

## BTS GUIDELINES

# Recommendations for the management of cough in adults

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*Thorax* 2006;61(Suppl 1):i1–i24. doi: 10.1136/thx.2006.065144 abstracted bullet points. The subsequent section begins with concise definitions for the key terms: *cough*, *acute cough* and *chronic cough*. Individual sections detailing guidelines for the management of acute and chronic cough with additional recommendations for specialist cough clinics follow. Each of these sections includes separate recommendations for management of cough in adults. The final section contains appendices which include a recommended cough management algorithm for adults (available online only at <http://www.thoraxjnl.com/supplemental>), together with a patient information sheet designed for primary care.

## 1. INTRODUCTION

### 1.1 Background

Patients with cough frequently present to clinicians working in both primary and secondary care.<sup>1,2</sup> Acute cough, which often follows an upper respiratory tract infection, may be initially disruptive but is usually self-limiting and rarely needs significant medical intervention. Chronic cough is often the key symptom of many important chronic respiratory diseases but may be the sole presenting feature of a number of extrapulmonary conditions, in particular upper airway and gastrointestinal disease. Even with a clear diagnosis, cough can be difficult to control and, for the patient, can be associated with impaired quality of life.<sup>3,4</sup> Sessions dedicated to cough at respiratory meetings are popular, suggesting that the pathophysiology, evaluation, and successful treatment of cough remain topics of keen interest to many medical practitioners.

### 1.2 Need and purpose of BTS recommendations on the management of cough

The American College of Chest Physicians (ACCP) and the European Respiratory Society (ERS)<sup>5,6</sup> have each endorsed their own set of guidelines on the management of cough; however, criticism<sup>7</sup> of their content and breadth suggest the need for further concise recommendations. The British Thoracic Society guidelines cover not only chronic cough but also acute cough and the organisational issues of cough clinics. International differences in delivery of respiratory health care and management strategies support the notion that such guidelines would be desirable. The British Thoracic Society Standards of Care Committee agreed to the development of a Working Group tasked with the job of producing a set of guidelines for the management of cough with the following key objectives:

- To produce guidelines that are relevant to the clinical management of cough in both primary and secondary care.
- To produce a critical review of the available literature.
- To highlight cough as a clinical and research area of considerable importance.
- To encourage extended cooperation between clinicians, scientists, and the pharmaceutical industry with the core aim of developing effective cough therapies.

### 1.3 Structure of the guidelines

The guidelines are prefaced with the key points and recommendations summarised as a table of

### 1.4 Methodology for generation of the guidelines

The members of the guideline group initially met to discuss content, format and purpose of the document and to consider the most appropriate methodology for the critical review of available literature and the generation of recommendations. Consensus was obtained on these points and members of the Guideline Group were allocated to one of three subgroups concerned with acute cough, chronic cough, or specialist cough clinics. These three clinical areas were further divided into sections and individuals were identified to conduct an independent literature search for each of these and to produce a discussion document based on their literature appraisal. The search engines recommended were Medline (1966 onwards), EMBASE, and the Cochrane Library database. These were applied to locate all English language studies relevant to the aetiology, diagnosis, severity staging, investigation, prognosis, complications, or treatment of chronic cough in adults over 16 years.

At a subsequent meeting of the Guideline Group these documents were presented, discussed, and recommendations agreed upon. The existing lack of evidence made the formulation of evidence based guidelines difficult. A striking example of this is that a search of the Cochrane Library database to 2005 for systematic reviews of treatment of cough in adults generated one article. Consequently, recommendations have been made based on the available reliability of evidence and, where indicated, on the clinical experience of the members of the Guideline Group.

Because of the generally poor level of evidence and the consequent arbitrary nature of the recommendations, a grading system was thought to be inappropriate.

Once the individual sections were complete, an initial document was drafted which was then circulated to the BTS Standards of Care Committee.

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## Summary of key points and recommendations

### Introduction

#### Key points

- Cough is a forced expulsive manoeuvre, usually against a closed glottis and which is associated with a characteristic sound.
- Cough frequently presents as a troublesome symptom to clinicians working in both primary and secondary care.

### Acute cough

#### Key points

- Acute cough is defined as one lasting less than 3 weeks.
- Acute cough is the commonest new presentation in primary care and is most commonly associated with viral upper respiratory tract infection.
- In the absence of significant co-morbidity, an acute cough is normally benign and self-limiting.
- It is the commonest symptom associated with acute exacerbations and hospitalisations with asthma and COPD.
- The cost of acute cough to the UK economy is estimated to be at least £979 million. This comprises £875 million to loss of productivity and £104 million cost to the healthcare system and the purchase of non-prescription medicines.

#### Recommendations

- Indications for further investigation include haemoptysis, prominent systemic illness, suspicion of inhaled foreign body, suspicion of lung cancer.
- Patients report benefit from various over-the-counter preparations; there is little evidence of a specific pharmacological effect.

### Chronic cough

#### Key points

- Chronic cough is defined as one lasting more than 8 weeks.
- It is reported by 10–20% of adults, commoner in females and obese.
- Cough accounts for 10% of respiratory referrals to secondary care.
- Most patients present with a dry or minimally productive cough.
- Decrement in quality of life is comparable with severe COPD.
- The presence of significant sputum production usually indicates primary lung pathology.
- In chronic cough a heightened cough reflex is the primary abnormality.

### Clinical evaluation of chronic cough

#### Recommendations

- A detailed history including a thorough occupational history should be performed in all patients.
- Physical examination should concentrate on the afferent sites identified as most commonly associated with cough.
- The evaluation of patients with chronic cough should include an assessment of health status and cough severity. Cough visual analogue scores are an alternative to cough specific quality of life questionnaires but are less well validated. (Audit)
- Chest radiograph and spirometry are mandatory. (Audit)
- Bronchial provocation testing should be performed in patients without a clinically obvious aetiology referred to a respiratory physician with chronic cough and normal spirometry.
- Bronchoscopy should be undertaken in all patients with chronic cough in whom inhalation of a foreign body is suspected.
- High resolution computed tomography may be of use in patients with chronic cough in whom other more targeted investigations are normal.
- Optimal management should comprise a combination of diagnostic testing and treatment trials based on the most probable aggravant(s).
- Treatment effects should be formally quantified. (Audit)

A recommended diagnostic algorithm for the evaluation of an adult with chronic cough is displayed in Appendix 2 (Parts 1 and 2) available online at <http://www.thoraxjnl.com/supplemental>.

### Management of specific aggravants

#### Key point

- Most cases of troublesome cough reflect the presence of an aggravant (asthma, drugs, environmental, gastro-oesophageal reflux, upper airway pathology) in a susceptible individual.

**Asthma/eosinophilic bronchitis****Key points**

- Cough may be the only manifestation of these syndromes.
- No currently available tests of airway function can reliably exclude a corticosteroid responsive cough.

**Recommendation**

- Cough is unlikely to be due to eosinophilic airway inflammation if there is no response to a two week oral steroid trial. (Audit)

**Drugs****Recommendation**

- No patient with a troublesome cough should continue on ACE inhibitors.

**Environment****Key point**

- One of the commonest causes of persistent cough is smoking and appears to be dose related.

**Recommendation**

- Smoking cessation should be encouraged as it is accompanied by significant remission in cough symptoms.

**Gastro-oesophageal reflux disease (GORD)****Key points**

- Failure to consider GORD as a cause for cough is a common reason for treatment failure.
- Reflux associated cough may occur in the absence of gastrointestinal symptoms.

**Recommendations**

- Intensive acid suppression with proton pump inhibitors and alginates should be undertaken for a minimum of 3 months. (Audit)
- Antireflux therapy may be effective in treating cough in carefully selected cases.

**Upper airway pathology****Key points**

- Rhinosinusitis is commonly associated with chronic cough.
- There is an association between upper airway disease and cough but a poor association between the various symptoms and cough.
- There is disparity in the reported efficacy of antihistamines.

**Recommendations**

- In the presence of prominent upper airway symptoms a trial of topical corticosteroid is recommended.

**Undiagnosed or idiopathic cough****Key points**

- Chronic cough should only be considered idiopathic following thorough assessment at a specialist cough clinic.
- The clinical history of reflux cough is often present in patients with idiopathic cough.
- A typical lymphocytic airways inflammation is seen in idiopathic cough.

**Treatment of cough due to other common respiratory diseases****Key point**

- Cough can be a debilitating symptom in many common acute and chronic respiratory diseases.

**Recommendation**

- Suppression may be relatively contraindicated especially when cough clearance is important.

**Specialist cough clinics****Key points**

- A systematic approach to diagnosis and treatment remains the most effective way to manage chronic cough.
- Important questions remain as to the complexity and cost effectiveness of existing diagnostic algorithms.

**Recommendations**

- No single existing diagnostic protocol can be recommended.
- A combination of selected diagnostic testing and empirical trials of treatment is likely to be most cost effective.
- Referral to a specialist cough clinic should be encouraged and a directory of specialist centres should be made available.

**Specialist investigations****Key point**

- Debate remains as to the interpretation and clinical utility of more complex investigations.

**Bronchial provocation testing****Recommendations**

- Bronchial provocation testing should be performed in patients without a clinically obvious aetiology referred to a respiratory physician with chronic cough and normal spirometry.
- A negative test excludes asthma but does not rule out a steroid responsive cough.

**Oesophageal studies****Recommendations**

- Empirical treatment should be offered to patients with cough and typical reflux symptoms before oesophageal testing.
- No current test of oesophageal function predicts treatment response.

**Upper airway investigations****Recommendations**

- Examination of ear, nose and throat should be performed in preference to sinus imaging in patients suspected of having rhinosinusitis, but with persisting cough despite an adequate trial of treatment directed at the upper airway.
- Specialist cough clinics should have access to fiberoptic laryngoscopy, preferably within the clinic setting.

**Cough provocation testing****Recommendations**

- There is no current evidence to support the routine use of cough challenge testing in the management of chronic cough.
- For research purposes, standardisation of methodology is required and accurate data on the distribution of cough responsiveness within the population are needed.

**Measurement and monitoring of cough****Recommendations**

- Accurate measurement of cough helps determine cough severity, assess treatment efficacy, and may provide diagnostic information.
- Ambulatory cough recording currently offers most promise in the objective assessment of cough, although further technical refinement is required if it is to be broadly accessible to physicians.

**Assessing airway inflammation****Recommendations**

- The demonstration of sputum eosinophilia has important treatment implications and should be available in cough clinics.
- Induced sputum should be requested after exclusion of the other common causes.
- There is insufficient evidence to recommend the routine use of exhaled breath measurements in the clinical evaluation of chronic cough.

**Potential new treatments for cough****Key point**

- There are no effective treatments controlling the cough response per se with an acceptable therapeutic ratio.

**Recommendation**

- There is a need for multicentre clinical trials on new drugs carried out across specialist centres using objective methods of cough counting as well as subjective quality of life and symptom indexes.

