# Review article: reflux in cough and airway disease

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## SUMMARY

Chronic cough was previously thought to be attributed to three main aetiologies; asthma, reflux and postnasal drip. There is little to differentiate these three different diagnoses in the patients with chronic cough in terms of histology, cytokine profile or clinical history. In fact, the uniform clinical history exhibited by patients with chronic cough points to a single aetiology – airway reflux. In support of this, a questionnaire has been developed which identifies key elements within the clinical history which is answered positively by the overwhelming majority of patients presenting to a cough clinic. A new technology, including airway pH and exhaled breath condensate pepsin levels provide supporting evidence for the hypothesis that chronic cough is really a single diagnosis which has been termed the cough hypersensitivity syndrome. The syndrome is not necessarily precipitated by acid reflux and therefore therapy is directed more at motility and inhibition of the hypersensitivity components of the syndrome. The application of these diagnostic methodologies to other airway diseases such as severe asthma and recurrent exacerbations of COPD has revealed that many of the features of the cough hypersensitivity syndrome are also present in these conditions.

## INTRODUCTION

Numerous reports in the 1980s and 1990s examined the profile of patients presenting with chronic cough, which is arbitrarily defined as cough lasting greater than 8 weeks.[1] These studies identified three common causes for chronic cough, asthma, postnasal drip syndrome (PNDS), more latterly called the Upper Airways Cough Syndrome and gastro-oesophageal reflux disease (GERD). The paradigm was applied around the world in clinics treating patients with cough. However, some patients steadfastly refused to be pigeonholed into one of these diagnostic categories and were labelled idiopathic cough.[2]

In the Hull Cough Clinic, we adopted a similar paradigm and developed a probabilistic based paradigm of therapeutic trials aimed at discovering the underlying cause of the cough.[3] It became increasingly apparent, however, that none of the diagnostic categories claimed in the original studies were well supported by the clinical observations in individual patient groups. Repeated attempts via histological examination,[4] or the detection of inflammatory markers and mediators[5, 6] were unsuccessful in differentiating objectively these diagnostic categories. The asthmatic cough was strikingly different from classic atopic asthma, with an onset of middle age often without obvious atopy and sometimes even without bronchoconstriction.[7] Here the term cough variant asthma was coined to describe patients with chronic cough and bronchial hyperresponsiveness but without overt bronchoconstriction. Sputum eosinophilia was present. In a further variation even bronchial hyperresponsiveness was dropped from the classification and chronic cough with sputum eosinophilia described.[8] This form of airway TH2 response was termed eosinophilic bronchitis, which in the eyes of enthusiasts became a separate condition. The 'disease' of postnasal drip syndrome has never found much credence in Europe. It was

chiefly a diagnosis found in the Americas. As far back as the 1800s, an English surgeon reported that on his visit to the United States he had come across a new condition – PNDS.[9] In the ACCP guidelines on chronic cough, it is defined by response to therapy with first generation antihistamines.[10] There are no objective tests to describe the syndrome. Reliance on therapeutic response to define a particular condition is at best risky and open to the problems associated with the use of old fashioned drugs developed with a multitude of activities. More recently the drug most frequently used in the treatment of PNDS in the Americas – dexbrompheniramine has been shown to be an antagonist of the capsaicin cough receptor, TRPV1.[11] Thus, while there is no doubt that patients with chronic cough can present with predominantly nasal and upper airway symptoms the response to a therapeutic agent cannot be said to define a particular syndrome, and PNDS is really a symptom which is a facet of a larger overall pathological process.[12.]

The final diagnosis within the 20th Century triad of chronic cough was reflux disease. Unfortunately, the term GERD had been commandeered by the gastroenterologists to describe the dyspeptic symptoms of heartburn and indigestion. Here acid is the predominant player in the evolution of the condition.[13] When close associations were sought between chronic cough and GERD, while there were correlations they were insufficient to prove causality.[14] This was because whilst acid is undoubtedly the major pathogenic factor in heartburn, non-acid reflux is the major precipitant of the symptoms associated with airway reflux.[15] Before this was realised, patients would be sent for conventional 24 h oesophageal pH assessment which clearly delineates heartburn-associated GERD. The report would read that there was no evidence of reflux. In fact, the true report should have read there was no evidence of liquid acid reflux.

It was thus by applying an unsatisfactory series of existing paradigms to the diagnosis of chronic cough that

HULL COUGH HYPERSENSITIVITY QUESTIONNAIRE

Name: _____

D.O.B:_____ UN:_____

DATE OF TEST:_____

Please circle the most appropriate response for each question

| Within the last MONTH, how did the following problems affect you? 0 = no problem and 5 = severe/frequent problem | | | | | | |
|---|---|---|---|---|---|---|
| Hoarseness or a problem with your voice | 0 | 1 | 2 | 3 | 4 | 5 |
| Clearing your throat | 0 | 1 | 2 | 3 | 4 | 5 |
| The feeling of something dripping down the back of your nose or throat | 0 | 1 | 2 | 3 | 4 | 5 |
| Retching or vomiting when you cough | 0 | 1 | 2 | 3 | 4 | 5 |
| Cough on first lying down or bending over | 0 | 1 | 2 | 3 | 4 | 5 |
| Chest tightness or wheeze when coughing | 0 | 1 | 2 | 3 | 4 | 5 |
| Heartburn, indigestion, stomach acid coming up (or do you take medications for this, if yes score 5) | 0 | 1 | 2 | 3 | 4 | 5 |
| A tickle in your throat, or a lump in your throat | 0 | 1 | 2 | 3 | 4 | 5 |
| Cough with eating (during or soon after meals) | 0 | 1 | 2 | 3 | 4 | 5 |
| Cough with certain foods | 0 | 1 | 2 | 3 | 4 | 5 |
| Cough when you get out of bed in the morning | 0 | 1 | 2 | 3 | 4 | 5 |
| Cough brought on by singing or speaking (for example, on the telephone) | 0 | 1 | 2 | 3 | 4 | 5 |
| Coughing more when awake rather than asleep | 0 | 1 | 2 | 3 | 4 | 5 |
| A strange taste in your mouth | 0 | 1 | 2 | 3 | 4 | 5 |

