

# COUGH

Professor Alyn H Morice  
Academic Department of Medicine  
Castle Hill Hospital  
Castle Road  
Cottingham  
East Yorkshire  
HU16 5JQ

Tel: 01482 624067

Fax: 01482 624068

Email: [a.h.morice@medschool.hull.ac.uk](mailto:a.h.morice@medschool.hull.ac.uk)

## Introduction

Cough is the commonest respiratory symptom, indeed it is probably the commonest of all symptoms which results in a consultation. The ten yearly morbidity Statistics in General Practice Survey reveal that consultation for cough and upper respiratory tract infection outweighs any other presenting condition by an order of magnitude. In the UK the market for cough remedies, most of which are at best poorly effective, is ten million pounds, whereas in the USA the cough/cold market is a staggering thousand million dollars. This massive health care burden is poorly understood in terms of etiological mechanisms and is very poorly treated, even with those drugs currently available. Because of a lack of knowledge of the pharmacology of these agents many patients are under treated.

In contrast to acute cough which is almost universally caused by a variety of viral respiratory pathogens, chronic cough is a diagnostic challenge which causes heart sink in most clinicians. In reality however the vast majority of chronic cough is easily explicable with a knowledge of the mechanisms sustaining cough. The problem is compounded by the fact that cough may arise from the upper respiratory tract – the realm of surgeons specialising in otolaryngology or the oesophagus and stomach, areas of expertise of the gastroenterologists. Yet, patients with chronic cough are mostly referred to chest physicians who have little or no training in either of these other areas. Thus, from general practice the patient is referred to the 'specialist' but unfortunately the specialist is poorly equipped to deal with the range of systems covered in the proper investigation and diagnosis of the chronic cough syndrome. Specialist cough clinics are relatively few in number and require the combined skills of specialist nursing staff, respiratory function tests not normally found within the average district general hospital, accurate and well tried oesophageal and gastric physiology departments and skilled and knowledgeable ENT and oesophageal surgeons. Without such a complex multidisciplinary approach many patients fall through the diagnostic net and are classified as 'idiopathic'. The complete and thorough investigation of a patient with chronic cough requires a true multidisciplinary approach. When such an approach is applied a remarkably high success rate is achievable. Some American authors claim a 100% success rate! On this side of the Atlantic the rates are less spectacular. The majority of patients, between 80 and 90% are successfully treated with sufficient resolution of symptoms to allow a return to a normal life.

My own experience in setting up a cough clinic after moving to Hull has confirmed that patients with chronic intractable cough can be treated successfully in specialist clinics. Our own success rate is running at about 90% over the past 250 referrals. What has been striking is that the quality of referrals has dramatically changed over this period of time. Instead of being asked to see patients who have had no trials of therapy for cough we are increasingly being asked to review patients who have undergone therapeutic challenge with all of the correct litany of drugs. This must mean that an increasingly large selection of patients are being successfully treated in general practice and one of the major aims of this monograph is to equip clinicians in primary care with the knowledge to enable all but the most intractable cases of chronic cough to be successfully treated without the need for referral.

Because acute cough and chronic cough have such widely differing causes and treatments I have made an attempt to strictly differentiate these two syndromes around the arbitrary cut off point of eight weeks. Because acute cough is a distressing but benign and self limiting condition current therapy is designed purely around suppression of cough. Whilst some of the suggested measures may be of use in the treatment of chronic cough, particularly in the short term, they should not be viewed as adequate

therapy for chronic cough. In contrast, chronic cough requires careful consideration of the diagnosis. Many hospital based authorities recommend rigorous evaluation using many tests, indeed, in the clinical protocol suggested by Palombini, all patients underwent a battery of 20, sometimes unpleasant, diagnostic tests. In contrast to this investigational feeding frenzy, most patients with chronic cough can be diagnosed from a careful history followed by appropriate therapeutic challenge. My objective is to provide the reader with the necessary knowledge to enable them to correctly advise and ameliorate both acute and chronic cough in the overwhelming majority of patients.