### 1.5 Updating of recommendations

It is envisaged that the Executive Committee of the Guideline Group will meet every two years to review any new published evidence obtained from a subsequent structured literature search. An additional purpose of these update meetings will be to formulate key clinical and research priorities.

### 1.6 Audit

A number of quality indicators were chosen from recommendations made in this document against which the quality of management of cough could be measured. The key indicators were:

- Chest radiography and spirometry are mandatory in the evaluation of chronic cough.
- The severity of the cough should be quantified.
- Treatment effects should be formally quantified.
- Intensive acid suppression with proton pump inhibitors should be undertaken for a minimum of 2 months.
- Decision to continue steroids made on the basis of a 2 week trial of oral corticosteroids.

## 2. DEFINITIONS

### 2.1. Cough

Debate exists as to the most appropriate clinical definition of a cough event.<sup>8</sup> For the purposes of this document, the members of the Task Force agreed the following definition: *“Cough is a forced expulsive manoeuvre, usually against a closed glottis and which is associated with a characteristic sound.”*

### 2.2 Acute and chronic cough Recommendations

- Acute cough is defined as one lasting less than 3 weeks.
- Chronic cough is defined as one lasting more than 8 weeks.

Classification of cough based on symptom duration is somewhat arbitrary. A cough lasting less than 3 weeks is termed *acute* and one lasting longer than 8 weeks is defined as *chronic*. Acute cough is usually a result of a viral upper respiratory tract infection as almost all such coughs resolve within this time period.<sup>9</sup> A post-infective cough may, however, persist for a considerable period of time. An upper respiratory tract infection (URTI) cough lingering for more than 3 weeks is usually termed “post-viral cough”. The grey area between 3 and 8 weeks of cough is difficult to define aetiologically since all chronic cough will have started as an acute cough, but the clear diagnostic groups of chronic cough are diluted by those patients with post-viral cough.

## 3. ACUTE COUGH

### 3.1 Epidemiology

#### Key points

- Acute cough is the commonest new presentation in primary care.
- It is most commonly associated with viral upper respiratory tract infection.
- In the absence of significant co-morbidity, it is normally benign and self-limiting.
- It is one of the commonest symptoms associated with acute exacerbations and hospitalisations with asthma and chronic obstructive pulmonary disease (COPD).

Acute cough is usually caused by a viral URTI but may arise from other aetiologies such as pneumonia or aspiration of a foreign body. The duration of a single episode of URTI associated cough varies but is rarely more than 2 weeks. A

cut off of 2 months for chronic cough has been arbitrarily agreed in both American<sup>10</sup> and European guidelines.<sup>6</sup> The economic impact of acute cough may be usefully thought of in terms of a series of patient thresholds that trigger interventions such as the purchase of a cough medicine or consultation with a general practitioner (GP).

#### 3.1.1 Incidence of URTI

Symptomatic URTI occur at rates of 2–5 per adult person per year, with school children suffering 7–10 episodes per year.<sup>11</sup> If one accepts the lowest rate of URTI of two episodes per person per year, then this translates into a conservative estimate of an incidence of 120 million episodes of URTI per year in the UK (fig 1).

#### 3.1.2 Incidence of acute cough

Only a proportion of cases of URTI are associated with cough as a symptom. In naturally acquired URTI, cough was present in 40–50% of patients.<sup>12–13</sup> This translates into an incidence of approximately 48 million cases of acute cough per year in the UK. The severity and duration of acute cough will vary widely but many will reach a threshold of severity that precipitates self-medication.

#### 3.1.3 Incidence of self-medication

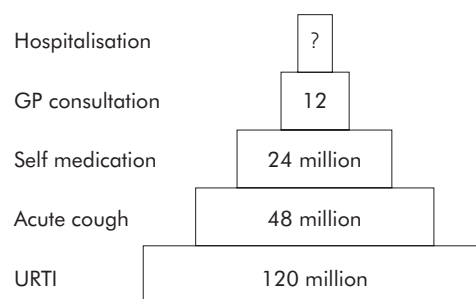
The sale of non-prescription liquid cough medicines grossed £96.5 millions in 2001 in the UK.<sup>14</sup> This sales figure is an underestimate of total sales as it is for sales from pharmacy and grocery outlets only, and does not include sales from outlets such as supermarkets and convenience stores. With cough medicines averaging £3–4 per unit, this represents at least 24 million episodes per year in the UK.

#### 3.1.4 Consultations with a general practitioner

Morbidity statistics from general practice for the period 1991–2 reported that more people consulted for respiratory illnesses (31%) than for any other single disease category.<sup>15</sup> With 20% of patients consulting for URTI, this translates into 12 million consultations per year, with acute cough representing “the largest single cause of consultation in primary care”.<sup>16</sup>

#### 3.1.5 Hospital admissions

In normal subjects acute cough associated with URTI is not usually a cause of hospital admission. However, in patients with co-morbidity such as asthma<sup>11</sup> and COPD,<sup>17</sup> viral URTI is the commonest cause of admission. Cough is a common symptom in this group of patients as well as those admitted



**Figure 1** Pyramid of incidence of acute cough. The base represents the population with an upper respiratory tract infection (URTI), some of whom will suffer from acute cough. Level 2 represents all those suffering from acute cough. Level 3 is the proportion of those suffering from acute cough who reach the threshold of severity of cough to trigger the purchase of a cough medicine. Level 4 is the proportion of those suffering from acute cough who reach the threshold of severity of cough to trigger a GP consultation. Level 5 is the proportion of those suffering from acute cough who are admitted to hospital. It is not possible to estimate the number of this latter group (see text).

to hospital for complications associated with infection with influenza or respiratory syncytial virus (RSV).

### 3.1.6 Sex differences

Between 16 and 64 years of age women are almost twice as likely as men to consult their GP for URTI,<sup>15</sup> and this may relate to a sex difference in the sensitivity of the cough reflex.

### 3.1.7 Age

The incidence of URTI is much greater in infants and children than in adults. The GP consultation rate for URTI for the age group 0–4 years is about four times greater than the adult rate of consultation.<sup>15</sup>

### 3.1.8 Seasonality

Acute viral URTIs exhibit seasonality, and this causes seasonality in the incidence of acute cough and sales of cough medicines<sup>18</sup> as well as hospital admissions with comorbidity. Cough is a common symptom associated with influenza and influenza-like illness, with 93% of patients suffering from influenza having cough as a symptom.<sup>19</sup> Influenza activity in the population shows a clear seasonality that usually peaks at the turn of the year around week 52.<sup>20</sup> The seasonality of influenza-like illness will contribute to seasonality of cough as a common seasonal symptom in the general population.

## 3.2 Economic impact of acute cough

### Key point

- The cost of acute cough to the UK economy is estimated to be at least £979 million. This comprises £875 million in loss of productivity and £104 million cost to the healthcare system and the purchase of non-prescription medicines. More accurate estimates specific to the UK are required.

The economic cost of cough is a combination of at least the following six factors:

- “on-the-job” productivity reduction;
- absenteeism from work;
- absenteeism due to care giving for others (mainly children) with URTI;
- physician consultation cost;
- prescription medication cost;
- non-prescription medication cost.

The economic burden of acute cough in the UK is not well characterised, so the figures quoted are extrapolations from US data where this subject appears to receive more attention.<sup>21–22</sup> In the US it is estimated that \$25 000 million is lost due to the common cold (excluding influenza-related URTIs), of which \$16 600 million is “on-the-job” productivity loss, \$8000 million is due to absenteeism, and \$230 million is due to caregiver absenteeism.

Assuming that the rate of viral URTI is the same in the UK as the US, adjustment for population differences (UK population estimates (2001) from [www.statistics.gov.uk/census2000/profiles/uk.asp](http://www.statistics.gov.uk/census2000/profiles/uk.asp)), US population estimates (2000) from [www.census.gov](http://www.census.gov)) suggests a total loss of

**Table 1** Common serious conditions presenting with isolated cough

- Neoplasm
- Infection, e.g. tuberculosis
- Foreign body inhalation
- Acute allergy – anaphylaxis
- Interstitial lung disease

**Table 2** Symptoms associated with acute cough prompting a chest radiograph

- Haemoptysis
- Breathlessness
- Fever
- Chest pain
- Weight loss

£3500 million, of which £2300 million is due to on-the-job productivity loss, £1100 million is due to absenteeism, and £32 million is due to care giving. Using UK figures which suggest up to 25% of URTI sufferers report cough as the main reason they consulted a healthcare professional, this translates into a loss of productivity of £875 million due to URTI associated cough.

The cost of medical consultation and non-prescription treatment for acute cough is estimated to be at least £104 million.<sup>14</sup>

## 3.3 Management of acute cough Recommendation

- Indications for further investigation include haemoptysis, prominent systemic illness, suspicion of inhaled foreign body, suspicion of lung cancer.

### 3.3.1 General

In the large majority of cases, acute cough is unlikely to need any investigation. General advice may be sufficient and a patient information sheet (see Appendix 1) may be helpful.

### 3.3.2 Taking a history

#### *At risk groups and danger signs*

Although cough is very common and usually self-limiting, it is sometimes the first indication of a serious condition (table 1).

For most of these patients cough is not the only symptom and the presence of a number of others should prompt a chest radiograph (see tables 2 and 3). These features—as well as a history of foreign body inhalation—should always be ruled out by direct questions.

Specialist referral for consideration of bronchoscopy is mandatory when there is a history of significant haemoptysis or possible foreign body inhalation. A change in the voice may indicate vocal cord palsy.

Acute cough with increasing breathlessness—while usually due to acute bronchitis—should be assessed for asthma or anaphylaxis and treated appropriately.

Acute cough with fever, malaise, purulent sputum, or history of recent infection should be assessed for possible serious acute lung infection.

**Table 3** Causes of acute cough with a normal chest radiograph

- Viral respiratory tract infection
  - Respiratory syncytial virus
  - Rhinovirus
  - Influenza
  - Parainfluenza
  - Adenovirus
  - Respiratory corona virus
  - Metapneumovirus
- Bacterial infection (acute bronchitis)
- Inhaled foreign body
- Inhaled toxic fume

### 3.3.3 Physical examination

At the outset of the common cold there may be clinical evidence of a rhinitis and pharyngitis with inflamed nasal mucosa and posterior pharynx with adherent or draining secretions. Inspection of the ears may reveal serious otitis. A computed tomographic (CT) study of the nasal passages and sinuses in the common cold has shown that widespread rhinosinusitis, which clears on resolution of the infection, is most typical.<sup>23</sup>

The findings on high resolution computed tomography (HRCT) scanning of the lung have been reported in a group of 76 young adults with a common cold.<sup>24</sup> No important pulmonary changes were reported which is consistent with the normal findings usually reported on examination of the lower respiratory tract.

Acute cough is common in any patient presenting with pneumonia. Physical findings on examination of the chest are often very helpful and include dullness on percussion, bronchial breathing, and crackles on auscultation.

