# Chronic Cough 1

## Prevalence, pathogenesis, and causes of chronic cough

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This is the first in a **Series** of two papers about chronic cough

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**Cough is a reflex action of the respiratory tract that is used to clear the upper airways. Chronic cough lasting for more than 8 weeks is common in the community. The causes include cigarette smoking, exposure to cigarette smoke, and exposure to environmental pollution, especially particulates. Diseases causing chronic cough include asthma, eosinophilic bronchitis, gastro-oesophageal reflux disease, postnasal drip syndrome or rhinosinusitis, chronic obstructive pulmonary disease, pulmonary fibrosis, and bronchiectasis. 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 idiopathic cough. Chronic cough is often associated with an increased response to tussive agents such as capsaicin. Plastic changes in intrinsic and synaptic excitability in the brainstem, spine, or airway nerves can enhance the cough reflex, and can persist in the absence of the initiating cough event. Structural and inflammatory airway mucosal changes in non-asthmatic chronic cough could represent the cause or the traumatic response to repetitive coughing. Effective control of cough requires not only controlling the disease causing the cough but also desensitisation of cough pathways.**

### Introduction

Cough is recognised as a defence reflex mechanism, with three phases: (1) an inspiratory phase; (2) a forced expiratory effort against a closed glottis; (3) opening of the glottis, with subsequent rapid expiration, that generates a characteristic cough sound. Physiologists make the important distinction between cough and the closely related defence expiratory reflex, which does not result in a cough.[1] A cough sound allows the clinician to distinguish cough from other symptoms, such as throat-clearing and sneezing; cough usually presents with a series of coughs known as a cough bout. Cough clears the larynx, trachea, and large bronchi of secretions such as mucus, noxious substances, foreign particles, and infectious organisms. Almost everybody has had cough after a common cold, which typically lasts 1–3 weeks. The protective nature of cough is well illustrated by the complications of cough suppression after general anaesthesia, which include retention of airway secretions, and infections. Cough can also be a warning sign of disease, and can cause the patient to seek medical attention, leading to diagnosis. When cough is excessive and chronic, it can be detrimental to the patient with complications such as vomiting, rib fractures, urinary incontinence, syncope, muscle pain, tiredness, and depression.

This Series will focus on chronic cough in adults, which is defined as cough that has lasted for at least 8 weeks, since such cough can present difficulties in diagnosis and management. The second part of this Series will cover management aspects of chronic cough. Previous reviews and guidelines were aimed mainly at the specialist;[2–4] however, this Series provides an up-to-date review not only for the specialist, but also for the non-specialist.

#### Search strategy and selection criteria

We did a detailed appraisal of peer-reviewed publications over the past 10 years with the NCBI PubMed website for English language publications with the keywords: "Cough", in combination with "treatment", "asthma", "postnasal drip", "eosinophilic bronchitis", "gastro-oesophageal reflux", "cigarette smoking", "guidelines", "prevalence", and "infections". We also had source publications that we have accumulated because of our association with cough treatment and research in the past 15 years. Review articles and book chapters are cited to provide readers with more details and more references than this review.

### Pathogenesis

Figure 1 shows the anatomy of cough pathways, and figure 2 the regulation and physiology of the enhanced cough reflex. A cough reflex can be triggered by several inflammatory or mechanical changes in the airways, and by inhalation of chemical and mechanical irritants, usually from upper airway sites, especially the larynx, the carina, and other points where the proximal airways branch.[5,6] Sensory nerve receptors responding to these stimuli are defined by their conductive properties as rapidly adapting receptors (RARs),[6–8] slowly adapting receptors (SARs),[9] or C-fibre receptors. RARs are stimulated by cigarette smoke, acidic and alkaline solutions, hypotonic and hypertonic saline, mechanical stimulation, pulmonary congestion, atelectasis, bronchoconstriction, and reduction in lung compliance—all of which can cause cough. C-fibre receptors are highly sensitive to chemicals such as bradykinin (a mediator released during inflammation), capsaicin (a vanilloid extract of peppers), and hydrogen ions (acid pH), and are often referred to as chemosensors.[10,11] Studies in the guineapig, which can cough (ie, produce a coughing sound), point to the presence of a cough receptor that is distinct from RARs or C-fibres;[12] although insensitive to capsaicin and bradykinin, these cough receptors respond to mechanical and acid stimuli that could be caused by inhaled particles or gastric acid reflux.[6] These cough receptors in guineapigs are located in the epithelial and subepithelial layer of the mucosa and interact with RARs and C-fibres to form a complex of cough sensors in the airways.

Cough receptors have mechanically gated ion channels, such as sodium channels; acid stimuli can interact with

voltage-gated sodium channels, which belong to the acid-sensing ion channel family.[13] A cationic ion channel—the transient receptor potential vanilloid-1 (TRPV-1) channel—seen on RARs and C-fibres, is the receptor for capsaicin, and is activated by heat, acid, bradykinin, arachidonic-acid derivatives, and adenosine triphosphate.[14] The TRPV-1 channel has been localised to epithelial nerves in human airways; its expression is increased in patients with chronic cough.[15] TRPV-1 inhibitors suppress the tussive response caused by allergen challenge in a sensitised guineapig model,[16] raising the possibility that they could act as antitussives. Bradykinin and prostaglandin E2 and F2α increase the tussive response to capsaicin,[17–19] by acting on specific voltage-gated sodium channels.[20,21]