**Figure 18** | Hull cough hypersensitivity questionnaire.

three separate 'diseases' were invented to describe the syndrome and those patients not fitting into these boxes were then assigned as idiopathic. In truth, the overwhelming majority of patients with chronic cough present with a remarkably uniform history, elements of which clearly and undoubtedly point to the origin in reflux disease.[16]

## Cough hypersensitivity syndrome

Patients with chronic cough give a remarkably uniform clinical history. This story has two components. Firstly, the precipitants of airway reflux, which is probably gaseous and mildly acidic in nature, give striking clues to the clinician. For example, patients not infrequently complain of cough after meals. This postprandial paroxysm of coughing typically occurs 10 min after the meal.[16] This of course is the peak time for lower oesophageal sphincter opening,[17] allowing the air swallowed during eating to be belched up. There is no heartburn as the food has neutralised gastric acid.

The second component of the syndrome is the consequence of the reflux, which leads to hypersensitivity of the irritant receptors on upper airway nerves. These nociceptors are mainly of the transient receptor potential (TRP) family.[18] While there are twenty-seven different TRP receptors described fortunately those of interest within the cough sphere are temperature receptors and, in particular, TRPV1, TRPA1 and TRPM8. These temperature receptors are promiscuous in binding to a wide range of environmental stimuli and provide the defence against the inhalation of noxious physical and chemical stimuli. In chronic cough (and probably in acute viral respiratory tract infection cough), these receptors are upregulated and increased in number.[19, 20] Thus, the patient with a chronic cough will complain of paroxysms induced by exposure to noxious chemical stimuli, including smoke (acreolin), or a change in atmospheric temperature (TRPV1 and TRPA1). These responses have previously been dismissed as nonspecific whereas in fact they represent specific adaption with increased nocoception in response to the challenge of airway reflux.


**Figure 19** | Demonstration of grossly abnormal episodes of airway pH in patient with severe asthma. The trace shows repeated falls in pH indicating episodes of gaseous acid reflux into the pharynx.

### The diagnosis of reflux cough

There is no readily available objective test which indicates the presence of airway reflux. The clinical history, however, has been codified into a fourteen point questionnaire, which has recently been validated[21] (Figure 18). Each question independently tests for the cough hypersensitivity syndrome and the upper limit of normal is 13 out of 70. Perhaps the greatest utility of the questionnaire is that it directs the questioning into aspects of the history which are unequivocally reflux associated with components of the non-acid reflux nature, such as the dysmotility associated with vomiting and retching and the repetitive throat clearances.

### New technologies for the diagnosis of airway reflux

Recently combined multichannel intraluminal impedance and pH testing (MII-pH) has been used to determine the role of reflux in patients presenting with chronic cough.

Multichannel intraluminal impedance-pH is extensively described by Arevelo, Sharma and Castell in their paper on Symptomatic Non-acid Reflux: The New Frontier in GERD in this supplement.

Two more recent modalities of examination of airway reflux have been developed. Firstly, the sampling of pharyngeal airway pH maybe undertaken by the Restech probe, which has been specifically designed to sit at the back of the pharynx and sample gaseous pH.[22] Thus, the gaseous belch responsible for airway reflux can be detected. However, many of these belches are of a neutral or mildly acid nature. None the less valuable information can be obtained proving airway reflux which had previously been misdiagnosed as other airway conditions. For example, in Figure 19 grossly abnormal episodes of airway pH are demonstrated in a female with severe 'asthma' who had multiple ITU admissions before curative fundoplication. The second modality is the estimation of airway pepsin using exhaled breath condensate. Previous methods for collecting exhaled breath condensate relied on laboratory based technologies. A recent development has been a device for the patient to take home and collect samples during attacks.[23] Here the presence of pepsin within the exhaled breath is indicative of a reflux during coughing, asthma or acute exacerbations of COPD.

### Airway reflux in other respiratory conditions

Many other respiratory conditions are misdiagnosed because airway reflux is not widely recognised. In asthma, a TH2 response maybe precipitated by the aspiration of airway reflux. This maybe a TH1 response with wheezing and neutrophils but often a TH2, eosinophilic led response occurs which mimics classic asthma.[24] Late onset asthma, i.e. asthma presenting in the 40s and 50s is often described as intrinsic asthma, because it was clearly differentiated by the early physicians from extrinsic allergic asthma. However, patients with this form of asthma, which is often resistant to conventional treatment, answer highly to the cough hypersensitivity questionnaire and fundoplication can lead to significant improvements.

In numeric terms, viral infections are clearly the most common cause of exacerbations of COPD, but in those patients who are 'frequent flyers', i.e. those patients with multiple admissions in a short period of time an alternative aetiology must be evident. Classic GERD is highly associated with COPD exacerbations.[25] We have recently surveyed our frequent flyers at Castle Hill Hospital and find that a highly abnormal score on the cough hypersensitivity questionnaire is the norm. We believe that these patients represent COPD patients with additional airway reflux. Finally, those patients with bronchiectasis, cystic fibrosis, lung transplantation rejection and fibrosing alveolitis also respond highly to questionnaires and associations with GERD have been reported.[26–28] So, airway reflux may not only be responsible for chronic cough but is a precipitating factor in a spectrum of respiratory disease, which was previously thought to be idiopathic in nature.

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