### 3.3.4 Treatment

#### Recommendations

- Acute viral cough is almost invariably benign and prescribed treatment can be regarded as unnecessary.
- Acute viral cough can be distressing and cause significant morbidity.
- Patients report benefit from various over-the-counter preparations but there is little evidence of a specific pharmacological effect.
- The simplest and cheapest advice may be to provide a “home remedy” such as honey and lemon.
- Central modulation of the cough reflex is common; simple voluntary suppression of cough may be sufficient to reduce cough frequency.<sup>25</sup>
- This may be the mechanism for the effect of simple drinks and linctuses.
- Opiate antitussives have a significant adverse side effect profile and are not recommended.

Because of the variable and episodic nature of acute cough, little firm evidence has been obtained in clinical studies. Cough challenge methodologies have, however, shown suppression of the cough reflex and active agents include:

- dextromethorphan;
- menthol;
- sedative antihistamines;
- codeine or pholcodine.

#### *Dextromethorphan*

This non-sedating opiate is a component of many over-the-counter cough remedies and has been shown to suppress acute cough in a single meta-analysis.<sup>26</sup> The generally recommended dosage is probably subtherapeutic. There is a dose response, and maximum cough reflex suppression occurs at 60 mg and can be prolonged.<sup>27</sup> Care must be taken in recommending dextromethorphan at higher doses since some combined preparations contain other ingredients such as paracetamol.

#### *Menthol*

Menthol by inhalation suppresses the cough reflex<sup>28</sup> and may be prescribed as menthol crystals BPC or in the form of proprietary capsules. Cough suppression is acute and short lived.

**Table 4** Over-the-counter antitussive preparations containing dextromethorphan or menthol

Adult Meltus <sup>®</sup> Expectorant with Decongestant (guaifenesin, pseudoephedrine, menthol)
Benylin Chesty Coughs <sup>®</sup> Original (diphenhydramine, menthol)
Benylin Cough and Congestion <sup>®</sup> (dextromethorphan, diphenhydramine, menthol, pseudoephedrine)
Benylin Dry Cough <sup>®</sup> (dextromethorphan, diphenhydramine, menthol)
Benylin Non-drowsy for Chesty Coughs <sup>®</sup> (guaifenesin, menthol)
Benylin Non-drowsy for Dry Coughs <sup>®</sup> (dextromethorphan)
Buttercup Syrup Honey and Lemon Flavour <sup>®</sup> (ipecacuanha, menthol)
Cabdrivers <sup>®</sup> (dextromethorphan, menthol)
Covonia Bronchial Balsam <sup>®</sup> (dextromethorphan, menthol)
Covonia Mentholated Cough Mixture <sup>®</sup> (liquorice, menthol, squill)
Covonia Night Time Formula <sup>®</sup> (dextromethorphan, diphenhydramine)
Expulin <sup>®</sup> (chlorphenamine, menthol, pholcodine, pseudoephedrine)
Histalix <sup>®</sup> (ammonium chloride, diphenhydramine, menthol)
Junior Meltus Dry Cough <sup>®</sup> (dextromethorphan, pseudoephedrine)
Meltus Dry Cough <sup>®</sup> (dextromethorphan, pseudoephedrine)
Multi-action Actifed Dry Coughs <sup>®</sup> (dextromethorphan, pseudoephedrine, triprolidine)
Night Nurse <sup>®</sup> (dextromethorphan, paracetamol, promethazine)
Nirolex for Dry Coughs with Decongestant <sup>®</sup> (dextromethorphan, pseudoephedrine)
Non-Drowsy Sudafed Linctus <sup>®</sup> (dextromethorphan, pseudoephedrine)
Robitussin Dry Cough <sup>®</sup> (dextromethorphan)
Robitussin Soft Pastilles For Dry Cough <sup>®</sup> (dextromethorphan)
Vicks Medinite <sup>®</sup> (dextromethorphan, doxylamine, ephedrine, paracetamol)
Vicks VapoSyrup for Tickly Coughs <sup>®</sup> (menthol)
Vicks VapoSyrup Dry Cough <sup>®</sup> (dextromethorphan)

#### *Sedative antihistamines*

First generation antihistamines with sedative properties suppress cough but also cause drowsiness. They may be a suitable treatment for nocturnal cough.

#### *Codeine or pholcodine*

These opiate antitussives have no greater efficacy than dextromethorphan but have a much greater adverse side effect profile and are not recommended.

Currently available over-the-counter cough treatments which contain dextromethorphan and/or menthol are listed in table 4.

## 4. CHRONIC COUGH

### 4.1 Epidemiology

In a European survey of young patients, which presumably included both acute and chronic cough, about 20% reported a non-productive or productive cough during the winter months.<sup>29</sup> In epidemiological surveys of the general population, persistent cough is reported in 18% of the US population, in up to 16% of a population in south-east England, and in 11% of the Swedish population.<sup>30–32</sup> The only study to grade cough severity found 7% of a general population had cough sufficient to interfere with activities of daily living on at least a weekly basis.<sup>33</sup> A higher prevalence of nocturnal and non-productive cough was reported in women than in men.<sup>34–35</sup> Most studies show a preponderance of females. This may be related to the increased sensitivity of cough reflex in women.<sup>36–37</sup> Cough is associated with a diagnosis of asthma, tobacco smoking in a dose related fashion, symptoms of reflux, irritable bowel syndrome, and obesity.<sup>33–38</sup> In the survey in south-east England, up to 16% of 9077 responders had cough every day on half the days of the year, and up to 13.2% had sputum every day or on half the days of the year; 54% of this cohort were current cigarette smokers.<sup>31</sup>

Exposure to pollutants or environmental irritants is an important aggravating factor. In adults and school children, productive cough or chronic nocturnal dry cough has been

associated with levels of the particulates, PM<sub>10</sub>.<sup>39-40</sup> Increases in levels of PM<sub>10</sub> are related to increased reporting of cough, sputum production, and sore throat in children with or without asthma.<sup>41</sup> Living close to heavy traffic may be associated with asthma symptoms and longstanding cough compared with those not living close to heavy traffic.<sup>42</sup> In the Italian Po Valley district, the increase in air pollution has been associated with an increase in cough incidence among females but not males.<sup>43</sup> Nocturnal cough in relation to indoor exposure to cat allergens was observed not only in sensitised but also in non-sensitised subjects.<sup>44</sup> There are no epidemiological data on the frequency of gastro-oesophageal reflux and rhinosinusitis with postnasal drip associated with chronic cough.

#### 4.2 Impact of cough on health status Recommendations

- Chronic cough has wide ranging and potentially profound effects of cough on health status.
- The evaluation of a patient with chronic cough should include an assessment of health status in clinical practice and research.
- The Leicester Cough Questionnaire is a well validated cough specific quality of life questionnaire that can be used to assess longitudinal changes in patients with chronic cough.
- Cough visual analogue scores are an alternative to cough specific quality of life questionnaires but are less well validated.

##### 4.2.1 Background

In acute cough, adverse effects on health status result from physical symptoms and are transient. In contrast, chronic cough is often perceived as a trivial problem but can be a disabling symptom associated with significantly impaired quality of life.<sup>3-4</sup> The impact on health status is varied, being minimal in some patients who do not seek medical attention to disabling in others, associated with impairment of quality of life comparable to other chronic respiratory disorders such as chronic obstructive pulmonary disease.<sup>45</sup> Physical, psychological, and social domains of health are commonly affected.<sup>3</sup> Patients with chronic cough frequently report musculoskeletal chest pains, sleep disturbance, and hoarse voice. More marked symptoms such as blackouts, stress incontinence, and vomiting can occur. The psychological impact of cough includes a high prevalence of depressive symptoms and worry about serious underlying diseases such as cancer and tuberculosis.<sup>46</sup> The impact of cough on social well being depends on individual circumstances and may result in difficulty in relationships, avoidance of public places, and disruption of employment.

Two recently developed self-completed cough specific quality of life questionnaires for acute and chronic cough can be used to facilitate communication with patients and establish information on the range of problems affecting them.<sup>3-4</sup> Both are well validated, repeatable, and have good responsiveness. The Leicester Cough Questionnaire (LCQ) is brief, easy to administer, and comprises 19 items divided into three domains: physical, psychological and social.<sup>3</sup> The standard deviation of the 2 week repeatability within-subject difference for the LCQ is 0.9 and a change of twice this is considered significant for an individual<sup>3</sup> (available at <http://thorax.bmjournals.com/cgi/content/full/58/4/339> – please seek permission from authors for use). The Cough Specific Quality of Life Questionnaire (CQLQ) is a 28-item questionnaire that has been developed and tested in North America.<sup>4</sup> The items are divided into six domains: physical complaints, extreme physical complaints, psychosocial issues,

**Table 5** Causes of chronic cough in patients with a normal chest radiograph

- Reflux disease
  - Gastro-oesophageal reflux
  - Laryngopharyngeal reflux
  - Oesophageal dysmotility
- Asthma syndromes
  - Cough variant asthma
  - Eosinophilic bronchitis
- Rhinitis

emotional well being, personal safety fears, and functional abilities. Studies to determine the minimal important clinical difference for both questionnaires are underway. Preliminary data suggest a good relationship between cough health status scores and cough visual analogue severity scores, but the relationship with cough diary scores has not been studied.<sup>3</sup>

##### Published evidence

Preliminary data from studies using cough specific quality of life questionnaires afford an insight into the effects of cough on health status. Quality of life is significantly impaired in acute cough; this impairment affects men and women equally.<sup>47</sup> In patients with chronic cough, quality of life is impaired and is worse in women than in men.<sup>48</sup> The psychological aspects of health status are particularly affected in patients with chronic cough.<sup>48-49</sup> There is good evidence that health status improves significantly after specific treatment for the cough.<sup>3-4</sup>

#### 4.3 Evaluation and management of chronic cough

##### 4.3.1 Taking a history

There is little evidence in the existing literature to determine the best questions to ask when taking a history from a patient with chronic cough. The same is true for clinical examination. Much of what is currently done derives from consensus as a result of individual physicians' experience. The aim is to exclude structural disease as a cause for cough. Non-specific associations also occur as a result of an abnormal cough reflex, itself associated with a number of factors. A detailed history will often suggest a likely association or trigger for chronic cough and should include a number of key components (table 5).

##### (a) Age and sex

- Chronic cough is more likely to occur in middle aged women.

##### Published evidence

Observational studies have shown a significant female preponderance.<sup>50</sup> The cough reflex is more sensitive in women with cough.<sup>37</sup>

##### (b) Smoking

- One of the commonest causes of persistent cough is smoking, which appears to be dose related. Patients often state that their cough changes in character with smoking cessation.

##### Published evidence

The prevalence of chronic cough is increased in smokers.<sup>29</sup> In a case-control study of almost 2000 subjects, Jansen *et al* reported an increased prevalence of chronic cough among smokers.<sup>51</sup> Smoking cessation leads to a short term increase in cough reflex sensitivity.<sup>52</sup>



**(c) Characteristics of the cough**

- Interpretation of the diagnostic characteristics of the cough should be done with caution.