Afferent fibres from cough receptors in the airways converge via the vagus nerves on brainstem sites in the nucleus tractus solitarius. The nucleus tractus solitarius is connected to respiratory-related neurons in the central respiratory generator, which coordinate the efferent cough response.[22] These respiratory neurons are frequently referred to as the cough centre or as a central cough generator (figures 1 and 2). C-fibre activation interacts centrally with activation of RARs or other afferent nerves such as SARs to promote coughing. Sensitisation of the cough reflex can also arise in brainstem neurons. Cough can be controlled via higher cortical centres,[23] so we can voluntarily inhibit or produce a cough.[24] The profound effect of placebo treatments in inhibiting cough might be related to the modulation of cortical control.[25] During sleep, chronic cough is suppressed to a large extent.[26–28] On functional MRI, the urge to cough evoked by inhalation of capsaicin was associated with activation of many areas of the cerebral cortex, including the insular cortex, anterior cingulate cortex, primary sensory cortex, and cerebellum, demonstrating cortical influences on cough.[29]

Patients with chronic cough were found to have an increased number of coughs to inhaled stimuli, such as citric acid or capsaicin, compared with non-coughers[30]—a cough hypersensitive response that could result from either an increased sensitivity of cough receptors (peripheral sensitisation) or from changes in central processing, brainstem (central sensitisation) (figure 2). Sensitisation includes changes in the release of neurotransmitters or neuromodulators, excitability of the postsynaptic neuron, and the structure of the nerve.[31] A guineapig model[32,33] of exposure to second-hand tobacco smoke showed that increased activity (ie, neuroplasticity) of neurons in the nucleus tractus solitarius underlies enhanced cough response, which was associated with the release of substance P in the brainstem. Under normal conditions, mechanical deformation of the cough receptor leads to a protective cough reflex, but irritation or inflammation causes neuroplastic changes, and the cough receptor could become sensitive to stimuli that it does not usually respond to or become hypersensitive to other tussive stimuli.

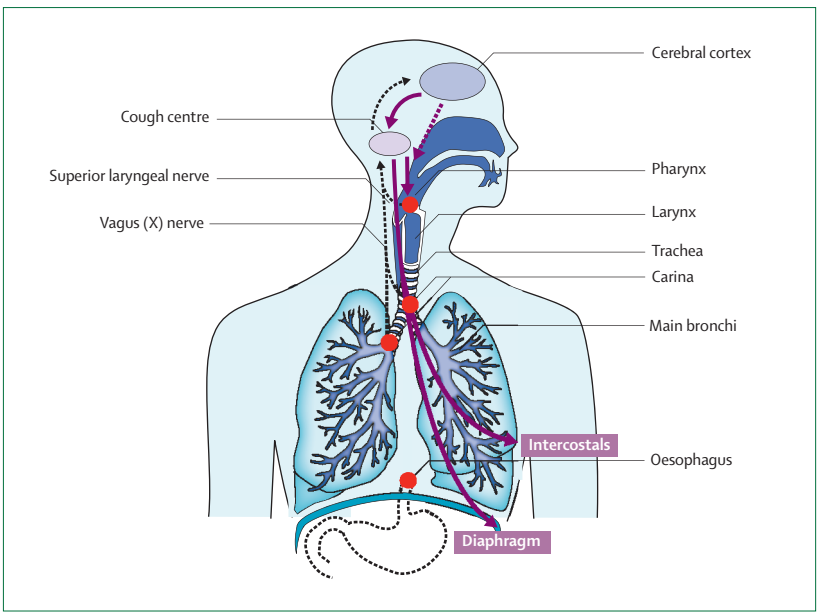


***Figure 1:*** **Anatomical representation of neural pathways for cough**
Cough receptors (shown in red colour) at the airway bifurcations, in the larynx and at the distal oesophagus, link to cough afferents through the vagus and superior laryngeal nerves to the cough centre and cerebral cortex. Efferent pathways coordinate the muscle response that leads to a cough.

## Prevalence

The prevalence of cough in many communities in Europe and the USA reported through questionnaire surveys is 9–33% of the population, including young children (table 1).[34–44] Chronic cough is often related to cigarette smoking.[34,36,39,40] Chronic smokers have a prevalence of chronic cough three times as high as people who have never smoked, or as ex-smokers.[44] Investigators have also noted associations with asthma, respiratory wheezing, and symptoms of gastro-oesophageal reflux.[36,38,39,41,42] Exposure to tobacco smoke in the home is a risk factor for chronic cough in school-children.[45–48] Productive cough and chronic, nocturnal dry cough are associated, in adults and schoolchildren, with exposure to environmental pollutants, especially PM10 particulates.[44–51] Bayer-Oglesby and co-workers[52] noted the reduction of cough prevalence in Swiss cities where PM10 concentrations had fallen. Increases in PM10 concentrations have been related to reductions in peak expiratory flow, and to increased reports of cough, sputum production, and sore throat in children.[53] Increasing nitrogen dioxide amounts have also been associated with rising prevalence of chronic cough.[44,50]

Cough can be the first indication of serious pulmonary or extrapulmonary pathological conditions; the differential diagnosis of cough includes infectious, inflammatory, and neoplastic conditions, and many pulmonary disorders (panel 1). The physician assessing a patient with chronic cough should aim to exclude serious conditions. The diagnostic approach to such patients is provided in the second part of this Series.

