Chronic Persistent Cough in Adults

Cough is a nonspecific reaction to irritation anywhere from the pharynx to the lungs. Cough can be divided into acute self-limiting cough, lasting less than three weeks, or chronic persistent cough, which usually lasts for more than eight weeks. Cough lasting for an intermediate period of 3-8 weeks is called subacute cough\textsuperscript{[1]}. Unexplained chronic cough causes significant impairments in quality of life\textsuperscript{[2]}. 

Epidemiology

- Chronic cough lasting for more than eight weeks is common in the community\textsuperscript{[1]}. Chronic cough is reported by 10-20\% of adults\textsuperscript{[3]}.
- Risk factors include atopy and smoking. Cough may be work-related and a thorough occupation history is very important in assessment.
- Despite thorough investigation and empirical management, a considerable proportion of people with subacute and chronic cough have unexplained cough, for which treatment options are limited\textsuperscript{[4, 5]}.

Physiology\textsuperscript{[1]}

The cough reflex is triggered by mechanical or inflammatory changes or irritants in the airways. The afferent pathway is via the vagus nerve to respiratory neurons termed the ‘cough centre’ in the brain stem. Higher cortical centres also control the cough. Chronic cough tends to be inhibited during sleep.

Chronic cough is often associated with bronchial hyper-reactivity (bronchial hyper-responsiveness), which can persist in the absence of the initiating cough event. Bronchial hyper-responsiveness is defined as a state of increased sensitivity to a wide variety of airway-narrowing stimuli - eg, exercise, dry or cold air and hypertonic or hypotonic aerosols. It occurs in asthma and chronic obstructive pulmonary disease (COPD) but also can occur in the absence of lung disease.

Aetiology\textsuperscript{[1, 6, 7, 8]}

Most cases of troublesome cough reflect the presence of an aggravant (asthma, drugs, environmental, gastro-oesophageal reflux\textsuperscript{[9]}, upper airway pathology) in a susceptible individual. The most common causes of chronic cough, other than smoking in adults, are postnasal drip, asthma and gastro-oesophageal reflux disease (GORD). Chronic refractory cough also often occurs after a viral infection\textsuperscript{[10]}.

Common causes

- Smoking (active or passive).
- Asthma (and its variants, ie cough-variant asthma, eosinophilic bronchitis) - all of which are steroid-responsive.
- COPD.
- GORD.
- Postnasal drip.
- Environmental pollution, especially PM10 particulates (particles of 10 micrometres or fewer).
- Angiotensin-converting enzyme (ACE) inhibitors.
- Occupational exposure to irritants (including farm workers, workers exposed to hot acidic conditions in a bottle factory, and workers exposed to hot chilli peppers).
- Whooping cough - in young adults and may be more common than previously supposed\textsuperscript{[11]}.

Less common causes

- Cardiovascular - left ventricular failure, pulmonary emboli, aortic aneurysm.
- Chronic infections - bronchiectasis, tuberculosis, cystic fibrosis, lung abscess.
- Postinfectious cough - may be more likely following infection with \textit{Mycoplasma pneumoniae}, chlamydial pneumonia and whooping cough.
- Parenchymal lung diseases - interstitial lung fibrosis, emphysema, sarcoidosis.
- Upper airway conditions (other than chronic rhinitis, above) - chronic tonsil enlargement, obstructive sleep apnoea, chronic snoring, irritation of external auditory meatus. Laryngeal problems are increasingly recognised as being part of chronic cough\textsuperscript{[12]}.
- Foreign body in large airways - recurrent aspiration, inhaled foreign body, endobronchial sutures.
- Rarely, cough may be due to cardiac arrhythmias\textsuperscript{[13]}.
- Cough only when supine - may be due to collapse of large airways.
- Diffuse panbronchiolitis - a recognised cause in Japan, responds to low-dose macrolide antibiotics (but resistant to steroids).
- Chronic cough may be a presentation of a complex involuntary tic (eg, as sometimes seen in Tourettes syndrome).
- One small study suggested that vitamin B12 deficiency contributes to chronic cough (perhaps due to sensory neuropathy)\textsuperscript{[14]}.
- Idiopathic or psychogenic - a diagnosis of exclusion.
Presentation

History
- Nature of cough - dry, sputum, blood.
- Pattern of cough - duration, frequency, nocturnal, association with eating or talking.
- Atopy - note if there is any history of this.
- Smoking and occupation.
- Drugs (especially ACE inhibitors).
- Red flags (see box).