*Published evidence*

One study has suggested that the character and timing of a cough are not diagnostically helpful.<sup>53</sup> However, others have suggested a characteristic pattern in reflux cough.<sup>54</sup>

Important areas of inquiry may establish that the cough is associated with frequent throat clearing or the sensation of post-nasal drip, occurs mainly at night or after meals, or is made worse with exercise or cold air. However, the symptoms of post-nasal drip in a patient may reflect only coexistent rhinitis and the absence of dyspepsia does not rule out reflux as the cause of cough. In one study the predictive values for cough characteristics and associated symptoms were calculated.<sup>55</sup>

A cough with a “honking” or “barking” quality and which disappears with sleep has been suggested as typical of a psychogenic or habit cough. Such characteristics have been frequently reported in the paediatric literature and may represent a tic cough.<sup>56</sup>

Consensus would suggest the following areas should be covered in the history in relation to the cough. It may be easier to ask the patients to complete a history questionnaire around which to structure the consultation (see Appendix 3 for suggested questionnaire framework).

*(i) Onset*

- Did coughing begin gradually or suddenly?

*Published evidence*

Cough of sudden onset may be clinically associated with foreign body aspiration.

*(ii) Duration*

- When did the cough start? How long have you had your cough?

*Published evidence*

There is no evidence linking the duration of cough to a particular association.

*(iii) Relation to infection*

- Did coughing begin after an initial upper respiratory tract infection—for example, a cold or sore throat?

*Published evidence*

Although patients commonly describe their persistent cough as starting after an infection, there are no data specifically linking ongoing viral infection to persistent cough. Viral infection enhances the cough reflex sensitivity<sup>57</sup> and may make subclinical bronchial hyperresponsiveness or reflux clinically apparent.

*(iv) Sputum*

- Is the cough dry/productive?
- Significant sputum production suggests primary pulmonary pathology

*Published evidence*

Numerous studies link chronic cough and sputum production. In a cross-sectional study in 18 000 Italian adults there was a 11.9% prevalence of cough and phlegm for a minimum of 3 months per year.<sup>58</sup> Primary pulmonary disease is more

likely in patients attending a specialist cough clinic with a productive cough.

*(v) Diurnal variation in cough*

- Patients cough less at night.
- A cough which abates overnight may be due to reflux (closure of the lower oesophageal sphincter).
- Asthma, infection, or heart failure can cause coughing which wakes patients.

*Published evidence*

Sleep is known to suppress the cough reflex. In a series of patients with lung disease and nocturnal cough, spontaneous cough was almost abolished during sleep stages 3 and 4.<sup>59</sup>

In an observational study in coughers, asthmatics and non-coughers, ambulatory recordings have shown a marked reduction in cough overnight.<sup>60</sup>

*(vi) Severe coughing spasms/paroxysms*

- Severe coughing paroxysms may be associated with syncope.
- The Driver and Vehicle Licensing Agency (DVLA) stipulates that those at risk of syncope should not be driving.

*Published evidence*

[www.dvla.gov.uk](http://www.dvla.gov.uk)

*(vii) Incontinence*

- Women with cough are often troubled by stress incontinence and this may be one of their major concerns.

*Published evidence*

In a questionnaire survey 55% of women reported urinary incontinence in association with chronic cough.<sup>54</sup>

*(viii) Origin of sensation*

- It is unlikely to be of diagnostic value to enquire where the sensation that leads to cough arises.
- Whatever the aetiology, the irritation leading to cough is usually localised to the throat or upper chest.

*Published evidence*

The site where cough sensations arise in the thorax tends to be poorly localised. One case study reported cough and tickly throat occurring during ventricular pacing.<sup>61 62</sup> These C-fibre sensations can be reproduced by systemic injections in both the throat and chest.

*(ix) Cough triggers and aggravants*

- Persistent cough may be perpetuated because the cough reflex is abnormally sensitive.
- A sensitised cough reflex is suggested if there is triggering of cough with change in air temperature, scent, sprays, aerosols, exercise.

*Published evidence*

Cough reflex sensitivity may vary from time to time, particularly when intercurrent respiratory infection occurs.<sup>57</sup> Other known cough aggravants have been shown to alter the sensitivity of the cough reflex—for example, angiotensin converting enzyme (ACE) inhibitors<sup>63</sup>—and diseases including asthma and gastro-oesophageal reflux disease (GORD).<sup>55</sup> The effect of air temperature, scent, sprays, aerosols, and exercise has not been studied.

**(x) Posture**

- Reflux is known to be related to posture, e.g. bending or lying down. However, there is no evidence demonstrating a connection between posture and reflux-related cough.

**Published evidence**

See Bonnet *et al.*<sup>64</sup>

**(xi) Food**

- Cough on eating and postprandially may indicate reflux cough.

**Published evidence**

Maximum stimulation for transient opening of the lower oesophageal sphincter is gastric distention which typically occurs 10 minutes postprandially.<sup>65</sup> In a retrospective review of patients with proven reflux cough, three quarters had cough with food or postprandial cough.<sup>66</sup>

**(xii) Cough on phonation**

- Cough on phonation such as talking on the telephone, laughing, or singing may indicate reflux because of lack of diaphragmatic closure of the lower oesophageal sphincter (LOS).

**Published evidence**

A retrospective review again showed that 90% of patients with reflux cough associated the symptom with phonation.<sup>66</sup>

**(d) Medications**

- Note all medications, particularly ACE inhibitors, and consider which might be causing or potentiating the cough. The cough may take some months to settle following withdrawal of ACE inhibitors.

**Published evidence**

Cough associated with ACE inhibitors was first reported with captopril in 1985.<sup>67</sup> It is a class effect, but the reported incidence variable may be as high as 16%. It is not dose related and time to onset is variable, occurring within hours or more than a year after start of treatment.<sup>68</sup> Studies identifying predisposing factors for the development of cough associated with ACE inhibitors have been largely inconclusive. A recent large retrospective cohort study has identified smoking, East Asian ethnicity, and previous ACE inhibitor associated cough as risk factors.<sup>69</sup> ACE inhibitors are associated with an increased sensitivity of the cough reflex, so they may aggravate cough due to other causes.<sup>63</sup> The cough invariably resolves on cessation of the drug. The median time to resolution is 26 days although it may be longer (up to 40 weeks) in some patients.<sup>68-70</sup> Most patients with ACE inhibitor associated cough can tolerate angiotensin II receptor blockers.<sup>71</sup>

There are only occasional reports of cough as a troublesome side effect of other drug treatments. One case report has attributed chronic cough to antiretroviral therapy in an HIV positive woman.<sup>72</sup> Dry cough has also been reported as a rare complication of interferon alpha treatment in chronic viral gastroenteritis.<sup>73</sup>

**(e) Occupation/hobbies/pets**

- A thorough occupational history should be sought as work place sensitisers can lead to chronic cough. The same is true of dust/chemical exposure at home.

**Published evidence**

Numerous studies and case reports provide accounts of persistent cough as a presenting feature of occupational sensitisation of the airways.<sup>74</sup> Significant excess cough was reported in workers exposed to hot acidic conditions in a bottle factory<sup>75</sup> and in workers exposed to hot chilli peppers.<sup>76</sup>

**(f) Past medical history and the association of cough with underlying disease****(i) Respiratory disease**

- Chronic cough is a common association of respiratory diseases and a thorough respiratory history should be sought.

Persistent cough is commonly associated with asthma including eosinophilic bronchitis and upper airway disease. These will be detailed in subsequent sections of this document. Common respiratory diseases which are readily appreciated as being associated with chronic cough will be addressed below.

**(ii) COPD**

Although patients with COPD commonly report cough, it is usually in association with production of phlegm and breathlessness.

**Published evidence**

Smokers with persistent cough may be at risk of developing COPD (GOLD).<sup>77</sup> A productive cough in patients with established airflow obstruction is predictive of lung function decline.

**(iii) Bronchiectasis**

Although usually associated with sputum production, "dry" bronchiectasis can cause persistent cough and a history of past respiratory insult as a potential trigger should be sought.

**Published evidence**

Patients with productive cough may have the same range of aetiologies as those with dry cough. The prevalence of bronchiectasis among patients attending specialist cough clinics is low, estimated at 4%.<sup>78</sup>

**(iv) Lung cancer**

Cough may arise as a consequence of the cancer itself, the treatment, or other co-existent disease.

**Published evidence**

Cough is the fourth commonest presenting feature of lung cancer.<sup>79</sup> Persistent cough contributes significantly to impaired quality of life. In one study, 39% of patients with inoperable non-small cell lung cancer scored cough prominently.<sup>80</sup>

**(v) Pertussis infection**

- Persistent pertussis infection can lead to chronic cough.

**Published evidence**

An increasing body of circumstantial evidence implicates pertussis as a cause of persistent cough. In a series of 180 prospective cases of chronic cough, 10% had nasal swabs positive for *Bordetella*.<sup>81</sup> In a case-control study of 201 patients with cough lasting up to 3 months, a significant increase in positive serology was reported for *Bordetella* in the patient group.<sup>82</sup>

**(vi) Atopic disease**

- There is an increase in respiratory symptoms in atopic individuals.

**Published evidence**

In a longitudinal comparative study in 620 adults, atopy was associated with bronchial hyperresponsiveness in symptomatic patients.<sup>83</sup> In Japan a separate syndrome of atopic cough is described,<sup>84</sup> although whether this is indeed a separate syndrome has been called into doubt.<sup>85</sup>

**(vii) Cardiovascular disease**

- Patients with heart disease can develop chronic cough and are at risk of myocardial infarction.

**Published evidence**

Analysis of the Framingham Heart Study data identified both chronic non-productive cough and productive cough as independent risk factors for myocardial infarction.<sup>86</sup>

**(viii) Organ-specific autoimmune disease**

- An association between chronic cough and organ specific autoimmunity has been reported.

**Published evidence**

An association between organ-specific autoimmune disease—in particular thyroid disease—has been reported.<sup>87</sup> In a case-control study, there was more autoimmune disease and a higher proportion of organ specific autoantibodies in patients with cough than in age and sex matched controls.<sup>87</sup>

**(f) Family history**

- Chronic cough may be familial, suggesting either an inherited anatomical abnormality or neurological condition.

**Published evidence**

A kinship of autonomic sensory neuropathy prevalence with reflux cough (possibly vagal) followed by peripheral sensory neuropathy was recently described.<sup>88</sup>

**4.3.2 Physical examination****Recommendation**

- Physical examination should concentrate on the afferent sites of the vagus nerve most commonly associated with the irritation leading to chronic cough.

The physical examination of the patient with chronic cough may demonstrate clinical signs of obstructive lung disease, lung cancer, bronchiectasis, pulmonary fibrosis, or cardiac failure. However, more often the examination reveals less specific findings.