*Andy I have use I a lot here. Should this be we and I think you need to add a bit about the kids section in this intro*

## The basic mechanism of cough

Cough is a protective reflex which removes inhaled foreign bodies and excessive secretions from the respiratory tract. Thus, the main anatomical areas stimulating the cough reflex are located in the upper airways, particular the larynx, and cough sensitivity diminishes as the airways divide until, in the smallest airways, cough cannot be elicited. It is important to realise that cough can be precipitated at sites other than at the respiratory tract. Instrumentation of the ear may precipitate coughing as can, in sensitive individuals, irritation of the oesophagus. The common thread which unites all of these disparate sites is that they are supplied by the vagus nerve. Stimulation of vagal afferents (there is still much debate as to the type of fibre which is stimulated) leads to stimulation of the brain stem. A distinct cough centre has never been clearly identified. Throughout this afferent part of the cough reflex neuronal traffic is subject to major modification. In man cortical influences are very important and it is possible to consciously suppress cough for considerable periods. Similarly the desire to cough may be inhibited by simple measures such as drinking cold water. This may result from stimulation of inhibitory pharyngeal receptors and a combination of pharyngeal and cortical effects may underlie the activity of cough linctus with a so called demulcent action.

Recent findings have made it clear that there is extreme plasticity of the afferent arm of the cough reflex and as a consequence, even when there is obviously a biochemical mechanism producing the cough as in ACE inhibitor cough, cough may persist for months after stopping treatment. In children such repetitive behaviour may underlie habitual cough. Whilst chronic cough may have very important psychological aspects we do not believe that psychogenic cough is common. Indeed, studies have shown that psychological abnormalities disappear once the organic underlying cause of the chronic cough is treated.

The efferent arm of the cough reflex is a coordinated contraction of the respiratory musculature against a closed glottis. The glottis then opens and the expelled air approaches the speed of sound shearing off any mucus within the airways. This gives rise to the characteristic low frequency component of a wet cough. Because of a high degree of coordination required in the respiratory musculature, particularly in the upper airways and larynx, neurological disorders such as stroke, motoneuron disease and Parkinsonism may have profound effects on the efferent arm of the cough reflex.

We are beginning to understand the basic biochemical mechanisms which translate chemical or mechanical stimulus into an afferent nervous impulse. In experimental cough the most frequently used agents for producing cough fall into two broad groups. Firstly acids, particularly complex organic acids, have been used to provoke cough since the 1950s. Since it seems immaterial as to which acid is used it is likely that cough receptor is sensitive to protons. Secondly the pungent extract of peppers, capsaicin and other vanilloid compounds such as resiniferatoxin are the most potent tussive agents known. The putative cough receptor is an ion channel located in sensory nerves which is sensitive to both acid and capsaicin. Since capsaicin is a vanilloid the receptor is called the vanilloid receptor or VR1. The vanilloid receptor is modulated by a range of inflammatory mediators, particularly by lipoxigenase products similar to the leukotrienes involved in asthma. Through this biochemical pathway asthma and other forms of inflammation may modulate the cough reflex and it is likely that viral cough also hijacks this receptor to produce what is the commonest symptom presenting in clinical medicine.

## Acute cough

The vast majority of acute cough is caused by upper respiratory tract viral infection. It makes a perfect sense for respiratory viruses and bacteria to have evolved the ability to cause cough. Once an organism has successfully invaded the respiratory tract its main problem for continued survival is how to spread to the next host. Some viruses do this by producing intense coryza and transmitting themselves from person to person by manual transmission of infected secretion. However, the majority are required to transmit themselves in aerosolised droplets. The ability to produce a cough is therefore a vital part of the pathogenic armamentarium of the respiratory tract virus. From the host's point of view there is little reason to suggest that the cough produced in an upper respiratory tract infection is useful. Whilst small amount of secretions may be expectorated they in no way contribute to the clearing of the airways in normal subjects. If one looks at a more extreme example of infective airway inflammation such as community acquired pneumonia, despite sometimes extensive consolidation only a few mls of sputum is produced, the vast majority of the purulent exudate being removed by phagocytosis via the blood stream. Thus, in normal subjects infective cough is likely to be detrimental and there is no evidence that effective cough suppression in respiratory tract infection is harmful, indeed, it may even reduce viral transmission.

An exception to this generalisation are subjects with pre-existing lung disease. In particular patients with bronchitis, bronchiectasis and related conditions such as cystic fibrosis should only have treatments designed to suppress cough under specialist supervision. Such patients can be easily identified however; they invariably have a history of chronic sputum production, usually of considerable volume. Such patients with chronic productive cough are at risk from extensive mucus plugging which can lead to a deterioration in the matching of ventilation and perfusion within the lung and the danger of consequential respiratory failure. In normal subjects there is no such risks. In patients with chronic sputum production the clinician's most important initial response is to send sputum for culture and sensitivity. This is because frequently 'viral' respiratory tract infections lead to an exacerbation of a colonising bacteria and such organisms may be not those usually found in infections in a previously normal respiratory tract. Bacteria such as *haemophilus influenzae*, *moraxella catarrhalis*, *pseudomonas aeruginosa* frequently do not respond to first line respiratory antibiotics such as amoxicillin and therapy should be directed by culture and sensitivities. In the rest of this chapter it will be assumed that suppression of cough is directed at patients with previously normal lungs.

