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Abstract (200 words)

Terminology used to define clinical cough is based on features such as duration, underlying causes and associated characteristics such as whether the cough is ‘dry’ or ‘productive’. Terms such as ‘Refractory Chronic Cough’, ‘Unexplained Chronic Cough’ and ‘Idiopathic Cough’ are commonly used to describe a cough that persists despite extensive investigation and therapeutic trials. The use of these terms, sometimes interchangeably, has led to a degree of confusion and with the emergence of the new clinical and mechanisitic concept associated with cough, ‘cough hypersensitivity syndrome’, there is a need for some clarity in the nomenclature used to describe this condition.

Introduction

Cough is a sufficiently troublesome clinical problem that frequentlyleads people to seek medical care, (1-4). Cough is also one of the most common symptoms presenting to respiratory physicians (5). There are a large variety of terms in clinical use to describe cough. , Historically, these have been based on symptom duration, characteristics of the cough in particular whether ‘dry’ or ‘wet’/‘productive’ and the underlying cause such as ‘asthmatic’ ‘rhinitic’ or ‘reflux’ cough. In circumstances when cough persists despite exhaustive investigation and trials of treatment, terms such as ‘idiopathic’, ‘refractory’ and ‘unexplained’ cough have been used. In light of recent international consensus on the term ‘cough hypersensitivity syndrome’, improved mechanistic understanding of cough and the emergence of novel treatments, this article aims to provide a brief review of current terms and their clinical utility.

1. What is cough?

Under normal physiological circumstances cough serves to protect the lung from inhalation of noxious agents and clear the airway of unwanted secretions. The pioneering experimental observations made in the 1950's by John Widdicome undertaking single fibre recording of the vagus nerve in response to mechanical probing and chemical stimulation of animal airways contributed much to what we now know regarding the neurophysiology of cough. A fundamental feature of cough is that it represents a temporary reconfiguration in the normal pattern of breathing, and in its purest form is defined as a triphasic event; an inspiratory effort (inspiratory phase), followed by a forced expiratory effort against a closed glottis (compressive phase) followed by opening of the glottis and a rapid expiratory airflow (expulsive phase) (6). Some have sought to distinguish this from other protective reflexes such as an 'expiratory reflex' elicited following stimulation of the larynx or trachea and characterized by an expulsive effort without a preceding inspiration (7). Over the years, issues such as developing a universally acceptable definition of cough, determining whether different types of cough exist and whether to distinguish single cough events within a 'peel' of multiple coughs have generated debate and confusion in equal measure (8). We suggest that such debate is prone to semantics and that our attention should focus on defining and measuring cough in a clinically valuable manner.

2. Clinical terms

Table 1: Clinical terms for cough

Term	**Frequency of use***

Chronic cough	947
Dry cough	518
Productive cough	463
Persistent cough	236
Acute cough	115
Cough hypersensitivity	74
Refractory cough	32
Unexplained cough	22
Idiopathic cough	17
Subacute	16
Laryngeal hypersensitivity	15
Disease associated: Lung disease- URTI-, exercise-, pertussis-, reflux-, asthma-, swallow-, pulmonary fibrosis- associated cough	10

** Number of published articles retrieved using Pubmed search with cough term in the title and/or abstract, or article keywords from Jan 1st 2014 to Dec 4th 2018 inclusive*

Cough as a medical problem can be assessed by its duration, characteristics, severity, aetiology, pathophysiology, or treatment response. We undertook a short survey of published literature terms for articles describing cough and the variety of terms used. Those terms related to cough duration and cough characteristics were most frequent used (Table 1). Cough duration was described as chronic, persistent, acute, or subacute in 53% of articles identified.

The next most frequent category of descriptors related to cough characteristics, such as dry or productive cough, which was used in 40% of articles.

Cough that persists despite investigation and treatment is a particular problem for patients and clinicians. This condition is referred to by several different names, such as refractory cough (1.3%), unexplained cough (0.9%), or idiopathic cough (0.7%) which together comprise 2.9% of cough terms used in recent literature.

New concepts are now appearing in the literature to describe cough, such as cough hypersensitivity (3%) and laryngeal hypersensitivity (0.6%) (Figure 1). These terms are important because they are proposed to address some of the limitations of the unexplained/refractory cough terms, and to better describe the underlying pathophysiology in chronic cough. The authors believe the term ‘Cough Hypersensitivity Syndrome’ (CHS) as first proposed by a European Respiratory Society Task Force has clinical utility as it emphasises a particular pathophysiology as a key feature, namely, cough reflex hypersensitivity, and reflects the symptom profile described by many patients.