Physical examination should concentrate on the afferent sites identified as most commonly associated with chronic cough.

An ear, nose and throat (ENT) examination may reveal evidence of nasal obstruction due to inflamed turbinates or the presence of polyps. The appearance of secretions draining in the posterior pharynx may be apparent. A “cobblestone” appearance of the oropharyngeal mucosa has been suggested but is an uncommon finding in the routine examination of patients with chronic cough.<sup>89</sup> Tonsillar enlargement is seen in some patients with chronic cough. Tonsillectomy can improve cough reflex sensitivity.<sup>90</sup>

Evidence of irritation of the larynx and pharynx on indirect laryngoscopy could suggest proximal gastro-oesophageal reflux.<sup>91</sup>

Examination of the chest is not useful in differentiating reversible airflow obstruction from fixed or partially reversible airflow limitation. Likewise, there are no features which easily distinguish cough variant asthma. Asking the patient

to inhale may trigger paroxysms of coughing. Chest auscultation may reveal wheezes and a prolonged expiratory phase on auscultation. Coarse crackles may be a prominent finding on examination of a patient with bronchiectasis, while widespread fine late inspiratory crackles are typical of diffuse parenchymal lung disease.

The presence of finger clubbing in a smoker together with evidence of a pleural effusion or lobar collapse on examination almost certainly points to a diagnosis of bronchogenic carcinoma.

In patients with a family history of chronic cough, neurological examination of the legs should be performed to look for signs of familial neuropathy.<sup>88</sup>

**4.3.3 Baseline investigations: primary care**

Cough is one of the most common symptoms of patients presenting to primary care, yet there are few studies investigating its management. One descriptive study found that 46% of patients presenting with a cough of more than 2 weeks' duration (28% of whom had a cough of more than 3 months' duration) had a diagnosis of asthma or chronic obstructive pulmonary disease.<sup>92</sup> This contrasts markedly with studies in secondary care and specialist cough clinics in which gastro-oesophageal reflux, cough predominant asthma, and rhinitis are the main causes. A number of reviews outlining the diagnosis and management of chronic cough in primary care have been published.<sup>93–95</sup> However, the evidence for these is predominately based on descriptive cohort studies and case studies/clinical experience from specialist centres.

**(a) Chest radiography****Recommendations**

- A chest radiograph should be undertaken in all patients with chronic cough and those with acute cough demonstrating atypical symptoms (see table 2).

**Published evidence**

There are numerous causes of chronic cough, many of which can be diagnosed from abnormalities on the chest radiograph. A study from a general respiratory clinic found that 31% of chest radiographs requested for the diagnosis of persistent cough were abnormal or yielded a diagnosis.<sup>2</sup> Studies using algorithms for the diagnosis of chronic cough have been validated in patients with normal chest radiographs.<sup>55 78 96–100</sup> If the patient has an abnormality on the chest radiograph that would account for his/her symptoms, this should be investigated appropriately and use of a diagnostic algorithm for chronic cough is not appropriate.

**(b) Assessment of pulmonary function****Recommendation**

- Spirometry should be performed in all patients with chronic cough.
- Patients with normal spirometry and bronchodilator response in whom the diagnoses of cough predominant asthma or eosinophilic bronchitis are being considered should be offered a therapeutic trial of prednisolone.

**Published evidence**

Spirometry is helpful in identifying cough caused by chronic airways obstruction.<sup>101</sup> If an obstructive pattern is identified on spirometry, forced expiratory volume in 1 second (FEV<sub>1</sub>) should be measured before and after inhalation of a short acting  $\beta_2$  agonist (for example, salbutamol 400  $\mu$ g by metered dose inhaler and spacer or 2.5 mg by nebuliser).<sup>102</sup> Normal

spirometry does not exclude asthma as a cause of chronic cough. In addition, many patients with asthma may not have spirometric reversibility sufficient to be defined as having asthma for the purpose of clinical studies.<sup>103</sup>

Single peak expiratory flow (PEF) measurements and, in particular, PEF to assess bronchodilator response are not as accurate as FEV<sub>1</sub> in diagnosing airflow obstruction as a cause of cough in primary care and should be avoided.<sup>104</sup> The role of serial PEF has not been studied in patients with persistent cough. Patients with “cough variant” or “cough predominant” asthma may not exhibit airways obstruction.<sup>99–105</sup> In addition, patients with cough due to eosinophilic bronchitis exhibit neither bronchial obstruction nor bronchial hyperresponsiveness.<sup>106</sup> Patients in whom the diagnosis is in doubt should be referred to a specialist centre.<sup>107</sup>

#### 4.3.4 Baseline investigations: secondary care

Studies from general respiratory clinics have reported poor diagnostic and treatment outcomes compared with specialist cough clinics that use comprehensive management algorithms.<sup>2–108–110</sup> Extrapulmonary causes, particularly gastro-oesophageal reflux, are frequently overlooked. The investigation of these conditions is dealt with under the specialist clinic section.

##### (a) Bronchoscopy

###### Recommendation

- Bronchoscopy should be undertaken in all patients in whom inhalation of a foreign body is suspected.
- Bronchoscopy may be useful in patients in whom other more targeted investigations are normal.

###### Published evidence

Bronchoscopy should be undertaken as an initial investigation in all patients suspected of having cough as a result of inhalation of a foreign body or aspiration. A retrospective study of 15 420 patients undergoing bronchoscopy without a history of inhalation of a foreign body, 91% of whom had a persistent cough and 63% of whom had normal chest radiographs, found that a foreign body was identified in only 0.3%.<sup>111</sup>

Descriptive studies have shown its diagnostic yield as part of a diagnostic algorithm for chronic cough is low (1–6%),<sup>78–98–100–112</sup> although in carefully selected cases the yield may be higher.<sup>113–114</sup> In addition, bronchoscopy allows inspection of the larynx for signs of chronic inflammation that may be a result of gastro-oesophageal reflux.<sup>91–115</sup>

##### (b) High resolution computed tomographic (HRCT) scanning of the thorax

###### Recommendation

- High resolution computed tomographic (HRCT) scanning may be of use in patients with persistent atypical cough in whom other more targeted investigations are normal.

###### Published evidence

The role of HRCT scanning of the thorax in the diagnosis of cough has not been properly evaluated. In a prospective study of patients with chronic cough and normal radiographs who had undergone a complex diagnostic protocol, HRCT scanning was claimed to be diagnostic in 24% of patients; however, multiple diagnoses were frequently reported in this study.<sup>100</sup> In carefully selected patients the diagnostic rate may be higher.<sup>116–117</sup> HRCT scanning is more sensitive and specific than plain chest radiography in diagnosing bronchiectasis and diffuse pulmonary diseases that may present with

chronic cough. Studies have shown abnormalities on HRCT scans in up to 42% of patients thought to have had a normal chest radiograph.<sup>118–120</sup>

#### 4.4 Diagnosis and management of specific cough syndromes

##### 4.4.1 Cough variant asthma and eosinophilic bronchitis

###### (a) Definition

An isolated cough in a patient without objective evidence of asthma—that is, variable airflow obstruction and evidence of eosinophilic inflammation. In cough variant asthma bronchial hyperresponsiveness is present, whereas in eosinophilic bronchitis it is absent.

These syndromes are a common cause of isolated cough, accounting for around 30% of cough referrals to cough clinics.<sup>50–121</sup> Clinical indicators of cough variant asthma include cough occurring nocturnally, after exercise, or after allergen exposure, although how reliable these features are is unclear. Some studies have highlighted overdiagnosis of cough variant asthma in children.<sup>122</sup>

###### (b) Diagnosis of cough variant asthma

###### Recommendations

Current methodology for measurement of airway hyperresponsiveness is well standardised and widely accepted. A negative test excludes asthma but does not rule out a steroid responsive cough.

###### Published evidence

This requires the demonstration of variable airflow obstruction and/or airway hyperresponsiveness. In patients with normal or near normal spirometric values (that is, FEV<sub>1</sub> >70% predicted), tests of airway responsiveness are more sensitive and specific than bronchodilator reversibility studies and PEF records.<sup>107–123</sup>

###### (c) Asthma syndromes and cough

###### Key points

- The presence of non-asthmatic corticosteroid responsive cough syndromes emphasises the importance of assessment of airway inflammation or, if this is not available, a trial of corticosteroids in all patients with chronic cough, irrespective of the results of tests of variable airflow obstruction and airway hyperresponsiveness.
- The test box provides clear guidance on interpretation of the results of treatment trials.
- The type of corticosteroid used in a trial and the duration of treatment is unclear; expert opinion is that cough is unlikely to be due to eosinophilic airway inflammation if there is no response to treatment with prednisolone 30 mg/day for 2 weeks.
- In patients with apparently corticosteroid resistant cough variant asthma, an alternative diagnosis should be considered.

###### Published evidence

Eosinophilic bronchitis is a common cause of cough.<sup>124</sup> It presents as an isolated chronic cough and is characterised by eosinophilic airway inflammation associated with increased Th2 cytokine expression<sup>125</sup> in the absence of airway hyperresponsiveness or variable airflow obstruction. It is unclear whether eosinophilic bronchitis represents a distinct clinical entity. Some patients with cough and asthma have non-eosinophilic airway inflammation.<sup>126</sup> This pattern of airway inflammation has been associated with corticosteroid

resistance,<sup>126 127</sup> theoretically it might be associated with a bronchodilator responsive but corticosteroid resistant cough. The prevalence of non-eosinophilic asthma in patients presenting with cough variant asthma is unclear.

#### (d) Management

##### Recommendation

- Management of cough variant asthma should follow national guidelines, except at step 3 where there is no evidence for use of a long acting  $\beta$  agonist.
- At step 3, evidence exists for the use of leukotriene receptor antagonists. Eosinophilic bronchitis and atopic cough respond to inhaled corticosteroids.
- There is insufficient evidence to give guidance on dose, preparation, and duration of inhaled corticosteroid therapy but use of the BTS asthma guidelines is recommended.
- There is some evidence to support the role of antihistamines and anti-leukotrienes in cough due to asthma and its variants, but larger scale studies are required.

##### Published evidence

Cough variant asthma responds to treatment with corticosteroids.<sup>128</sup> Leukotriene receptor antagonists have also been reported to be effective in reducing cough in this condition.<sup>129</sup> High dose antihistamines have been shown to dramatically reduce cough in seasonal asthma<sup>130</sup> but have not been specifically investigated in cough variant asthma. Eosinophilic bronchitis is characteristically resistant to treatment with inhaled bronchodilators but responds to inhaled steroids.<sup>131</sup>

Longitudinal studies have shown that up to one third of patients who present with cough variant asthma later develop the typical wheezing of classical asthma.<sup>84 132 133</sup> In contrast, the development of wheezing or airway hyper-responsiveness is extremely uncommon in eosinophilic bronchitis.<sup>134</sup>

#### 4.4.2 Gastro-oesophageal reflux disease (GORD)

##### (a) Background

Chronic cough due to gastro-oesophageal disorders has been reported in prospective studies in 5–41% of cases.<sup>97 100 110</sup> Confusion between different diagnostic criteria, symptoms of dyspepsia, extra-oesophageal reflux, and pH monitoring make quantification of cough due to GORD difficult.