It is helpful to understand the natural history of some of the more common respiratory tract pathogens since this can predict the time course and intensity of disease. Unfortunately in our present state of knowledge there is only a relatively few areas where we can specifically intervene in the etiology of cough. It is clear from cough challenge studies where subjects are asked to inhale increasing doses of agents such as capsaicin or citric acid that the cough reflex is heightened during the viral respiratory tract infection. This explains the precipitation of cough by non specific stimuli such as cold air and pollutants such as tobacco smoke. How viruses cause this up-regulation of the reflex remains a mystery.

## Common precipitants of acute cough

Epidemiological studies have shown that the average person has a clinically observable respiratory tract infection by virus three or four times per year. The viruses causing these infections include influenza, parainfluenza, rhinovirus, adenovirus, respiratory syncytial

and the respiratory corona virus. All of these viruses share a common short incubation period of between one and four days.

## Influenza viruses

Because of its ability to undergo antigenic shift and genetic recombination influenza occurs in epidemics. Influenza viruses are RNA viruses of the orthomyxoviruses group and are classified into three serotypes, A, B and C. Influenza A is the commonest and most severe type. The viral structure is important in terms of therapy since the viral proteins required for successful binding to the host cell, haemagglutinin and neuramidase, are targets for therapy; in particular neuramidase is blocked by the anti-influenza drug Relenza. Clinically influenza has an incubation period of two days. A presentation of a patient with fever in the presence of a known outbreak of influenza is sufficient for accurate diagnosis. Typically the cough comes on within six hours of start of illness and maybe prolonged for at least two to three weeks after other symptoms have resolved. The patient failing to respond, particularly those with diseased lungs, bacterial super-infection should be considered.

## Specific therapy

The most widely used method of prophylaxis against influenza is the use of vaccination. Two types of vaccine are available, one consisting of inactivated whole virions and the second 'split' subunits. They are administered in two doses in children, one month apart, and annually to susceptible individuals.

Because of the changing nature of the influenza virus, each year a different vaccine will be required. The actual nature of the vaccine is recommended by the World Health Organisation and the antigenic type thought to be the most likely to be responsible for the coming season's infections are grown on chick embryos. This latter method of culture leads to them being contraindicated in those with hypersensitivity to eggs.

Because of the annual variation in the influenza virus and the necessity of the vaccine being a best guess, vaccination is not a universally successful strategy and protection may range around 75% on average. This is too little to prevent epidemics but is a useful strategy in individual patients. Influenza vaccine is therefore recommended only for high risk individuals. The following groups are specifically targeted:

- chronic respiratory disease including asthma
- chronic heart disease
- chronic renal failure
- diabetes melitis
- immunosuppression due to disease or treatment, including asplenia or asplenic dysfunction

Immunisation is also recommended for all persons over 65 years and for residents of residential homes for the elderly and long stay facilities. In pandemic years vaccination of medical staff is also recommended.

Amantadine hydrochloride has been shown to be effective in short term prophylaxis for influenza infection. It probably acts by inhibiting viral uncoating or transcription of the

viral RNA. Amantadine is not without side effects and should only be used for high risk patients.

### Parainfluenza viruses

Parainfluenza viruses differ from influenza viruses in that they are much more antigenically stable and have a different pattern of assembly within infected cells. There are four subtypes. Types one and three are particularly important causing serious lower respiratory tract infections, croup and tracheobronchitis in infants and young children. In all parainfluenza viruses are thought to be responsible for a fifth of all non bacterial respiratory tract disease in childhood.

Clinically the disease may present with abrupt croup but is more commonly gradual onset progressing over two to three days. The condition usually remits within two weeks. Since immunity to re-infection is only transient it is one of the commonest causes of the typical infective cough which plagues families with small children. There is no current method of control or specific therapy.

### Respiratory syncytial virus

Respiratory syncytial virus (RSV) is the single most important aetiological agent in cough in infancy. RSV occurs in epidemics, usually between the autumn and early spring. Each outbreak lasts between two and three months and can involve as many as half of all families with children. It seems that older family members introduce the virus to the younger children, in whom most of the serious effects are seen. There is also a second peak of infectivity in the elderly.