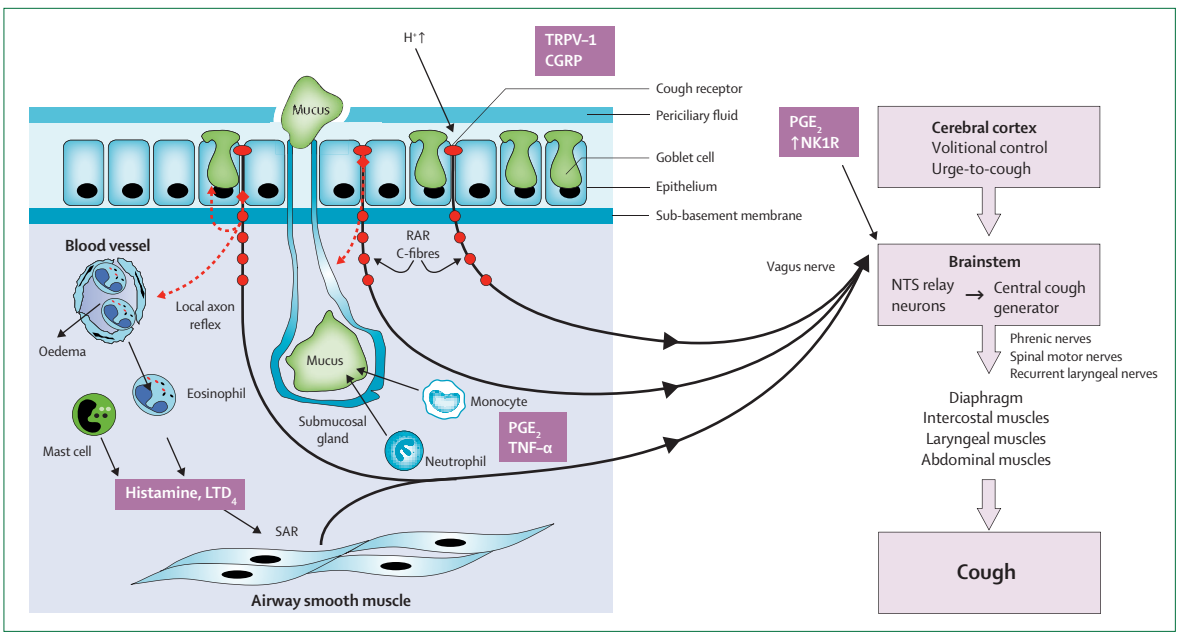


***Figure 2:*** **Representative scheme of afferent and efferent pathways that regulate cough, and of the pathophysiology of the enhanced cough reflex**
Laryngeal and pulmonary receptors, such as rapidly adapting receptors (RARs), C-fibres, and slowly adapting fibres (SAR), and cough receptors provide input to the brainstem medullary central cough generator through the intermediary relay neurons in the nucleus tractus solitarius (NTS). The central cough generator then establishes and coordinates the output to the muscles that cause cough. An output to airway smooth muscle and mucosal glands (not shown) is also present. The cerebral cortex can control the motor output of cough volitionally, or influence the urge-to-cough sensation. Factors that act in the upper airways or brainstem, to enhance the cough reflex, are illustrated. CGRP=calcitonin gene-related peptide. $LTD_4$=leukotriene D4. $PGE_2$=prostaglandin E. NK1=neulokinin-1. TRPV=transient receptor potential vanilloid. TNF=tumour necrosis factor.

Cough is one of the most frequent reasons for consultation with a family doctor, or with a general or respiratory physician. Patients with chronic cough probably account for 10–38% of respiratory outpatient practice in the USA.[54,55] Only a small part of the population identified in epidemiological surveys seek medical help or advice for their symptom. Many cigarette smokers have a chronic cough, but they rarely seek medical advice unless they notice a change in the pattern or intensity of their cough, that could suggest an infection or cancer.

Cough can be divided into acute self-limiting cough, lasting (by definition) less than 3 weeks, or chronic persistent cough, which usually lasts for more than 8 weeks. Some types of cough can last for an intermediate period of 3–8 weeks, which is called subacute cough. Acute cough is usually the result of an upper-respiratory-tract viral infection that clears within 2 weeks in two-thirds of people. Non-viral causes of acute cough include exacerbation of existing asthma, and exposure to environmental pollutants. In North America and Europe, the common conditions associated with chronic cough, with a normal chest radiograph, include corticosteroid-responsive eosinophilic airway diseases such as asthma, cough variant asthma, and eosinophilic bronchitis, and a range of conditions typically associated with cough resistant to inhaled corticosteroids; these conditions include gastro-oesophageal reflux disease (GORD), and the postnasal drip syndrome or rhinosinusitis (table 2). The frequency of these causes varies in different series, dependent on the location of the clinic and its particular interest, the age of the patient, and local definitions of diseases.[72] For example, atopic cough and sinobronchial disease is commonly diagnosed in Japan, whereas GORD is relatively uncommon.[73,74]

## Conditions associated with chronic cough

Chronic cough can arise in asthma in various clinical settings, and is not always associated with airflow obstruction, wheezing or dyspnoea. Asthma can predominantly present with cough, which is often nocturnal; the diagnosis is supported by the presence of bronchial hyper-responsiveness.[75] Elderly people with asthma can also present with a history of chronic cough, with little or no wheezing. Cough is often the symptom most reported by patients with chronic asthma, despite achieving good asthma control with inhaled corticosteroids.[76] Cough can be the first sign of worsening of asthma; doctors should look for a fall in early morning peak flows.