Patients with GORD have an increased cough reflex sensitivity which improves with antireflux therapy.<sup>135–137</sup> GORD related cough may be induced by microaspiration of gastric content into the larynx and tracheobronchial tree.<sup>138–140</sup> A second proposed mechanism is through a vagally mediated oesophageal reflex stimulated by acid or non-acid volume reflux.<sup>141–143</sup> Oesophageal motor dysfunction<sup>144–148</sup> and reduced oesophageal clearance<sup>149</sup>—but not delayed gastric emptying<sup>150</sup>—can contribute to both of these mechanisms. The presence of a self-perpetuating cough-reflux cycle has also been suggested.<sup>143 151</sup>

##### (b) Does antireflux therapy improve cough associated with GORD?

##### Recommendations

- Proton pump inhibitors (PPIs) such as omeprazole 20–40 mg twice daily or equivalent taken before meals for at least 8 weeks.
- Prokinetic agents such as metoclopramide 10 mg three times daily may be required in a proportion of patients.

- Elimination of medications that potentially can worsen GORD should be considered.

##### Published evidence

A number of uncontrolled studies have reported that antireflux therapy produces an improvement in chronic reflux cough in 75–100% of cases.<sup>98 99 135</sup> In contrast, randomised controlled trials suggest that proton pump inhibitors (PPIs) twice daily improve cough in 36–57% of patients with gastro-oesophageal reflux related cough when given for 8 weeks.<sup>152 153</sup> Ranitidine 300 mg daily for 2 weeks improved cough in 54% of patients.<sup>154</sup> However, PPIs may be superior to H<sub>2</sub> antagonists.<sup>99 155</sup> Twice daily dosing and dosing before meals may be more appropriate.<sup>156 157</sup> Full acid suppression may only be achieved by a combination of twice daily PPIs and nocturnal H<sub>2</sub> antagonists.<sup>158</sup> A trial of treatment should be at least 8 weeks.<sup>96 98 152 153 159</sup> Prokinetic agents may be helpful in a proportion of patients.<sup>78 96 98 160</sup> Elimination of medications potentially worsening reflux (bisphosphonates, nitrates, calcium channel blockers, theophylline, progesterones) may also help.<sup>160</sup>

The GABA agonist baclofen increases lower oesophageal tone and decreases lower oesophageal opening and, in an open study, decreased the incidence of GORD related cough resistant to other treatment.<sup>161</sup> A non-specific effect on the cough reflex has also been demonstrated.<sup>162</sup>

##### (c) What is the role of antireflux surgery?

##### Recommendation

- Antireflux surgery may be effective in treating cough in carefully selected cases.

##### Published evidence

Some patients with GORD related cough may benefit from surgical intervention such as fundoplication.<sup>160 163 164</sup> However, the timing and indications for surgery remain undefined. Prior to surgery a careful evaluation should be undertaken including exclusion of other causes of cough, oesophageal ambulatory 24 hour pH measurement (measuring acid and alkaline reflux and the temporal association between cough and reflux events), oesophageal manometry, barium meal, gastric emptying studies, Bernstein acid infusion tests, trial of PPI treatment, and elimination of medications potentially worsening reflux.<sup>160 164 165</sup> Abnormal oesophageal motility may be associated with a less satisfactory outcome following surgery.<sup>145</sup>

#### 4.4.3 Upper airway disease and cough

##### (a) Definition

Upper airway disease causes a cough commonly accompanied by nasal stuffiness, sinusitis, and the sensation of secretions draining into the posterior pharynx from the nose or sinuses, sometimes termed post-nasal drip.

##### Key points

- There is an association between upper airway disease and cough but a poor association between the various symptoms and cough.
- There is disparity in the reported efficacy of antihistamines.
- In the presence of prominent upper airway symptoms, a 1 month trial of topical corticosteroid is recommended.

##### Published evidence

Post-nasal drip syndrome (PNDS) has been reported in the American literature as the most common cause of chronic

cough,<sup>97-99</sup> although this is not a universal finding.<sup>110</sup> A broad range of diseases of the upper airway are associated with post-nasal drip and cough. In contrast, many patients with observable post-nasal secretion do not cough. Whether PNDS is a distinct syndrome or merely a symptom has been debated.<sup>166</sup>

Symptoms<sup>89</sup> and clinical findings<sup>99</sup> are not reliable discriminators in establishing post-nasal drip upper airways disease as a cause of cough. A successful response to treatment directed at the upper airway is one recommended diagnostic approach.<sup>5</sup>

In the USA, recommended treatment involves a first line approach with a sedating antihistamine/decongestant combination.<sup>5</sup> The first generation antihistamines recommended in this document are not available in the UK and there is conflicting evidence as to the efficacy of second generation (less sedating) antihistamines in the treatment of cough.<sup>167 168</sup> There have been no randomised controlled studies evaluating the role of topical steroids in chronic cough, although one randomised placebo controlled trial has suggested that intranasal steroids given for 2 weeks are effective in the treatment of cough due to allergic rhinitis.<sup>169</sup> Intranasal steroids appear to be ineffective in the treatment of common cold symptoms including cough.<sup>170</sup> A number of prospective studies suggest that topical nasal steroids given for 2–8 weeks to patients with cough and post-nasal drip are effective.<sup>55 171</sup>

#### 4.4.4 Undiagnosed or idiopathic chronic cough

##### Key points

- Chronic cough should only be considered idiopathic following thorough assessment at a specialist cough clinic.
- The clinical history of reflux cough is often present in patients with idiopathic cough.
- A typical lymphocytic airways inflammation is seen in idiopathic cough.

##### Published evidence

In up to 20% of referrals to cough clinics<sup>55 87 172 173</sup> the cause of cough remains unclear after extensive investigations and treatment trials. It has been suggested that these patients represent a separate subgroup that should be labelled as idiopathic chronic cough. However, the clinical history usually suggests non-acid reflux and opinion is divided as to whether, in the absence of a definitive diagnostic or therapeutic intervention, this represents the underlying aetiology. If reflux is the underlying cause, then the airway changes seen in these patients represent the response to the refluxate. The alternative view that there is a separate syndrome is discussed below.

Patients with idiopathic cough are predominantly middle aged women who typically present with a long standing chronic dry cough which starts around the time of the menopause<sup>87 172 174</sup> and often appears to follow a viral respiratory tract infection.<sup>173</sup> Organ-specific autoimmune disease is present in up to 30%; autoimmune hypothyroidism is particularly common.<sup>87 172</sup> Patients have objective evidence of abnormal airways with a heightened cough reflex,<sup>175</sup> evidence of lymphocytic airway inflammation,<sup>87 174 176 177</sup> increased numbers of mast cells in bronchoalveolar lavage fluid,<sup>178 179</sup> and increased concentrations of tussive mediators such as histamine, prostaglandin (PG)D<sub>2</sub> and PGE<sub>2</sub> in induced sputum.<sup>180</sup> A plausible explanation for the development of cough is amplification of previously subclinical airway inflammation at the time of the menopause.<sup>174 181 182</sup> In some cases this airway inflammation may be as a result of

aberrant homing of inflammatory cells to the lungs from a primary site of autoimmune inflammation.<sup>87 183-185</sup>

When evaluating a patient with idiopathic cough, it is important to recognise common pitfalls in managing chronic cough. Treatment for idiopathic chronic cough is disappointing and is largely limited to non-specific antitussive therapy such as dextromethorphan and drugs with weak evidence of benefit such as baclofen and nebulised local anaesthetics (lidocaine, mepivacaine).<sup>186</sup> Low dose morphine has recently been shown to be helpful.<sup>187</sup>

#### 4.4.5 Treatment of cough due to other common respiratory diseases

Cough may be a prominent and debilitating symptom in a number of common respiratory diseases including lower respiratory tract infections (acute tracheobronchitis and pneumonia) COPD, lung cancer, diffuse parenchymal lung disease, and bronchiectasis.

##### Key points

- Cough can be a debilitating symptom in many common acute and chronic respiratory diseases.
- Suppression may be relatively contraindicated, especially when cough clearance is important.

##### Published evidence

In some conditions, in particular pneumonia and bronchiectasis, cough clearance is important and its suppression would be undesirable. The treatment of COPD is mainly directed at the control of symptoms and reduction of exacerbations, but no studies have evaluated the effectiveness of a particular treatment on the cough itself.<sup>188</sup> The majority of lung cancer patients experience cough.<sup>189</sup> Radiotherapy and both opioid and non-opioid antitussives have been recommended ([www.rcseng.ac.uk](http://www.rcseng.ac.uk)). Breathlessness is usually the most distressing symptom for patients with diffuse parenchymal lung disease. However, cough is frequently reported and can be debilitating;<sup>190</sup> only limited information is available on its treatment.<sup>191</sup> There are no randomised trials evaluating the benefit of treatment directed solely at cough. The treatment of diffuse parenchymal lung disease is outside the scope of this document and the reader is referred to the appropriate BTS guidelines on this topic ([www.brit-thoracic.org.uk](http://www.brit-thoracic.org.uk)).

## 5. GUIDELINES FOR SPECIALIST COUGH CLINICS

### General recommendation

- A systematic approach to diagnosis and treatment remains the most effective way to manage chronic cough. Important questions remain as to the complexity and cost effectiveness of existing diagnostic algorithms.

### 5.1 Introduction

The evaluation and management of cough in specialist clinics has been widely reported in the literature. Patients attending specialist cough clinics generally comprise non-smokers with a female preponderance of approximately 2:1.<sup>50</sup> They have often had a combination of baseline investigations and trials of empirical treatment before referral.

Studies in the primary literature from specialist cough clinics consist mainly of descriptive cohort studies and reports of clinical experience from centres with recognised expertise in cough evaluation and management. There have been no comparative studies of diagnostic methodology within or between specialty clinics. The recommendations for specialist clinics in this document will therefore comprise a review of the published evidence and the clinical experience of the Guideline Development Group.

## 5.2 Do specialist cough clinics offer superior diagnostic/management outcomes?

### Recommendations

- All clinics managing patients with chronic cough should ensure management protocols consider pulmonary and extrapulmonary causes of cough.

### Published evidence

Three studies have reported poor diagnostic and treatment outcomes in hospital based clinics where no established management algorithm for cough existed.<sup>2 108 109</sup> The experience in such clinics markedly contrasts with the generally high treatment success attributed to the specialist approach.<sup>55 98 99 171 192</sup> In non-specialist clinics extrapulmonary causes, particularly GORD, appears to be overlooked.

### 5.2.1 Comparison of specialist cough clinic protocols and outcomes

#### Recommendation

- Specialist protocols should continue to evaluate pulmonary and extrapulmonary causes for cough. Comparative studies of cough algorithms are required. No single existing diagnostic protocol can be recommended. A combination of therapeutic trials and targeted investigation is recommended when diagnostic doubt exists.