The usual incubation period is one to four days and the onset is characterised by rhinitis. The disease rapidly reaches a peak and is characterised by paroxysmal cough, wheezing and frequently respiratory distress in the younger patient. Stridor may or may not be present and in its absence the mistaken diagnosis of asthma is sometimes made. Unfortunately, immunity to RSV infection is transient so re-infection is common.

### Specific therapy

Ribavirin may be given by inhalation for the treatment of the severe bronchiolitis caused by RSV in infants.

Palivizumab is a recently introduced monoclonal antibody indicated for the prevention of RSV infection in infants. Its use is restricted to those at severe risk.

### Adenoviruses

There are over 100 serotypes of adenovirus. Perhaps eight of these serotypes are important in the production of a syndrome of severe acute cough. Clinically adenovirus infection may be detected by the presence of pharyngitis and/or conjunctivitis. Indeed, the phrase pharyngoconjunctival fever has been described as the illness associated with adenoviral infection. Immunity following infection is good but since so many serotypes are associated with cough then there is plenty of opportunity for repeated infections within a lifetime. There is no specific therapy.

## Rhinoviruses

Rhinoviruses are known as the common cold virus. In fact, they represent over 100 serotypes and are the major cause of mild upper respiratory tract infection and cough in children and adults. Because of the myriad of serotypes of rhinoviruses immunity to the clinical disease is very poor and there is no current specific therapy.

## Coronaviruses

These viruses are similar in clinical presentation to rhinoviruses and may be responsible for between 5 and 10 % of human coughs and colds.

## Post viral cough

When cough, which has been precipitated by viral respiratory tract infection persists for longer than eight weeks the syndrome is termed post viral cough. This clinically recognised condition is represented within the European literature but is not mentioned in studies from America. This is one of a number of examples of different appreciation of 'diseases' in different societies.

Some patients endure repeated episodes of post viral cough and it seems that they are predisposed to sustained increase in the cough reflex following viral inflammation. This heightened sensitivity can be demonstrated with inhalational cough challenge. It is possible that the receptors responsible for transmitting cough are upregulated by the inflammation of respiratory tract infection and that the upregulation continues well after the virus has disappeared. Post viral cough can be resistant to treatment. Both short acting bronchodilators and anti cholinergic agents have been tried and been found to be ineffective. Inhaled steroids may work in some patients but evidence is difficult to obtain in a condition which remits spontaneously. Once again clinical trials with adequate numbers of patients have not been performed. A pragmatic approach would be to treat post viral cough in the same fashion as viral cough and await spontaneous resolution.

## Epidemiology of acute cough

A number of interesting features of acute cough may be gleaned from the Morbidity Statistics in General Practice Survey. The data set is collected by participating practices and represents a snapshot of consultation and diagnosis within England and Wales. Presentation with upper respiratory tract infection is by far the commonest consultation in general practice and, therefore, represents an enormous workload within the National Health Service. The rate of consultation varies enormously with age and sex. Perhaps unsurprisingly children, or rather their parents, consult at a very high rate: a mean of six consultations per annum. The rate rapidly falls in childhood and at age 15 a very interesting gender difference appears in consultation rates. During the reproductive years consultations are twice that for women than they are for men. After the age of 55 consultation rates in both men and women become equal again. Whilst this could be explicable by societal differences in that women have easier access to general practice and consult more, this is not borne out by examination of the statistics for other symptoms and there are intriguing clues to the fact that women may have a heightened cough reflex compared to men. Women exposed to cough challenge with protussive agents cough twice as much as men or conversely cough the same amount at a lower

dose. This could be explained as being an artifact of inhaling drug into a smaller lung volume but women are also over-represented in those patients who develop ACE inhibitor cough. Again, the ratio of men to women is approximately two to one. Thus, it is possible that the increased consultation rate seen in women in the reproductive years is due to an intrinsically heightened cough reflex in women.

The reason for the well recognised winter exacerbation of respiratory tract infection induced cough is unknown. In recent years this has only been in part due to influenza. The other major viruses circulating causing the winter exacerbation are adenoviruses and respiratory syncytial virus. The seasonal nature of acute cough makes for predictable strain on the Health Service. The few specific remedies available to us such as influenza vaccination and the prophylactic use of drugs such as Relenza may have an impact on winter exacerbations but there is still each year an increase of ten fold in the number of consultations. One method of reducing patient contact may be by supplying simple written advice such as that detailed in Table 1.