Three other related conditions have been described: cough-variant asthma, atopic cough, and eosinophilic bronchitis (table 3). Cough-variant asthma presents with a dry cough, often nocturnal, without other symptoms of asthma; it is characterised by bronchial hyper-responsiveness, and eosinophilic inflammation in sputum, bronchoalveolar lavage fluid, or airway submucosa.[77–80] Sub-basement membrane thickness is also increased, but less than in classic asthma.[81] Fujimura and colleagues[77,82,83] described atopic cough as an isolated

| | Cohort | Prevalence | Features |
|---|---|---|---|
| USA[34] | 1109 | 18% | Chronic cough related to smoking |
| Northern Sweden[35] | 6610 (Ages: 35–36, 50–51, 65–66 years) | 11% | 22% of people who coughed report sputum production |
| South-east England[36,37] | 9077 | 16% (13·2% produced sputum) | Cough everyday or half the days of the year. 68% of chronic sputum producers were associated with cigarette smoking |
| North England[38] | 4003 | 12% (severe in 7%) | Regurgitation and irritable bowel syndrome were strong predictors of coughing |
| Italy[39] | 18 000 (20–44 years) | 11·9% (similar sex prevalence) | Have you had cough and phlegm on most days for at least 3 months of the year and for at least 2 successive years? |
| USA (whites only)[40] | 5743 (>45 years) | 9·3% in those without airflow obstruction (8·3% with sputum) | Increasing prevalence with increasing airflow obstruction; 49% of patients with $FEV_1$<35% had a chronic cough |
| Europe (ECHRS)[41] | 18 277 (20–48 years) | 33%; 20% productive or non-productive cough in winter | Woken by attack of cough in past 12 months? |
| Sweden (part of ECHRS)[42] | 623 (Mean age: 31 years) | 11% non-productive cough; 8% productive; 38% with nocturnal cough | Non-productive cough associated with female sex and anxiety; productive cough with asthma, allergic rhinitis, gastro-oesophageal reflux, smoking, and anxiety |
| USA (Seattle)[43] | 2397 schoolchildren (11–15 years) | 7·2% | Chronic productive cough for at least 3 months per year. Associations with current asthma and environmental tobacco smoke exposure |
| Switzerland[44] | 9651 (3232 current smokers) 18–60 years | current smokers: 9·2%; never smokers: 3·3% | Prevalence of chronic cough and sputum greater in current smokers |

ECHRS=European Community Respiratory Health Survey. $FEV_1$=forced expiratory volume in 1 second. *These studies are published in English on the epidemiology of cough as a respiratory symptom in the general population.

***Table 1:*** **Prevalence of cough in the community by country***

chronic cough characterised by an atopic background, eosinophilia in sputum (but not in bronchoalveolar lavage), cough hypersensitivity, normal pulmonary function, and airway responsiveness. Whether these conditions represent variants of asthma, all characterised by eosinophilic inflammation of the airway is unclear.

The clinical condition of eosinophilic bronchitis is characterised by a troublesome cough without other symptoms of asthma or bronchial hyper-responsiveness, but with increased numbers of eosinophils in the sputum.[84] These patients also show a rise in capsaicin sensitivity, which becomes less pronounced with inhaled corticosteroid therapy.[85,86] Such patients could account for 10–15% of those with chronic cough attending respiratory clinics in the UK.[65] Pathological features of the airway submucosa are similar to those of asthma (table 3)[87,88] apart from an absence of mast cells within airway smooth-muscle cells in eosinophilic bronchitis.[89] However, mast cells are activated outside smooth-muscle cells, since sputum concentrations of prostaglandin D2 and histamine are increased in eosinophilic bronchitis.[90]

Cough can be stimulated by several mechanisms linked to the inflammatory process. Cough receptors in asthma can be triggered by constriction of bronchial smooth muscle, which is induced by the release of constrictor stimuli, such as histamine or sulphidopeptide leucotrienes. Asthmatic cough and cough-variant asthma are frequently helped by inhaled β2-adrenergic agonists. Inflammatory mediators, such as bradykinin, tachykinins, and prostaglandins, can also sensitise cough receptors in the airways.[17,18,91] Eosinophilic-associated cough is usually controlled by inhaled corticosteroids, implying a role for inflammatory factors. Although patients with classic asthma do not usually have an enhanced cough reflex, patients with cough-variant asthma might do so,[92] as do patients with eosinophilic bronchitis and atopic cough. Inflammatory cells, such as eosinophils, have been implicated, since corticosteroids reduce eosinophilic inflammation and also inhibit cough. A case-report of hypereosinophilic syndrome also supports a direct effect of eosinophils on the cough reflex.[93] This syndrome is caused by a fusion gene *FIP1*-like-platelet-derived growth factor receptorα that encodes a tyrosine kinase, and presents with chronic cough, which is controlled by a tyrosine-kinase inhibitor, imatinib. Sensitivity to capsaicin, in asthmatic patients who are allergic to birch pollen, increases during the birch pollen season,[94] suggesting that allergic

***Panel 1:*** **Causes of cough**

- Acute infections: tracheobronchitis, bronchopneumonia, viral pneumonia, acute-on-chronic bronchitis, pertussis
- Chronic infections: bronchiectasis, tuberculosis, cystic fibrosis
- Airway diseases: asthma, chronic bronchitis, chronic postnasal drip
- Parenchymal diseases: chronic interstitial lung fibrosis, emphysema, sarcoidosis
- Tumours: bronchogenic carcinoma, alveolar cell carcinoma, benign airway tumours, mediastinal tumours
- Foreign bodies
- Irritation of external auditory meatus
- Cardiovascular diseases: left ventricular failure, pulmonary infarction, aortic aneurysm
- Other diseases: reflux oesophagitis, recurrent aspiration, endobronchial sutures
- Drugs: angiotensin-converting enzyme inhibitors