'Red flag' symptoms in chronic cough[^6]
- Copious sputum production (bronchiectasis).
- Systemic symptoms - fever, sweats, weight loss (tuberculosis, lymphoma, bronchial carcinoma).
- Haemoptysis (tuberculosis, bronchial carcinoma).
- Significant dyspnoea (heart failure, COPD, fibrotic lung disease).

Examination
- Systemic signs - eg, fever, weight loss, clubbing, lymphadenopathy.
- Upper airway signs - eg, hoarseness, nasal speech.
- Focal chest signs.
- Cardiovascular system.
- Peak expiratory flow rate.

<table>
<thead>
<tr>
<th>Common causes of cough and their symptoms[^1, ^6]</th>
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<tbody>
<tr>
<td><strong>Asthma</strong></td>
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<tr>
<td>- History of atopy.</td>
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<td>- Nocturnal cough.</td>
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<td>- Wheeze.</td>
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<tr>
<td>- Peak flow rate variable by &gt;20% or reversible changes on spirometry (these 'rule in' asthma but their absence does not rule it out).</td>
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<tr>
<td><strong>Gastro-oesophageal reflux disease (GORD)</strong></td>
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<tr>
<td>- Heartburn (but may have no gastrointestinal symptoms).</td>
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<td>- Cough worse at night.</td>
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<tr>
<td>- Cough when eating/talking.</td>
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<tr>
<td>- Hoarseness.</td>
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<tr>
<td>- Sour taste.</td>
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<tr>
<td><strong>Postnasal drip syndrome</strong></td>
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<td>- Subjective symptoms - postnasal drip, having a recurrent need to clear the throat.</td>
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<tr>
<td>- Persistent nasal blockage.</td>
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<tr>
<td>- Persistent nasal discharge.</td>
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Initial assessment, investigation and treatment in primary care [6]

Studies have shown a low frequency of serious pulmonary conditions in patients who have an isolated chronic dry cough and normal physical examination, CXR and spirometry [7].

A suggested strategy for primary care, using the principle of diagnosis by 'test of treatment' is:

- History and examination. Look for 'red flags' which require early investigation (see box).
- Assuming there are no red flags, obvious cause or abnormal signs on examination, proceed as follows:
  - For smokers, initial investigations are CXR and spirometry, with advice to stop smoking. If smoking is the cause, cough should improve within eight weeks of smoking cessation.
  - For non-smokers, if taking an ACE inhibitor, trial of stopping/replacing this drug. ACE inhibitor-induced cough should improve within four weeks of stopping the drug. Then consider CXR and spirometry (or serial peak flow measurements, if spirometry is unavailable).
- Assess the likely diagnosis and refer/instigate trial of treatment accordingly:
  - Serious disease? - refer to the chest clinic.
  - Asthma? - see separate Asthma article.
  - GORD? - trial of high-dose proton pump inhibitors (may require up to 12 weeks for improvement).
  - Postnasal drip syndrome? - trial of antihistamines or nasal steroids.

In the context of considering the possible diagnosis of cancer, the National Institute for Health and Care Excellence (NICE) recommends arranging a CXR for any patient presenting with [15]:

- Unexplained cough, aged 40 years and over, who has ever smoked (possible lung cancer or mesothelioma).
- Unexplained cough, aged 40 and over, with a history of exposure to asbestos (possible mesothelioma).
- Unexplained cough, aged 40 and over, with any one of the following: fatigue, shortness of breath, chest pain, unexplained weight loss or unexplained loss of appetite (possible lung cancer or mesothelioma).