## The treatment of acute cough

By definition acute cough is benign and self-limiting. A case can be made therefore for withholding treatment and indeed this is what the majority of the population does. However, some infections produce cough of such distressing intensity that treatment may be requested or even demanded. Such treatment was recently reviewed by the Drug & Therapeutics Bulletin and it was concluded that there was no effective treatment. This is because there is a marked lack of clinical trial evidence in this area. Whilst this observation is correct I believe the conclusion to be wrong. The problem with determining what is efficacious in cough arises from the extreme difficulty of performing proper randomised, double blind studies in a variable symptom such as acute cough. Cough itself is a very variable and episodic phenomenon and within a given population there is also a marked intersubject variation in cough intensity and duration. Finally, in a symptom caused by a wide variety of different organisms of varying natural history, providing adequate power to compare treatment with the control group requires vast numbers of patients. Thus, there is no gold standard clinical study in the literature on which to base treatment strategies. I believe however, absence of evidence is not evidence of absence (of therapeutic effect).

If one takes second line evidence, such as those obtained from cough challenge studies and there is a wealth of evidence suggesting that many treatments available do have a significant effect on the cough reflex.

## Symptomatic treatment of acute cough

As alluded to previously there have been very few well conducted studies in the treatment of acute viral cough. Based on indirect evidence from challenge studies treatment aimed at cough suppression can be considered at least partially evidence based.

### Dextromethorphan

This antitussive agent is virtually unknown within the prescribing medical community and yet is the commonest used antitussive. Its efficacy in cough suppression has been shown in several studies but dosing in over the counter medicines is rarely adequate. Being the dextro isomer of morphine dextromethorphan is virtually devoid of opiate side effects and causes little constipation, drowsiness or euphoria except at extremely high

doses. Because of its very good safety profile it is found in the majority of cough remedies. There is a dose response in terms of efficacy on the cough reflex and in normal adults 60 mg will give significant suppression of the cough reflex. We have demonstrated that the effects of dextromethorphan are long lived and, indeed, one study showed significant suppression of cough 24 hours after dosing. The schedule for dosing in most cough remedies therefore is illogical and is not based on a knowledge of pharmacokinetics. Patients should take an adequate first dose of medication ie 60 mg in the adult and repeat dosing should be infrequent rather than the qds recommended.

Dextromethorphan has an interesting metabolism in that it is converted to the less active compound dextrorphan in the liver by the cytochrome P4502D6. This cytochrome is polymorphic in that approximately 1 in 10 of the caucasian population has little or no enzyme activity. These slow metabolisers will have long lived high drug levels, but given the safety of dextromethorphan this appears to have no deleterious effects.

## Codeine

Unlike dextromethorphan codeine is an agonist at the conventional opiate receptors. Treatment of cough with codeine produces the usual spectrum of side effects, which at a dose required for effective antitussive activity may be unacceptable to many patients. In a recent clinical study 60 mg of codeine was equivalent in terms of cough suppression to dextromethorphan but a considerable number of our subjects suffered profound hypotension, nausea and dysphoria. So, whilst codeine is often seen as the gold standard in terms of antitussive therapy its side effect profile makes it unsuitable for routine clinical practice. This tendency for side effects has been got over in many products by inadequate dosing leaving the codeine portion of any remedy little more than a placebo.

## Alcohol

Alcohol in the form of spirits has been demonstrated to effectively suppress the cough reflex. In adult patients this can be particularly successful for nocturnal cough suppression. In my own hands a 10 year old malt whisky from Islay appears particularly effective.

## Menthol

Menthol is an effective cough suppressant working on ion channels to diminish the activity of the afferent neurons of cough reflex. The major problem with menthol therapy is that there is no suitable delivery device. Suppression of evoked cough has been demonstrated even with chest rubs. Oral therapy is ineffective due to the rapid metabolism of the menthol. Sustained release of menthol from buccal absorption is the most usual strategy used in cough linctus. Some patients with chronic cough find sucking of menthol or menthol/licuorice lozenges useful. In infants menthol solutions may be administered by application to clothing or bedding.

## Chronic cough

The three common causes of chronic cough, cough predominant asthma, oesophageal disease and rhinitis may present without any other clues to diagnosis. However, every effort should be made to find a specific diagnosis in an individual patient since therapy is frequently lifelong and therefore errors are costly. Clues to the diagnosis may be obtained in the history but this should be considered in the light of the therapeutic response. A common presentation to the cough clinic is "asthma" without any response to medication. The cough remits on withdrawal of inhaled medication and institution of treatment for the otherwise asymptomatic reflux or rhinitis.