| | Number (women) | Diagnosis | | | | |
|---|---|---|---|---|---|---|
| | | Asthma/CVA/EB/AC | GORD | PNDS | Idiopathic | Other |
| **USA** | | | | | | |
| Irwin[54] | 102 (59) | 24% | 21% | 41% | 1% | CB (5%) |
| Irwin [55] | 49 (27) | 43% | 10% | 47% | 0 | CB (7%) |
| Poe[56] | 139 (84) | 35% (mostly CVA) | 5% | 26% | 12% | CB (7%) |
| Pratter[57] | 45 (28) | 31% | 11% | 87% | 0 | Overlap of diagnosis with PNDS |
| Smyrnios[58] | 71 (32) | 24% | 15% | 40% | 3% | .. |
| Mello[59] | 88 (64) | 14% | 40% | 38% | 2% | .. |
| French[60] | 39 (32) | 15% | 36% | 40% | 2% | .. |
| Irwin[61] | 24 (13) | 21% | 33% (rhinitis included) | 33% (GORD included) | 46% | .. |
| **UK** | | | | | | |
| O'Connell[62] | 87 (63) | 10% | 32% | 34% | 27% | .. |
| McGarvey[63] | 43 (29) | 23% (CVA) | 19% | 21% | 19% | .. |
| Brightling[64] | 91 (NR) | 31% (EB 13%) | 8% | 24% | 7% | .. |
| Birring[65] | 236 (NR) | 24% | 15% | 12% | 26% | .. |
| Niimi[66] | 50 (39) | 26% | 10% | 17% | 40% | .. |
| Kastelik[67] | 131 (86) | 24% | 22% | 6% | 7% | Postviral (8%); bronchiectasis (8%); ILD 8% |
| **Japan** | | | | | | |
| Fujimura[68] | 176 (NR) | 66% (36% asthma; 29% atopic cough) | 2% | 0 | 12% | Sinobronchial disease in 17% |
| Shirahata[69] | 55 (NR) | 42% (CVA) | 0 | 7% | 13% | 31% improved on non-specific cough therapy |
| **Brazil** | | | | | | |
| Palombini[70] | 78 (51) | 59% | 41% | 58% | 0 | .. |
| **Australia** | | | | | | |
| Carney[71] | 30 (20) | 23% | 73% | 93% | .. | ACEI in 23%; overlap of diagnoses or symptoms |

ACEI=angiotensin-converting enzyme inhibitor. AC=atopic cough. CB=chronic bronchitis. CVA=cough-variant asthma. EB=eosinophilic bronchitis. GORD=gastro-oesophageal reflux disease. PNDS=postnasal drip syndrome or rhinosinusitis. ILD=interstitial lung disease. NR=not recorded.

***Table 2*: Associated causes of chronic cough in specialist respiratory clinics**

inflammation can trigger neurogenic mechanisms of sensitisation.

In gastro-oesophageal reflux, acid and other gastric contents move from the stomach, via the oesophagus, to the larynx and trachea, because of impaired function of the lower oesophageal sphincter.[95] GORD is commonly implicated as the cause of chronic cough, in all age groups. It is probably overdiagnosed, especially in children presenting with chronic cough; moreover, the link between acid reflux and cough is not always consistent. Typical symptoms of acid reflux, other than cough, are heartburn, chest pain, a sour taste, and regurgitation. There might be very few or even no symptoms associated with gastro-oesophageal reflux or impaired with clearance of gastro-oesophageal acid. Long-term exposure of the lower oesophagus to acid can lead to oesophagitis, oesophageal ulceration and stricture, and bleeding. Reflux of gastric contents to the larynx (laryngopharyngeal reflux) can cause reflux laryngitis with thickening, redness, and oedema of the posterior larynx.[96] The patient might report few symptoms of heartburn and regurgitation, but might present with throat-clearing, persistent cough, globus pharyngeus, and hoarseness.

Panel 2 shows the potential mechanisms of GORD-associated cough. Jack and co-workers[97] have recorded direct aspiration of gastric contents into the larynx and upper airways that could directly stimulate cough receptors and increase tracheal acidity during episodes of reflux. However, direct infusion of acid into the distal oesophagus of patients with chronic cough caused by GORD induces cough, which shows that acid can directly cause cough through an oesophageal-bronchial reflex;[98] lidocaine directly infused into the distal oesophagus reduced coughing, suggesting the presence of afferent receptors for the cough reflex in the distal oesophagus. In the same study, ipratropium bromide by the inhaled route, but not when directly infused into the oesophagus, blocked the acid-induced cough, indicating involvement of vagal cholinergic pathways.[98] The infusion of acid into the distal oesophagus of patients with GORD-associated cough does not always induce cough.[99] This finding could be related to the degree of oesophagitis associated with GORD or that acid is not the only cause of cough. Most coughs in this disease do not coincide with an acid reflux episode,[100,101] indicating that the direct effect of acid on putative oesophageal receptors to induce cough is not common. Patients with GORD often continue to cough despite the use of inhibitors of gastric acid secretion, such as proton-pump inhibitors,[102] which supports the possibility that substances such as bile, pepsin, and other gastric enzymes could induce cough. Antireflux surgery could help some of these patients.[103] The alternative possibility is that the link between GORD and chronic cough is weak.