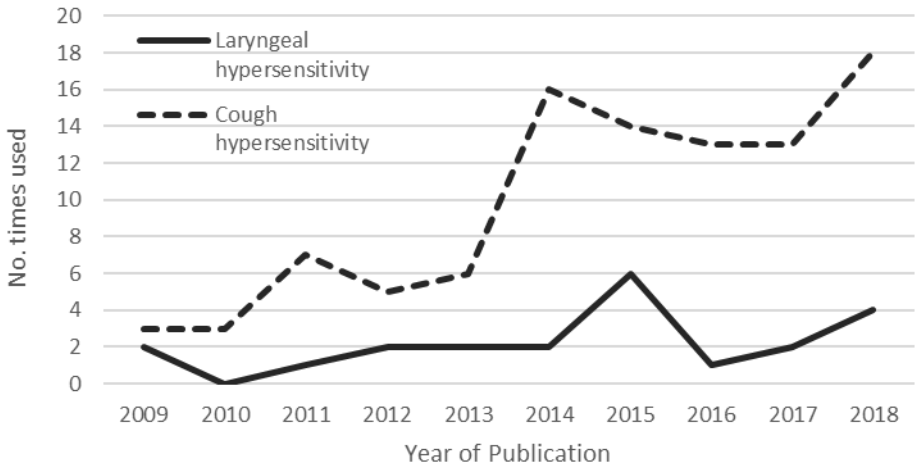

Figure 1: Use of terms 'cough sensitivity' and 'laryngeal sensitivity' in the last 10 years Number of published articles retrieved using Pubmed search with term in the title and/or abstract, or article keywords from Jan 1st 2009 to Dec 4th 2018 inclusive.

What terms are useful to clinicians?

Cough duration

- Irwin et. al (12) performed a systematic review of the usefulness of cough classification by duration. While the evidence quality was low, the authors found that classifying cough by duration (acute, subacute, chronic) appeared to be useful in diagnosing and guiding treatment in patients with cough, and that this classification could be applied globally. They proposed that: **'**For adult patients around the globe complaining of cough, we suggest that the cough be managed using evidence-based guidelines that are based upon duration of cough';*Acute cough* is defined as <3 weeks duration
- *Subacute cough* is defined as 3-8 weeks duration
- *Chronic cough* is defined as >8 weeks duration

Cough characteristics

Classification by cough characteristics, i.e. productive, wet, or dry, has given mixed results. A systematic assessment of cough characteristics was not found to add value to determining an aetiological diagnosis in adults (13). This contrasts to cough in children where the cough characteristics form a major classification and aid a diagnosis of protracted bacterial bronchitis (PBB) which is one of the main causes of subacute and chronic cough in children (14).

Idiopathic, unexplained, and refractory chronic cough

A clinically significant chronic cough that persists despite appropriate investigation and treatment, can occur under several different circumstances. The terms idiopathic chronic cough (ICC), unexplained chronic cough (UCC), and refractory chronic cough (RCC) each describe a nonresponsive condition, but we suggest these terms should not be used interchangeably. RCC relates to a cough which persists despite optimal treatment for the presumed associated common and uncommon condition(s) according to published best practice guidelines in an adherent patient. UCC refers the circumstances where no diagnosable cause for cough has been found (despite extensive assessment for common and uncommon causes). Although the term ICC is still in current use, UCC is now preferred as the diagnostic term to describe cough that remains unresolved after a thorough diagnostic and treatment approach (15)

Therefore, when using the terms UCCor ICC, important considerations relating to intervention fidelity should be made . Intervention fidelity refers to ‘the extent to which an intervention was delivered as conceived and planned—to arrive at valid conclusions concerning its effectiveness in achieving the target outcomes’ (16,17) . If a person has had an

incomplete diagnostic work-up then they may appear to have UCC/ICC but in reality the cause of their cough has not been adequately assessed or diagnosed.

New treatment options are now available that result in significant improvements in both cough frequency and quality of life for patients with UCC or ICC . These treatments include neuromodulators (gabapentin, pregabalin, morphine), speech pathology management, and P2X3 antagonists. Since patients previously considered to have RCC respond to these treatments, the term 'refractory' is no longer appropriate for these patients. We are of the opinion that CHS as a concept underpinning cough, whether explained, unexplained or refractory, is likely to be a central to the new direction that clinical assessment, scientific discovery and drug development in this field will take.