## Asthmatic Cough

A major difficulty with the diagnosis of asthmatic cough is the varied understanding of what is meant by a diagnosis of asthma. In the minds of many clinicians asthma is characterised by variability in lung function, either spontaneously or induced by pharmacological agents. Indeed, such 'reversibility' is frequently used as entry criteria for trial of anti-asthma therapy. In clinical practice however less than 10% of patients in asthma clinics may actually exhibit the required 15% reversibility to high doses of inhaled salbutamol. So, whilst this criteria is good for including patients with definite asthma in clinical studies it is very poor at identifying all patients with asthma.

Another feature of asthma that is commonly used in epidemiological studies to define the size of a problem in a population is a challenge test with an inhaled bronchoconstricting agent. This is usually a substance such as methocholine or histamine which either directly or indirectly causes spasm of bronchial smooth muscle and thus wheezing. Asthmatic subjects wheeze and bronchoconstrict at much lower concentrations than normal subjects. Such tests, whilst more accurately defining asthmatics, do miss a considerable number of subjects. Either patients with mild bronchial hyperresponsiveness due to other atopic diseases such as hay fever are included or alternatively subjects with bronchospastic asthma may on rare occasions not exhibit hyperresponsiveness. Thus bronchial hyperresponsiveness, whilst being fairly closely associated with asthma, is not an absolute necessary requirement for the diagnosis. In any case such tests are usually restricted to hospital practice and even then performed relatively rarely.

Other attempts to objectively define asthma have focused around the type of inflammation within the airways peculiar to asthma. The detection of eosinophils in the sputum or markers of inflammation for breath such as NO are taken by some as being the best non-invasive test to establish a diagnosis of asthma. However, examining the sputum for eosinophils is fiercely difficult and requires skilled technical support which is not available in most hospitals.

In this volume a practical approach to the diagnosis of asthma is taken. That is, if there is an appropriate response to anti-asthma treatment then whatever the result of the various tests it is still asthma or rather one of the asthma syndromes.

## Asthma syndromes

## Classic asthma

In classic asthma there is evidence of variable airflow obstruction. Such evidence is easy to obtain in ordinary clinical practice by asking patients to fill out a home diary record card with peak flow monitoring, readings being made morning and evening. An observation period of peak flow measurements before starting therapy in isolated chronic cough (ie when wheezing and shortness of breath are absent) is important to establish whether there is indeed evidence for classic asthma. Diurnal variation revealed as a sort of pattern on the peak flow chart is characteristic of classic asthma. Morning dipping first described by Sir John Floyer 400 years ago is a cardinal feature. However, such obvious diagnostic clues are rare in patients with isolated asthmatic cough. A much more frequent pattern is variability in peak flow of a small degree (less than 10%) without particular pattern. On starting anti-asthma medication variability decreases and often there is a gradual rise in peak flow compared with pre-treatment baseline. Final peak flow pattern is one without variability. Because of the difficulty in definition of "asthmatic cough" the term cough preponderant asthma has become established and the asthmatic syndromes without bronchoconstriction are discussed below.

## Cough preponderant asthma

In 1986 Irwin described six patients with cough who responded to anti-asthma treatment but who did not have bronchoconstriction. When tested for bronchial hyperresponsiveness these patients exhibited typical asthmatic responses. Thus, he defined what he called cough variant asthma as cough responding to anti-asthma treatment in the presence of bronchial hyperresponsiveness but without bronchospasm. This entity is commonly seen in the cough clinic. Because there is a lack of significant bronchoconstriction many referring clinicians are put off the diagnosis of asthma. Clues that this is the correct diagnosis may be found in the history. There is often a history of atopy and either childhood eczema or hay fever. This may be present in either the patient or a first degree relative. Frequently the cough is productive of small quantities of coloured sputum. The green colour is due to the eosinophils. Unfortunately, a history of specific trigger factors is often not helpful. Patients with a variety of other cough mechanisms also cough to inhalation of fumes, perfume, tobacco smoke etc.

Key to the diagnosis of cough preponderant asthma is the response to therapy. Corticosteroids are the cornerstone of this therapeutic trial. Inhaled corticosteroids usually provide at least some clinical response. As always there are enormous problems with drug delivery of inhaled medication. I recommend the use of dry powder inhalers, particularly those not containing any excipient, since these are less likely to cause cough during inhalation. In the absence of response as defined by the diary record card and/or peak flow either the diagnosis is incorrect or the patient may be relatively resistant to inhaled medication. In the absence of any other obvious diagnosis then it is permissible to undertake a therapeutic trial of oral prednisolone 20 mg a day for two weeks. The patient should be fully informed that this is a therapeutic trial as an experiment to see whether there is any reduction in cough. There is a small but significant minority of patients with cough preponderant asthma who only respond to parenteral treatment with steroids. If such a response does occur then attempts to wean oral steroids using second line agents such as leukotriene antagonist, long acting beta agonist or anti IgE therapy (which should be available shortly) are appropriate.