Studies have reported the increased sensitivity of the tussive response to capsaicin in patients with GORD, whether or not they have a chronic cough.[62,104] Acid infusion into the distal oesophagus of patients with bronchial asthma led to an increase in capsaicin sensitivity, without changes in lung function.[105] Benini and colleagues[106] showed enhanced capsaicin sensitivity in patients with reflux oesophagitis, which improved after treatment with omeprazole, especially in patients who also had posterior laryngitis. Infusion of acid and pepsin into the lower oesophagus of the guineapig stimulates afferent pathways, which send signals to the brainstem nuclei, including the NTS, that in turn could activate cough efferent pathways.[107] Finally, a perpetuating cycle of cough has been proposed, since not only can gastro-oesophageal reflex precipitate cough, but cough caused by any cause can result in further reflux.[98]

Postnasal drip (also known as nasal catarrh or rhinosinusitis) is characterised by a sensation of nasal secretions or of a drip at the back of the throat, accompanied often by the frequent need to clear the throat (throat-clearing) and is associated with nasal discharge or nasal stuffiness. Studies have shown that between 6% and 87% of people attending hospital-based clinics with cough had rhinitis and postnasal drip syndrome (table 2).[108] The wide variation of such reporting could be related to the absence of agreed diagnostic criteria, and differences in the definitions of symptoms between countries. Pratter and co-workers[57] attributed cough to postnasal drip after treating chronic cough in patients with a combination of a first-generation antihistamine plus a decongestant such as pseudoephedrine, although the latest non-sedating antihistamines are regarded as less effective than previous formulations.[109] Some otorhinolaryngologists believe that cough is not a predominant symptom of patients with postnasal drip,[110] and that cough could be related to laryngopharyngeal reflux rather than to any postnasal problems. The term upper airway cough syndrome is proposed as an alternative, to emphasise the association of upper airway disease with cough.[111] The sinobronchial disease described in Japan encompasses chronic sinusitis and chronic neutrophilic inflammation of the lower airways, such as chronic bronchitis, bronchiectasis, and diffuse panbronchiolitis.[74] The pathogenesis of cough in postnasal drip syndrome can be related to direct pharyngeal, laryngeal, or sublaryngeal stimulation by mucoid secretions from the rhinosinuses; the secretions contain inflammatory mediators, which induce cough. Although laryngeal afferent nerves regulating cough are vagal in origin, it is less clear where pharyngeal afferent nerves arise from, but they could arise from glossopharyngeal nerves. The extrathoracic airway of patients with sinusitis seems to be hypersensitive and could be caused by reflexes arising from pharyngeal receptors.[112]

Cough is the most commonly reported symptom of chronic obstructive pulmonary disease (COPD), being present in 70% of patients, with 46% reporting daily symptoms.[113] Cigarette smoking is the most important risk factor for cough and sputum production.[39] COPD patients with airflow obstruction have a high risk of the development of chronic cough.[40] Chronic cough and sputum are independent predictors of COPD.[114] Patients cough very frequently when awake, with a frequency of 21 coughs per hour (range 10·1–59·9)[27] or with the number of seconds of cough per hour of 7·5 (range 2·7–23·1).[115] Capsaicin cough responsiveness is increased in COPD patients, and is independent of the amount of airflow obstruction.[92,116] A positive correlation between cough counts and the cough response to citric acid suggests that cough reflex sensitivity can be used as an indicator of the severity of cough. In severe airflow obstruction, the inability to produce a sufficiently large expiratory flow leads to ineffective clearing of mucus and secretions, which could trigger persistent ineffective coughing. Mucus retention in the small airways is favoured by impaired mucociliary clearance especially during infectious exacerbations.

Bronchiectasis cough is associated with excessive secretions from overproduction, together with reduced clearance of airway secretions. Usually, the patient produces about 30 mL or more of mucoid or mucopurulent sputum per day, sometimes accompanied by fever, haemoptysis, and weight loss. Cough can be the only presenting symptom. Bronchiectasis can be associated with postnasal drip and rhinosinusitis, asthma, GORD, and chronic bronchitis. Common pathogens cultured from sputum include *Haemophilus influenzae*, *Staphyloccocus aureus*, and *Pseudomonas aeruginosa*. The chest radiograph can show increased thickening of the bronchial wall, especially in the lower lobes in advanced cases, but thin-section axial CT of the chest can reveal early changes: intrapulmonary thickening of the airway wall, dilatation and distortion of intrapulmonary airways, with mucus plugging, and evidence of bronchiolitis.

| | Asthma | Cough variant asthma | Atopic cough | Eosinophilic bronchitis |
|---|---|---|---|---|
| Symptoms | Cough, breathlessness, wheeze | Cough only | Cough only | Cough and sputum |
| Atopy | Common | Common | Common | As in general population |
| Variable airflow obstruction | + | ± | – | – |
| Airway hyper-responsiveness | + | + | – | – |
| Capsaicin cough hyper-responsiveness | ± | ± | – | + |
| Bronchodilator response | + | + | – | – |
| Corticosteroid response | + | + | + | + |
| Response to $H_1$ antagonist | ± | ± | + | NK |
| Progression to asthma | n/a | 30% | Rare | 10% |
| Sputum eosinophilia (>3%) | Frequent | Frequent | Frequent | Always (by definition) |
| Submucosal eosinophils | ↑ | ↑ | ↑ | ↑ |
| BAL eosinophilia | ↑ | ↑ | ↓ | ↑ |
| Mast cells in ASM | ↑ | ↓ | NK | ↓ |
| Basement membrane thickness | ↑ | ↑ | NK | ↑ |

ASM=airway smooth muscle. BAL=bronchoalveolar lavage. n/a=not applicable. NK=not known. ±=sometimes present. –=not present. +=often present. ↑=increased. ↓=not increased.

