral causes of the common cold and also by side effects [27].

Although there is limited clinical evidence to support their use for cough associated with the common cold, the expectorant Guaiphenesin, is found in a wide range of common cold medications, often in combination with an antitussive. Guaiphenesin can reduce the viscosity of respiratory tract mucus, which could increase the efficacy of the cough reflex and mucociliary clearance to clear secretions [28]. It is unclear, however, how this would decrease the cough of the common cold, which is predominantly an upper airway process. If the cough is due primarily to acute bronchitis then perhaps the effect on mucus and mucociliary function might be useful.

Opioids (e.g., codeine) are believed to inhibit cough primarily by their effect on the cough center. Because of the potential for abuse and addiction with opioids, non-opioid antitussives (e.g., dextromethorphan) may be preferred for the treatment of acute cough. They are widely available without prescription. A meta-analysis of six studies concluded that 30 mg of dextromethorphan, on average, reduced cough by 15% compared with placebo, but other studies have demonstrated that efficacy is at best marginally superior to placebo [29].

Benzonatate has an anesthetic action similar to that of benzocaine. This action is the rationale for its purported antitussive effect on peripheral cough receptors. Little evidence is available to support its use. In one study the effect of benzonatate did appear to be potentiated when combined with Guaiphenesin [30].

Acute bronchitis should be considered when the acute cough is productive or associated with LRT symptoms, including wheezing, shortness of breath, or chest tightness. The possibility that the symptoms are actually a result of viral-induced exacerbation of asthma must be considered. Because acute bronchitis is primarily a viral illness, routine treatment with antibiotics is not justified. Even when bacterial infection is suspected, antibiotics are still not recommended routinely because clinical trials suggest that antibiotics at best only modestly reduce the duration of symptoms. Specifically, a meta-analysis of eight trials of acute bronchitis suggested that the duration of symptoms was reduced by only a fraction of a day by the use of erythromycin, doxycycline, or trimethoprim–sulfamethoxazole [31]. Although the results were statistically significant, they appear clinically trivial. The 2006 ACCP guidelines on cough do not recommend the routine use of antibiotics to treat acute bronchitis [18].

A difficult issue is whether physicians can reliably recognize the occasional patient with acute cough due to a cause (e.g., *Bordetella pertussis*, *Mycoplasma*, or chlamydia) that will respond to early antibiotic therapy. Certainly if one suspects *Bordetella pertussis* the prompt institution of an antibiotic seems to be appropriate. Both the ACCP guidelines [18] and those of the Centers for Disease Control and Prevention (CDC) recommend macrolides as first-line therapy for pertussis [32]. According to the 2006 ACCP guideline, antitussive agents are only occasionally useful and the routine use of inhaled bronchodilators or mucolytic agents is not indicated [18]. When a patient has evidence of airflow obstruction or wheezing, β2 agonists can be helpful. The routine use of inhaled anticholinergics is not recommended [33].

In its January 2006 publication, the CDC did recommend that for suspected influenza A infection that antiviral therapy with oseltamivir or zanamivir is appropriate. The current concern about H1N1 "Swine Flu" serves to heighten the importance of this recommendation in cases of suspected influenza A infection especially if associated with significant respiratory symptoms. In contrast, based on evidence that many strains of influenza A virus are resistant to both amantadine and rimantadine these drugs are not recommended [34].

If the cause of acute cough is related to irritant or allergic exposures, then eliminating or avoiding the causative agents would make logical sense. Despite a lack of published data, the use of second-generation antihistamines, nasal steroid preparations, or leukotriene inhibitors would appear to make sense in this setting.

Conclusions

Acute cough is most commonly caused by a viral URTI (i.e., the common cold). PND was postulated to be the main mechanism involved, but based on the 2006 ACCP guidelines, direct irritation and inflammation of upper airway structures is a plausible alternative causative factor. Therefore, upper airway cough syndrome (UACS) is now the recommended term to describe most upper airway causes of cough [18].

Although acute cough is by definition transient and self-limited, it is one of the most common reasons that patients seek medical attention. Despite the fact that most of the time it will be due to a viral etiology, patients often request and physicians often inappropriately prescribe antibiotics. There are a number of OTC medicines purported to be useful for treatment of the symptoms of the common cold despite the lack of convincing evidence for efficacy. The best evidence for treatment of cough associated with the common cold is the use of a combination first-generation antihistamine and an effective decongestant (i.e., pseudoephedrine). This is not to imply that every patient with an acute cough related to the common cold requires treatment. Typically, the common cold is a self-limited illness and the potential for side effects from first-generation antihistamines and oral decongestants must be weighed against the moderate efficacy of the treatment.

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