Despite adequate doses, up to 800 mcg, of inhaled steroids many patients remain symptomatic. There is little or no evidence that pushing the dose of inhaled steroids above moderate doses has any effect. Indeed, the potential for local side effects within the larynx and pharynx particularly thrush and myopathy increase rapidly with

increasing doses. Second line agents should be construed as add in therapy. Here the approach differs from classical asthma where it is quite clear that the majority of patients will respond to one of the long acting beta agonist in addition to moderate doses of inhaled steroids. Since cough preponderant asthma is not characterised by bronchoconstriction a long acting beta agonist may not be the second line agent of choice. Two small studies show that leukotriene antagonists are effective in this circumstance and may be a more logical treatment here since lipoxygenase products have recently been demonstrated to directly stimulate the putative cough receptor.

## Eosinophilic bronchitis

The term eosinophilic bronchitis is reserved for patients who again respond to anti-asthma medication but do not exhibit either bronchoconstriction or bronchial hyperresponsiveness. As the term implies sputum examination reveals eosinophils. Whether eosinophilic bronchitis represents a separate disease or is part of a spectrum of asthma is hotly debated and obviously depends on which definition of asthma is used. Patients with eosinophilic bronchitis may be relatively resistant to anti-asthma therapy, only responding to high doses of parenteral steroids or more severe immunosuppression. Attempting to control the disease is important since a proportion of these patients do on to develop fixed airflow obstruction or bronchiectasis.

## Cough due to gastroesophageal disease

In approximately one quarter of patients with chronic cough the cause is gastroesophageal disease. Whilst many patients suffers symptoms of heart burn and acid reflux chronic cough can be the only presenting symptom of reflux oesophagitis. Patients can be identified by clinical history. An exacerbation of cough by certain foods can be characteristic, chocolate, hot spicy foods, and dry foods such as biscuits are most frequently mentioned. Some patients find that the cough occurs before food is actually placed in the mouth. Other important clues to the diagnosis are exacerbation on recumbency or bending. Worsening of symptoms on holiday or business trips also occurs. One useful strategy to identify causal relationships is to ask the patient to keep a diary. This can be done in association with peak flow recordings in order to differentiate between reflux-associated cough and asthma. Most peak flow diary record cards provided by the pharmaceutical industry are more than adequate to record cough as well. However, the majority of them do not try and score symptoms in any detail and we routinely ask the patients to look back over the previous 24 hours and score their cough on a 0 –9 scale. It is sometimes helpful to ask the patient's partner to also note cough frequency since some patients have a very poor appreciation of the degree of symptomatology.

Having identified a patient as having cough possibly due to gastroesophageal disease the next step is a therapeutic trial of antireflux therapy. There are two important considerations in the treatment of cough due to reflux. Firstly, therapy should be at a high dose and secondly that therapy should be prolonged – probably at least two months – before the trial is said to be unsuccessful. The reason for the delay in therapeutic response in some patients is unknown but probably relates to the mechanism whereby oesophageal disease causes cough.

Until recently it was thought that cough associated with reflux was exclusively due to aspiration of stomach contents. Whilst this is maybe an important mechanism in certain conditions in such as motor neurone disease, in otherwise normal subjects this 'up and over' hypothesis does not explain the production of cough in all patients. In an elegant study from Australia Ing et al. demonstrated that in patients with reflux cough instillation

of small amounts of acid in the lower oesophagus reproduced symptoms. Indeed, whilst many of these patients were very sensitive to acid, some also coughed to saline solution. It appears in these patients with reflux cough that there has been an increased sensitivity of cough receptors located within the oesophagus and this resetting of the reflex may explain the need for prolonged therapy before resolution of the symptoms occurs.

We recently studied a number of patients with chronic cough that was thought to be due to gastroesophageal disease. We found that a number of patients who did not have reflux as defined by the criteria for heartburn did however have marked abnormalities on oesophageal manometry. The commonest abnormality was weak lower oesophageal sphincter but gross dysmotility was also observed. We believe in addition to classic acid reflux in the oesophagus and larynx other abnormalities such as 'volume reflux' caused by stomach contents of neutral pH refluxing into the oesophagus and oesophageal spasm may also cause chronic cough. Thus prokinetic therapy with metoclopramide and domperidone may be usefully added to proton pump inhibitor therapy. Response to these prokinetic agents is however relatively infrequent and in selected case it may be necessary to prescribe cisapride on a named patient basis.