### Published evidence

No direct comparisons of management protocols between specialty clinics have been published. However, treatment success reported from specialist clinics ranges from 68% to 100%.<sup>55 97–100 171 192</sup> Thus, despite the specialist evaluation of cough, a significant number of patients remain undiagnosed. It is not clear whether this variance reflects differences in referral population.

### 5.2.2 Cost effectiveness of diagnostic cough algorithms employed by specialist cough clinics

#### Recommendation

- A combination approach of selected diagnostic testing and empirical trials of treatment is likely to be most cost effective.

### Published evidence

Algorithms for cough evaluation typically used in specialist clinics range from sequential trials of empirical treatment<sup>99</sup> to exhaustive diagnostic testing in all cases before any trial of treatment.<sup>100</sup> Only one study has explored the cost efficacy of such diagnostic cough algorithms.<sup>193</sup> The “investigate all then treat” approach was the most expensive, but with the shortest time to success compared with sequential trials of empirical treatment.

### 5.2.3 Is there a specific role for specialist cough clinics and when to refer?

#### Recommendation

- Referral to a specialist cough clinic should be encouraged when there has been a failure of empirical treatment.
- A directory of specialist centres should be made available.

The specialist cough clinics from Europe,<sup>55 124 148 194</sup> Asia-Pacific,<sup>84 192 195</sup> and the Americas<sup>98 100</sup> broadly report successful outcomes when comprehensive diagnostic protocols are

implemented. It would be desirable if all physicians were able to refer to a specialist cough clinic. Advice on how to set up a specialist cough clinic is given in Appendix 4. Appropriate referral criteria are:

- lack of availability of relevant diagnostic testing in primary or secondary care;
- failed trials of empirical treatment directed at asthma, GORD, and rhinosinusitis;
- a history suggestive of serious cough complication such as syncope or chest wall trauma;
- patient preference; and
- recruitment and participation in clinical trials of anti-tussive therapy.

## 5.3 Specialist investigations

### 5.3.1 Background

Mandatory investigations in patients with chronic cough are chest radiography and spirometry. This section will deal with more complex diagnostic tests where the interpretation remains open to debate, tests with largely research implications, and new innovations.

### 5.3.2 Bronchial provocation testing

#### Key points

- Current methodology for measurement of airway hyperresponsiveness is standardised and widely accepted. A negative test excludes asthma but does not rule out a steroid responsive cough.

#### Recommendations

- Bronchial provocation testing should be performed in patients without a clinically obvious aetiology referred to a respiratory physician with chronic cough and normal spirometric values.

### Published evidence

Most of the published accounts from specialist cough clinics have described their experience with bronchial provocation testing. The methods of measurement of airway hyperresponsiveness have been well standardised. In cough clinics, direct methods using methacholine or histamine are most commonly employed,<sup>55 98 171</sup> although indirect methods have been described.<sup>196</sup> There is broad agreement between cough centres that a positive test is suggestive of asthma and should prompt treatment with inhaled steroids.<sup>55 98 192</sup> The positive predictive value of this test ranges from 78% to 88%.<sup>55 98</sup> While a negative test in a patient with cough rules out asthma, it does not eliminate a cough which may respond to steroids. A number of independent centres have reported steroid responsive cough in patients with no evidence of airway hyperresponsiveness.<sup>124 195 196</sup>

Extrathoracic airway responsiveness can be assessed by recording the maximal inspiratory flow/volume curve during conventional bronchial challenge testing. Three groups have used this method in the assessment of cough.<sup>192 197 198</sup> There is no wide agreement as to the interpretation of this test.

### 5.3.3 Oesophageal testing

#### Key point

- Failure to consider GORD as a cause of cough is a common reason for treatment failure.

### Recommendation

- Empirical treatment should be offered to patients with cough and typical reflux symptoms before oesophageal testing.
- 24 hour pH monitoring poorly predicts the therapeutic response but may be indicated in cases of diagnostic doubt and in patients thought to require fundoplication.

#### *Published evidence*

Objective investigation for GORD—including barium studies,<sup>96 100</sup> upper gastrointestinal endoscopy,<sup>141</sup> and ambulatory oesophageal pH testing<sup>55 84 98 100 141 149</sup>—have been described. Ambulatory oesophageal pH monitoring is often regarded as the most sensitive and specific investigation for the diagnosis of GORD. A long term follow up study (median 30 months) has recently reported that less than 30% of patients with a “positive” oesophageal pH study respond to antireflux therapy, and no features on pH monitoring accurately predict the response.<sup>199</sup> One study has described a high prevalence of motility disorders in cough patients using oesophageal manometry testing.<sup>148</sup> As cough may arise as a consequence of non-acid reflux, impedance testing may offer new insights into GORD related cough.<sup>200</sup> No published reports of its application in cough currently exist. One study has advocated the use of empirical therapy in place of oesophageal testing.<sup>152</sup>

### 5.3.4 Sinus imaging

#### Key point

- Rhinosinusitis is commonly associated with chronic cough.

#### Recommendation

- Examination of ear, nose and throat should be performed in preference to sinus imaging in patients suspected of having rhinosinusitis but with persisting cough, despite an adequate trial of treatment directed at the upper airway.

#### *Published evidence*

Existing cough guidelines make few recommendations on the role of sinus imaging, preferring to observe the response to a course of specific treatment for nasal disease.<sup>10</sup> In selected patients (chronic cough and excess sputum production) a sinus radiograph has a reported positive predictive value of 81% and negative predictive value of 95%.<sup>78</sup> However, sinus radiographs are less sensitive than CT imaging of the sinuses.<sup>201</sup> In a prospective study, routine CT sinus scanning was no better than an ENT examination in accurately identifying upper airway disease as a cause of the cough.<sup>55</sup>

### 5.3.5 Fiberoptic laryngoscopy

#### Recommendation

- Specialist cough clinics should have access to fiberoptic laryngoscopy, preferably within the clinic setting.

#### *Published evidence*

Pernasal fiberoptic laryngoscopy provides a quick and simple method of viewing the laryngeal apparatus without sedation. The presence of laryngopharyngeal reflux may be determined by the characteristic changes associated with laryngeal inflammation and oedema.<sup>202</sup> These include pseudosulcus (subglottic oedema), obliteration of the laryngeal ventricle, erythema of the arytenoids, oedema of the posterior laryngeal wall, and laryngeal mucus.

### 5.3.6 Cough provocation testing

#### Recommendations

- There is no current evidence to support the routine use of cough challenge testing in the management of chronic cough.
- For research purposes, standardisation of methodology is required and accurate data on the distribution of cough responsiveness within the population are needed.

#### *Published evidence*

A variety of methods to measure cough reflex sensitivity have been described in the specialist cough clinic setting. These include tidal breathing challenge with low chloride solutions, and single breath challenges with capsaicin<sup>55 171 203</sup> and citric acid.<sup>37</sup> Although safe and relatively simple to perform, a review of cough provocation testing has highlighted the need for consensus on methodology.<sup>204</sup>

Unlike bronchial hyperresponsiveness, cough challenge reveals a wide range of normal cough reflex sensitivity. Cough provocation testing therefore has no clear diagnostic applications and is likely to be confined to the clinical research of cough.

### 5.4 Measurement and monitoring of cough

#### Key points

- Accurate measurement of cough helps determine cough severity, assess treatment efficacy, and may provide diagnostic information.
- Ambulatory cough recording currently offers most promise in the objective assessment of cough, although further technical refinement is required if it is to be broadly accessible to physicians.

#### *Published evidence*

A number of methods to measure cough frequency, intensity and severity have been described. Visual analogue scales and self-report cough diary cards have been used but do not consistently correlate with objective methods such as ambulatory cough monitoring.<sup>205</sup> The use of a series of different ambulatory cough recording monitors has been reported in both adult<sup>60 206</sup> and paediatric<sup>207–209</sup> literature. Although some technical limitations currently exist, they offer the best objective means of recording cough. Differences in the characteristics of the cough sound and flow pattern between asthma, bronchitis, and interstitial fibrosis have been reported.<sup>210</sup> Recently, analysis of overnight cough recording determined differences in character and intensity of cough sounds between patients with cystic fibrosis and those with cryptogenic fibrosing alveolitis.<sup>211</sup> These observations open the diagnostic possibilities for cough monitoring.

### 5.5 Assessing airway inflammation

#### 5.5.1 Induced sputum

#### Recommendations

- The demonstration of sputum eosinophilia has important treatment implications and should be available in cough clinics.
- Induced sputum should be requested after exclusion of other common causes.

#### *Published evidence*

A number of independent groups have adapted conventional diagnostic strategies for chronic cough to include induced sputum.<sup>84 124 195</sup> The demonstration of airway eosinophilia (>3% sputum eosinophil count) in patients without the



functional abnormalities (particularly bronchial hyperreactivity) associated with asthma has helped define eosinophilic bronchitis as a distinct cause for chronic cough. Eosinophilic bronchitis may account for up to 15% of cases of cough referred for specialist attention,<sup>124</sup> although debate remains as to whether eosinophilic bronchitis exists as a separate diagnostic entity.<sup>212</sup>

### 5.5.2 Exhaled breath

#### Recommendations

- There is insufficient evidence to recommend the routine use of exhaled breath measurements in the clinical evaluation of chronic cough.

#### Published evidence

Exhaled nitric oxide (NO) levels appear to be lower in non-asthmatic coughers, allowing some differentiation from asthmatic patients with cough.<sup>213</sup> Exhaled NO may represent a simpler alternative to induced sputum tests but currently it has no clear diagnostic role in the management of chronic cough. An increase in nitrite levels has been reported in exhaled breath condensate from asthmatic children with cough but not from non-asthmatic children with cough.<sup>214</sup> Measurement of many different inflammatory molecules in breath condensate, although currently a research procedure, may have a place in the future diagnosis of chronic cough.

### 5.6 Recommended diagnostic protocol (see Appendix 2, Parts 1 and 2)

The evaluation and management of cough in an adult should comprise two phases. The approach suggested in phase 1 is applicable to all physicians (primary and secondary care) encountering the patient for the first time. Treatment failure should prompt phase 2 of the evaluation algorithm. The algorithm is available online only at <http://www.thoraxjnl.com/supplemental>.

## 6. POTENTIAL NEW TREATMENTS FOR COUGH

### Recommendations

- There is an urgent need for multicentre phase II trials on new drugs carried out across specialist centres using objective methods of cough counting as well as subjective quality of life and symptom indices.