***Table 3:*** **Cough caused by eosinophilic airway diseases**

***Panel 2:*** **Potential mechanisms of gastro-oesophageal cough**

- Direct effect of reflux contents (acid or pepsin) or volume on lower oesophageal afferent nerves
- Direct effect of reflux contents (acid or pepsin) or volume on laryngeal afferents or tracheobronchial afferents
- Stimulation of oesophageal-bronchial interconnecting neural pathways
- Increased cough reflex
- Increased gastro-oesophageal reflux caused by cough

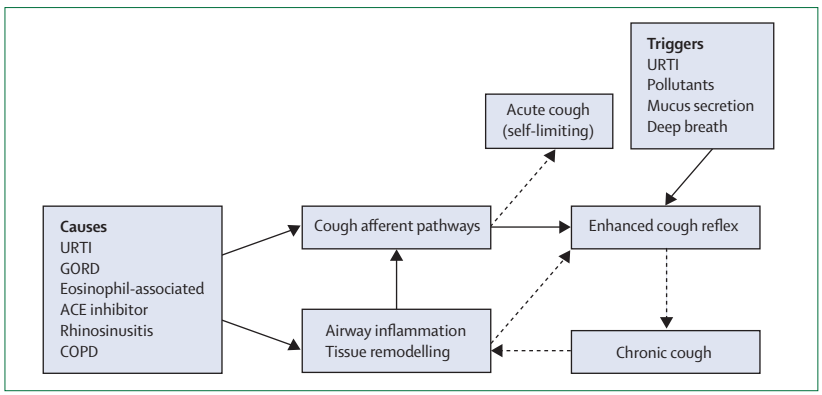


***Figure 3:*** **Interactions between causes, cough pathways, and airway inflammation**
Various causes activate cough afferent pathways that can lead to acute self-limiting cough, but induction of an enhanced cough reflex is important to maintain chronic cough. Additionally, causes of cough and the cough itself can induce upper airway mucosal inflammation and tissue remodelling, which could also modify the cough reflex that contributes further to cough maintenance. Once the cough reflex is enhanced, triggers can persistently induce cough. Chronic cough is described as idiopathic when there is no evidence for a cause. ACE=angiotensin-converting enzyme. COPD=chronic obstructive pulmonary disease. GORD=gastro-oesophageal reflux disease. URTI=upper respiratory tract infection (often viral).

Bronchiectasis cough is caused by the continuous presence of sputum and airway secretions in the airways, often infected and associated with mucus stasis because of impaired mucociliary clearance. Cough serves as a useful function in helping with clearance of excessive mucus. A small increase in the capsaicin tussive response is possibly the result of chronic inflammatory response in the airways.[117]

Angiotensin-converting-enzyme (ACE) inhibitors are prescribed for the treatment of hypertension and heart failure; 2–33% of patients report a dry cough.[117–119] The cough can arise within a few hours of taking the drug, but can also only become apparent after weeks or even months; it improves within days or weeks after withdrawal of the drug, but can take longer to resolve completely. Patients with ACE inhibitor cough show an enhanced response to capsaicin inhalation challenge. ACE inhibitor cough can be caused by the accumulation of bradykinin and prostaglandins, which directly sensitise cough receptors.

11–25% of patients with chronic cough report postinfectious cough.[56,120] In a series of subacute cough, the most common type was postinfective.[121] 25–50% of patients have a persistent cough after a *Mycoplasma* spp or *Bordetella pertussis* infection.[122] *B pertussis* infection is now increasingly recognised as a cause of both acute and chronic cough,[123,124] especially in children.[125] Respiratory viruses (respiratory syncytial virus and parainfluenzae) and other infections such as *Mycoplasma* spp, *Chlamydiae* spp, and *B pertussis* have been implicated in children.[126] The cough of *B pertussis* is spasmodic with a typical whoop; it usually lasts for 4–6 weeks, but can last much longer than that. In most patients with a postinfectious cough, the initial trigger is an upper respiratory tract infection; the cough that is expected to last for only a week persists for many months, and is often severe. Such patients are frequently referred to a cough clinic, and investigated for other causes of cough. The physician assumes that persistent damage to the cough receptor or persistent airway inflammation could have been induced by the virus. Bronchial epithelial inflammation and damage are present in children with chronic cough after lower respiratory tract illness. As a result of epithelial damage, cough receptors can be more readily exposed to inhaled irritants, which can lead to a vicious circle, in which cough-induced damage maintains and triggers further cough. Increases in tachykinin release and in the expression of the neurokinin-1 receptor can enhance the cough reflex.[127]

Other conditions causing cough include bronchial carcinoma, metastatic carcinoma, sarcoidosis, chronic aspiration, interstitial lung disease, and left ventricular failure. Such conditions can often be diagnosed by clinical examination and chest radiography. 80% of people with idiopathic pulmonary fibrosis, which typically presents with progressive breathlessness, have an irritating dry cough, that can be resistant to conventional antitussive therapies and specific intensive treatment.[128] In up to 50% of cases, other causes of chronic cough can be identified;[129] hence, exclusion of chronic sinus disease, gastro-oesophageal reflux, and eosinophilic airways disease is important. Potential mechanisms for cough in lung fibrosis include small-airways distortion secondary to parenchymal fibrosis, leading to activation of RARs, and enhanced sensitivity to cough reflex.[130–132] Hope-Gill and co-workers[132] reported higher than average amounts of nerve growth factor and brain-derived neurotrophic factor in airway secretions of patients with idiopathic pulmonary fibrosis, and that these neurotrophins could affect neuronal plasticity in the airways. Treatment of patients with idiopathic pulmonary fibrosis with high-dose prednisolone not only led to much reduction in cough symptoms, but also to a reduction in cough sensitivity to capsaicin.