3. New directions

Recent advances in neurobiology have improved our understanding of clinical cough and current thinking is that an inflammation-induced injurious effect (neuro-inflammation) of the neural pathways (in the airway and the brain) leads to a state of sensitization (10). This has promoted the concept that chronic cough reflects a cough hypersensitivity syndrome (CHS) defined as, '…*a clinical syndrome characterised by troublesome coughing often triggered by low levels of thermal, mechanical, or chemical exposure*' (11). Clinically, this is manifest by triggering of cough by seemingly innocuous stimuli such as changes in ambient temperature, taking a deep breath, laughing, talking on the phone and exposure to aerosols, perfumes or eating crumbly dry food (termed allotussia), and triggering of cough by low level exposure to cough stimuli (termed hypertussia) . This is also often accompanied by a persistent urge-to-cough, a distinct and often debilitating sensation of airway irritation or 'itch' which is not satiated by the act of coughing (termed laryngeal paraesthesia). CHS is remarkably similar in

presentation to some of the chronic pain syndromes also characterised by heightened perception of pain and discomfort to relatively innocuous or mildly irritating stimuli, and the specific naming of the symptoms of CHS can facilitate this recognition. Work is ongoing to identify the factors that establish and maintain this hypersensitive state so that new effective antitussive therapies may be developed.

Is chronic cough a disease?

Whether chronic cough as a clinical problem, as distinct from cough as a symptom, is a disease in its own right is a topic of regular debate. One definition of disease states that, 'disease is any deviation from or interruption of any body part, organ or system that is manifested by a characteristic set of symptoms or signs whose aetiology, pathology and prognosis may be known or unknown' (9). The proponents of such a notion argue that recognizing chronic cough as a distinct pathological state is important in raising the general awareness of the associated healthcare burden and encouraging the development of specific therapies. Counter arguments suggest the lack of a consistent evidence to support a pathological process underlying chronic cough weakens the case for chronic cough as a disease. From a personal perspective, the authors argue that because chronic cough represents a clinical state which deviates beyond the protective physiological role of cough, and for which associated pathological features (neural hypersensitivity) and accompanying symptomatology are recognized, then chronic cough could reasonably be considered as a disease entity. For the moment however, R05 is a specific ICD-10-CM code which is used to indicate 'cough' as a diagnosis for reimbursement and administrative purposes.

4. Implications for practice

What is a useful approach in clinical practice?

The initial clinical classification of cough in both adults and children, should be based on the duration of the symptom at the time the patient presents for assessment and management. These categories are acute cough (<3 weeks), generally the result of a viral upper respiratory tract infection associated with the common cold, subacute cough (3-8 weeks), likely due to a slowly resolving post-viral cough and chronic cough (>8 weeks). The next steps are then directed by relevant management guidelines and associated algorithms for investigation and management. The terms ICC/UCC/RCC are now imprecise because patients with these conditions may respond to newer therapeutic approaches. There is a need to use better terminology for this group of patients with chronic cough. The term CHS and its related symptom patterns (allotussia, hypertussia, paraesthesis) are emerging as potentially useful terms (see Table 2)

5. Optimising clinical trial design

Early phase clinical studies of novel antitussives have come with mixed success. While efficacy has been observed with gabapentin (18) and the blocker of the ATP receptor, P2X3 (19) trials of compounds that block TRPV1 (20) and TRPA1 (21) have been negative. This has raised two important issues; firstly, can we improve the predictive value of existing pre-clinical cough model systems and secondly, can we optimize clinical trial design. Study participants in the studies conducted to date were recruited from specialist cough centres, and reported cough lasting more than 12 months and after evaluation according to BTS/ACCP guidelines were considered to have a diagnosis of RCC or UCC. Additional eligibility criteria required participants to exceed minimum thresholds for objective (ambulatory cough) and/or subjective (visual analogue scales) measures of cough. While the early 'proof of concept' studies require a carefully characterized and homogeneous study population, there is a need for deeper understanding of the heterogeneity of chronic cough and CHS. Furthermore,

identifying the genetic and biological characteristics that define the subgroups of 'responsive' cough patients to novel anti-tussive therapies is important.

6. Conclusions

The significant clinical problem of chronic cough for both patients and clinicians is compounded by imprecise terminology. New developments in treatment options for patients with previously refractory symptoms offer an important opportunity to improve the management of this condition. Cough terminology needs to support the communication of both the clinical problem and the advances in understanding and therapy. The assessment of cough based on its duration is an important first step in clinical assessment. The incorporation of terms that describe CHS and its related symptoms offers a potentially useful approach to the new developments that are occurring in chronic cough.

Key words: cough

Abbreviations:

ACCP: American College of Chest Physicians, ATP: adenosine 5'-triphosphate , BTS: British Thoracic Society, CHS: cough hypersensitivity syndrome, ICC: idiopathic chronic cough, ICD, international classificantion of diseases, P2X3: purinergic receptor 2X ligand-gated ion channel 3, PBB: persistent bacterial bronchitis, RCC: refractory chronic cocugh, TRPA1: transient receptor potential ankyrin 1, TRPV1: transient receptor potential vanilloid 1, UCC: unexplained chronic cough, URTI: upper respiratory tract infection

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