### 6.1 Background

Chronic cough is associated with many inflammatory airways diseases such as asthma, COPD, post-viral infections, pulmonary fibrosis, and bronchiectasis.<sup>10</sup> In some cases certain drugs can be used to inhibit the underlying inflammatory process that, under certain conditions, cause cough—for example, corticosteroids for the treatment of asthma or COPD, or PPIs as treatment for gastro-oesophageal reflux. However, there are patients who cough who do not respond to treatments directed at the cause of the cough, and there are patients in whom there is no identifiable cause to treat. Therefore, there is also a requirement to develop compounds that are targeted to inhibit sensory nerve activity directly (by inhibition of peripheral or central mechanisms), which should in theory inhibit cough of any aetiology.

### 6.2 New treatments under investigation

#### 6.2.1 Opioids

Attempts have been made to improve the therapeutic index by topical administration of a peripherally acting polar enkephalin analogue, BW443C81, which was shown to inhibit citric acid induced cough in guinea pigs.<sup>215</sup> However, in humans there was no effect on capsaicin induced cough in

normal volunteers.<sup>215</sup> A novel opioid peptide, nociceptin, which binds to the opioid receptor-like 1 receptor (NOP) has been shown to suppress capsaicin induced cough in guinea pigs and mechanically induced cough in the cat, but so far no data exist in humans.<sup>216 217</sup>

#### 6.2.2 Neurokinin receptor (NK) antagonists

The NK<sub>2</sub> receptor antagonist SR 48968 has been shown to inhibit citric acid induced cough in conscious guinea pigs,<sup>218 219</sup> and an antitussive effect of NK<sub>1</sub> receptor antagonists is still under debate. Although there is a report suggesting an antitussive effect of a dual NK<sub>1</sub>/NK<sub>2</sub> receptor antagonist (FK224) on bradykinin induced cough in asthmatics,<sup>220</sup> other studies have failed to demonstrate any antitussive action of compounds of this type.<sup>221</sup> Recent data have implicated a role for NK<sub>3</sub> receptor activation in evoking a tussive response possibly via a peripheral mechanism of action,<sup>222 223</sup> even though there have been no reports of the presence of functional NK<sub>3</sub> receptor antagonists in the human lung.

#### 6.2.3 Gamma-aminobutyric acid (GABA<sub>B</sub>) receptor agonists

GABA<sub>B</sub> agonists (such as baclofen) have been shown to inhibit capsaicin induced cough in the conscious guinea pig<sup>224 225</sup> and in normal volunteers,<sup>226</sup> and provided some benefit in patients with chronic cough.<sup>227</sup>

#### 6.2.4 Cannabinoid CB<sub>2</sub> receptor agonists

CB<sub>2</sub> receptor agonists inhibit guinea pig and human sensory nerve activation in vitro and the cough reflex in guinea pigs, which suggests that the development of CB<sub>2</sub> agonists, devoid of CB<sub>1</sub> mediated central effects, will provide a new and safe antitussive treatment for chronic cough.<sup>228</sup> No clinical data exist in humans.

#### 6.2.5 Local anaesthetics

Local anaesthetics such as lignocaine are delivered locally to the airways and have been shown to attenuate capsaicin induced cough in man.<sup>229</sup> However, the effect is transient and the antitussive effect is accompanied by oropharyngeal anaesthesia leading to an increased risk of aspiration of airway secretions and food.

#### 6.2.6 Transient receptor potential (TRP) channels

The cold and menthol sensitive receptor (CMR1) has recently been characterised and cloned.<sup>230</sup> Interestingly, menthol has been proposed as an antitussive therapy and has been shown to inhibit citric acid induced cough in normal volunteers.<sup>28</sup> The heat sensitive channel TRPV1 is activated by capsaicin, the main pungent ingredient in hot chilli peppers,<sup>231 232</sup> and capsazepine, a blocker of this channel, inhibits capsaicin and citric acid induced cough in the guinea pig.<sup>233</sup> An increase in epithelial nerve profiles expressing TRPV1 has been reported in patients with non-asthmatic chronic cough.<sup>234</sup> Compounds of this type are currently in clinical development.

#### 6.2.7 Potassium channel openers

NS1619, an opener of large conductance calcium activated potassium (BKCa) channels, has been shown to inhibit sensory nerve function and cough induced by citric acid in the guinea pig.<sup>235</sup> ATP sensitive potassium channels may also be a good target.

### 6.3 Conclusions

Treatment of the causes of cough can often be an effective treatment strategy. However, at the moment there are no effective treatments controlling the cough response per se with an acceptable therapeutic ratio. The future looks promising with several novel mechanisms identified;

however, most of these studies have been carried out in animal models and these may not be predictive of effects in man as evidenced by the compound attrition rate from preclinical to clinical studies of antitussives tested in the past. Furthermore, there have been no large scale clinical trials of antitussive drugs as most of the studies illustrated have investigated drug efficacy in simple capsaicin challenge protocols in normal volunteers. There is therefore an urgent need for multicentre phase II trials of new drugs carried out across specialist centres using objective methods of cough counting as well as subjective quality of life and symptom indices in these patients with chronic cough.

## 7. RESEARCH DIRECTIONS

- Determining the best methodology for investigation of antitussive therapy.
- Simple diagnostic test, particularly for gastro-oesophageal reflux.
- Causes of familial cough (genetic basis?).
- Relationship between cough/reflux/asthma.
- Fundoplication versus medical treatment.



The algorithm for the evaluation of chronic cough in adults is shown in Appendix 2 (Parts 1 and 2) available online at <http://www.thoraxjnl.com/> supplemental.

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## APPENDIX 1 PATIENT INFORMATION SHEET

### Patient information sheet



Most short term coughs are due to a virus infection. Antibiotics won't help, even if you are bringing up phlegm, and you probably don't need to see a doctor.

You'll probably feel tired, with a running or blocked nose, and perhaps have a mild fever and aching bones.

We recommend a home remedy, such as honey and lemon if you feel the need for treatment.

You can get treatment from a pharmacist (chemist). Cough remedies that contain dextromethorphan may be the most effective. Take some paracetamol. Menthol lozenges or vapour might help too.

Stop making it worse – **STOP SMOKING**

Remember, coughs and sneezes do spread diseases, try not to infect others! Use a handkerchief and don't forget to wash your hands.

You should see your doctor if

- You cough up blood
- You are breathless
- You have prolonged fever and feeling unwell
- You have a medical condition such as chronic bronchitis (COPD), heart disease, diabetes, asthma
- You have recently been in hospital
- Your symptoms persist for more than three weeks

## APPENDIX 2 PROTOCOL FOR THE EVALUATION OF CHRONIC COUGH IN AN ADULT

Appendix 2 Parts 1 and 2 is available online only at <http://www.thoraxjnl.com/supplemental>.

**APPENDIX 3 COUGH ASSESSMENT QUESTIONNAIRE**

Name			
Age			
Smoker:	y / n / never	packyears:	
Occupation:			
Duration of cough:			
Preceding URTI:	y / n		
<u>Describe cough (patients' words)</u>			
<hr/>			
<u>Dry / Productive</u>			
Sudden onset ? aspiration			
Phlegm (if produced):			
Nocturnal:	y / n		
Wakes from sleep:	y / n		
Difficulty getting to sleep:	y / n		
<u>Typical precipitants</u>			
Exercise:	y / n	Talking/laughing/singing:	y / n
Cold air:	y / n	Eating:	y / n
Aerosols:	y / n	Positional:	y / n
Cough on rising:	y / n	Eating and postprandial:	y / n
<u>Relieving medication (tick if tried y / n for response)</u>			
<input type="checkbox"/> Over the counter:	y / n	<input type="checkbox"/> Inhaled medication:	y / n (give details)
<input type="checkbox"/> Oral steroids course:	y / n	<input type="checkbox"/> Anti-reflux:	y / n (give details)
<input type="checkbox"/> Antibiotics:	y / n	<input type="checkbox"/> Nasal sprays:	y / n (give details)
<input type="checkbox"/> Codeine/opiates:	y / n	<input type="checkbox"/> Homeopathic:	y / n (give details)
<u>Associated respiratory symptoms</u>			
Wheeze:	y / n		
SOB:	y / n	Chest pain:	y / n
<u>Associated symptoms</u>			
Heartburn/epigastric pain:	y / n		
Postnasal drip:	y / n		
Voice change:	y / n		
<u>PMHx (respiratory)</u>			
Childhood wheeze:	y / n		
Atopy:	y / n	– cats / dogs / grasses / foods	
<u>PMHx (non-respiratory)</u>			
<u>DHx (particularly ACE I / <math>\beta</math>-blocker/NSAID):</u>			
<u>Family history of cough</u>			
<u>Systematic questions</u>			
<u>Examination</u>			
<u>Investigations to date</u>			

## APPENDIX 4 SETTING UP A SPECIALIST COUGH CLINIC SERVICE

### Why set up a cough clinic service?

A specialist cough clinic service offers a number of distinct advantages

- (1) Improved patient outcomes: treatment success is considerably higher for patients managed in a specialist cough clinic than in general respiratory clinics.
- (2) Avoidance of inappropriate prescribing: diagnostic uncertainty often leads to inappropriate use of antibiotics and inhaled corticosteroids.
- (3) Training: specialist cough clinics provide an environment for training and skill development for physicians (often specialist registrars in respiratory training programmes), pulmonary function technicians, and respiratory nurse specialists.
- (4) Clinical research: an improved understanding of the pathophysiology of cough and need to develop and evaluate new cough treatments requires the collaboration of clinicians, scientists, and the pharmaceutical industry. Specialist cough clinics ensure the accurate characterisation of patients with cough and provide opportunities for trusts with an interest in clinical research and pharmaceutical trial participation.

### Where to set up a cough clinic service?

A specialist cough clinic should provide a combination of diagnostic testing and treatment trials. Although specialist cough clinics have generally been set up in secondary care, they could be developed within a Primary Care Trust. There are no comparisons of treatment outcome or cost to recommend one or other.

### Core requirements

- (1) A named consultant or GP should have responsibility for the service.

- (2) All staff should be provided with training appropriate to their role in providing care.
- (3) To adequately supervise trials of treatment including assessment of cough severity (visual analogue scales and quality of life questionnaires).
- (4) Pulmonary function testing with spirometry as a minimum requirement.
- (5) Access to chest radiography and bronchial provocation challenge testing (methacholine inhalation challenge testing).
- (6) Facility to refer for oesophageal testing in appropriate circumstances.
- (7) Ear, nose and throat (ENT) assessment either on site (facility for direct laryngoscopy) or direct access to ENT clinic.
- (8) Access to bronchoscopy and chest CT scanning in appropriate circumstances.
- (9) The outcomes of the service should be subject to regular review.

### Desirable requirements

- (1) Facility to obtain and analyse induced sputum samples.
- (2) Cough provocation testing.

### Cost implications

#### Capital costs

- Essential items: spirometer (£200–2500)
- Non-essential: flexible laryngoscope (approximately £7000); cough provocation testing, dosimeter and nebuliser (approximately £4000).

#### Recurring costs

- Staff costs should include physician, pulmonary function technician, nurse specialist, and clerical time.
- Consumables—for example, methacholine challenge testing (approximately £50 per test).