Chronic cough can be a prominent symptom of occupational exposure. A report highlights a new cause of cough: workers in glass-bottle factories exposed to low-molecular-weight irritants, hydrochloric acid, and organic oils developed chronic cough with cough reflex hypersensitivity, but not with airways hypersensitivity.[133,134] This emphasises the importance of excluding exposure to dust particles in the workplace as a cause of cough. Exposure to high concentrations of dust and organic materials probably caused cough in fire-fighters and other survivors of the World Trade Centre collapse; these patients also had airway hyper-responsiveness.[135,136]

Cough arising only in the supine position can result from collapse of the large airways, and this cough can be suppressed by continuous positive airway pressure to the nose, which keeps the airways patent in the supine position.[137] Kok and others[138] described a new syndrome of hereditary sensory neuropathy, in which patients have autonomic dysfunction (causing hypohydrosis, absent sympathetic skin response, and peripheral adrenergic impairment), cough, and gastro-oesophageal reflux.

Perhaps autonomic dysfunction causes the cough;[139] this is supported by reports of an association between Holmes-Adie pupil, autonomic dysfunction, and cough.[140]

Cough can be triggered by irritation of the auricular branch of the vagus nerve (Arnold's nerve), in up to 3% of healthy people, by direct stimulation of the external acoustic meatus. The presence of cerumen (wax), foreign bodies, or any irritation in the external auditory meatus is a rare cause of cough.

Chronic cough is also a common problem in children, with a favourable prognosis in most.[141] Causes in otherwise healthy children include viral bronchitis, postinfectious cough, pertussis, cough-variant asthma, psychogenic cough, and gastro-oesophageal reflux. Conditions in children with serious disorders include congenital abnormalities such as vascular rings, tracheobronchomalacia, pulmonary sequestration, mediastinal tumours, foreign bodies in the airways or oesophagus, aspiration caused by poor coordination of swallowing or oesophageal dysmotility, immune deficiencies, cystic fibrosis, primary ciliary dyskinesia, and heart disease. Cough as a vocal tic or habitual cough can arise in young children; psychogenic cough, sometimes also called honking cough, has a stereotypical and recognisable barking noise. Psychological influences can exaggerate cough, especially in children. Tourette's syndrome, a neurobehavioural disorder characterised by involuntary, repetitive, and stereotypical movements, can present as an isolated cough.[142]

Earlier series of chronic cough rarely identified patients in whom no recognisable cause was identified, or in whom specific treatment had failed. More recent series, especially from the UK, have identified 7–46% of patients as having idiopathic cough, despite a thorough diagnostic investigation (table 3).[54–71] Such patients tend to be middle-aged women, who frequently give a history of cough onset around menopause, and can have organ-specific autoimmune disease, especially autoimmune hypothyroidism.[143,144] A plausible explanation for the development of cough is amplification of previous subclinical inflammation of the airway at menopause, as a result of sex-hormone-related changes in lung immunity.[145,146] In some cases, airway inflammation can be a result of aberrant migration of inflammatory cells to the lungs from a primary site of autoimmune inflammation. An alternative explanation is that the initiating cause of the cough could be transient, such as an upper-respiratory-tract viral infection, or an exposure to toxic fumes, but its effect on enhancing the cough reflex could last longer. The repetitive mechanical and physical effects of coughing bouts on airway cells could cause the release of inflammatory mediators;[147] the causes of cough, or the act of coughing itself, might also contribute to tissue remodelling. Inflammation and tissue remodelling might well cause an enhanced cough reflex, which in turn could maintain cough, via a positive feedback process (figures 2 and 3).

Psychogenic or habitual cough needs to be considered, but this is a diagnosis of exclusion that could respond to treatment for anxiety and depression, or resolution of social or domestic issues. Patients frequently complain of a persistent tickling or irritating sensation in the throat, and sometimes in the chest, which often leads to paroxysms of coughing. Triggers such as changes in ambient temperature, taking a deep breath, laughing, talking over the phone for more than a few minutes, cigarette smoke, aerosol sprays, perfumes, or eating crumbly dry food are common. The cough response to capsaicin is invariably increased.

Mucosal biopsies taken from a group of non-asthmatic patients with chronic dry cough showed evidence of epithelial desquamation and inflammatory cells, especially lymphocytes,[143,148,149] and also increased numbers of submucosal mast cells (but not neutrophils or eosinophils), goblet cell hyperplasia, subepithelial fibrosis, and increased vascularity.[150] Increased numbers of mast cells have also been seen in bronchoalveolar lavage fluid[64] and increased numbers of neutrophils in induced sputum,[151] with increased concentrations of histamine, prostaglandin D2, prostaglandin E2, tumour necrosis factor-α, and interleukin 8 in induced sputum.[152] These inflammatory changes might not be specific for idiopathic cough, because they could represent the sequelae of chronic trauma to the airway wall after repeated episodes of cough.[133,147,149] Chronic airway-wall remodelling might also represent the effects of the putative causal factor for cough such as the growth factors released that induced the remodelling changes, and that might also change the cough receptors. Enhanced cough reflex in idiopathic cough can be associated with a lower pH of exhaled breath condensate,[153] indicating the possibility of acidification of the epithelial fluid layer. The expression of vanilloid receptor subtype 1 (TRPV-1), which is activated by acid, is increased in epithelial nerves of patients with non-asthmatic chronic cough (figure 2).[15]

**Conflict of interest statement**

KFC is co-Editor-in-Chief of an online Journal, *Cough*. He was co-organiser of the Fourth International Cough Symposium in 2006 that received educational grants from AstraZeneca, GlaxoSmithKline, and Novartis. He declares no other conflict of interest. IDP was one of the developers of the Leicester cough questionnaire. He receives occasional payments for the use of the questionnaire in commercially sponsored clinical trials. He declares that he has no other conflict of interest for this Series.

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