Further assessment [3, 7, 16]

Next steps

- Blood tests - FBC (infection, eosinophilia), ESR/CRP (infection, malignancy, connective tissue disorders).
- Assess for other contributing factors - eg, reflux disease, rhinitis, occupation (there may be more than one factor causing chronic cough). Try treating these (or removing the cause, if occupational) for a limited period to observe response.

Possible further investigations in secondary care [17]

These include:

- Bronchial provocation testing (methacholine or histamine) - positive result supports diagnosis of asthma but cough may be steroid-responsive even if negative.
- Assess for eosinophilic airway inflammation - by induced sputum analysis or trial of steroids (prednisolone 30 mg daily for two weeks).
- Bronchoscopy - if inhalation of a foreign body is suspected, or where common causes have been excluded.
- Echocardiogram or other cardiac investigations - if a cardiac cause is suspected clinically.
- 24-hour ambulatory oesophageal pH testing and/or oesophageal manometry.
- Radiology of sinuses - eg, CT or MRI scanning.
- High-resolution CT scan of thorax - however, there is low diagnostic yield in this scenario.

Assessment of response

May use a cough assessment tool such as the cough visual analogue scale or the Leicester Cough Questionnaire [18].

Management [3, 16]

- Treat the underlying cause(s), if possible (see 'Initial assessment, investigation and treatment in primary care' and 'Further assessment' sections, above).
- A 'trial of treatment' strategy is often appropriate, ensuring that each treatment is used for a sufficient time - eg, eight weeks for inhaled steroids, 12 weeks for anti-reflux treatment [6].
- Smoking cessation; avoid exposure to irritants.
- If initial management is unsuccessful, referral to secondary care may be required. This may involve a chest physician, ENT specialist and/or gastroenterologist, depending on the individual context [3].

Symptomatic treatment of cough

Drug treatment [19]

There are various drugs which may partially suppress cough, although the cough reflex is exceedingly difficult to abolish. Also, there is a lack of evidence for the efficacy of most antitussive drugs. British Thoracic Society guidelines state: "There are no effective treatments controlling the cough response per se with an acceptable therapeutic ratio [3]."
When there is no identifiable cause, cough suppressants may be useful, particularly if sleep is disturbed. They may cause sputum retention and this may be harmful in patients with chronic bronchitis or bronchiectasis.

Codeine may be effective but can cause dependence. Dextromethorphan and pholcodine have fewer side-effects. Sedating antihistamines are used as the cough suppressant component of many compound cough preparations on sale to the public. Morphine or diamorphine at higher doses may be used for severe, distressing cough in palliative care.

Mucolytics (eg, carboxisteine or erdosteine) are prescribed to facilitate expectoration by reducing sputum viscosity. In some patients with COPD and a chronic productive cough, mucolytics can reduce exacerbations. Mucolytic therapy should be stopped if there is no benefit after a four-week trial. Steam inhalation with postural drainage is effective in bronchiectasis and in some cases of chronic bronchitis.

Demulcent cough preparations contain soothing substances such as syrup or glycerol and may be used to relieve a dry irritating cough. Preparations such as simple linctus have the advantage of being harmless and inexpensive.

Expectorants are claimed to promote expulsion of bronchial secretions but there is no evidence that any drug can specifically facilitate expectoration.

Centrally acting neuromodulators such as gabapentin and pregabalin may be useful for chronic refractory cough[10].

**Non-drug treatments**

Speech therapy techniques have shown benefit for chronic refractory cough[10].

**Further reading & references**

- British Guideline on the management of asthma; Scottish Intergovernmental Guidelines Network - SIGN (2016)

8. Cough; NICE CKS, June 2015 (UK access only)
19. British National Formulary (BNF); NICE Evidence Services (UK access only)

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