If a patient with suspected oesophageal cough has a partial response to therapy but is unsatisfied with the thought of long term drug treatment or the cough is still disruptive then an option is operative treatment. A Nissen fundoplication performed by laparoscopic techniques is relatively atraumatic and whilst the procedure does have some side effects, the inability to rapidly bolt food and some weight loss, these are usually accepted by patients. Some patients selected for surgery find a dramatic improvement in quality of life.

## Rhinitis and the post nasal drip syndrome

The reported incidence of rhinitis and post nasal drip vary enormously between different cough clinics. This is probably for two reasons. Firstly, the difficulty in defining and therefore quantifying post nasal drip syndrome and, secondly, in a difference in the patient reporting and understanding of symptom complex. An interesting example of this is a large telephone survey conducted by Proctor and Gamble in which subjects were asked whether they had a cold in the last six months. If the answer was positive they were then questioned as to what symptoms they had during the illness. Over one third of North Americans questioned said that post nasal drip was a prominent feature. This was considerably less in Europe and South America. This may go some way to explain the difference in prevalence seen in the various cough clinic studies.

Whether the syndrome is called post nasal drip or rhinitis there is little doubt that upper airway inflammation causes cough in a significant number of patients. It seems likely that the upper airway inflammation reflects inflammation in the area of the larynx which leads to exacerbation of cough rather than there being any physical 'dripping' onto the larynx which is presumably the main source of stimulation of the cough reflex.

Patients with upper airway nasal symptoms should be given a therapeutic trial of intranasal steroid and/or antihistamines. It is North American practice to give combination therapy. However, in Europe it is more common to prescribe individual agents in a stepwise fashion. The choice of antihistamine is interesting. Whilst there is little clinical trial evidence available the older agents appear to have greater efficacy than some of the more modern non sedating antihistamines. One possible explanation for this observation is that many of the modern highly specific H1 antagonists have been designed and shown to block only the H1 receptor. Recent research has shown that there are at least four histamine receptors with the H3 receptor playing a possible

important role in allergic inflammation. The agents such as Cetirizine may be more efficacious because of their broader spectrum of activity.

## ACE inhibitor cough

That this systemically active drug for hypertension should cause, as a side effect, chronic dry cough was such a surprising finding was that it was not found in any of the large post marketing surveillance studies following the launch of captopril and enalapril. In fact ACE inhibitor cough occurs in approximately 15% of patients started on therapy and its onset is very variable. Severe intractable cough can come on after as little as four doses and conversely the cough may not present as a side effect until a number of years of apparently innocuous therapy has passed. Shortly after the discovery of ACE inhibitor cough a number of studies, including our own (see figure) demonstrated that the cough is due to a resetting of the cough reflex. Given that we now know that women have an intrinsically heightened cough reflex it is not surprising that women outnumber men in ACE inhibitor cough by two to one.

## Clinical characteristics of ACE inhibitor cough

The history in ACE inhibitor cough is quite characteristic. The patient feels that there is a tickle at the back of the throat which leads to paroxysms of coughing. These may be extreme enough to lead to vomiting. Between episodes the patient is asymptomatic and ACE inhibitor cough is not associated with the other known class related side effects of ACE inhibitors such as angio oedema or dysgeusia. In addition there is no association with asthma predisposition and if the patient's main complaint also includes shortness of breath then other causes such as worsening heart failure should be sought.

## The diagnosis of ACE inhibitor cough

The majority of patients with ACE inhibitor cough are fairly easily diagnosed by cessation of therapy. Unfortunately, a group of patients continue to cough for prolonged periods after stopping ACE inhibitors. Referral to the cough clinic frequently is accompanied by remarks in the referral letter that the cough could not be due to ACE inhibitors since these have been stopped for a period of time and the cough remained. The patient has usually then been put back onto ACE inhibitors. The correct diagnostic test should be cessation of therapy or substitution with an angiotensin II receptor blocker for a period of at least four months. Not infrequently in patients with a prolonged ACE inhibitor cough there is a second underlying reason for cough such as gastroesophageal reflux. The ACE inhibitor causes exacerbation of cough on this background making it difficult for the patient to differentiate the underlying cough from the superadded effects of the ACE inhibitor. A harmless way to prove this is to undertake a re-challenge with ACE inhibitor and the patient, because of their previous experience, usually recognise the onset of this 'different' cough.

Table ? – Advice for patients with cough of recent onset

- Most short term cough is due to a virus and so antibiotics do not help
- Coughs and sneezes do spread diseases. Try not to infect others
- Effective treatment is available over the counter at the pharmacy. Ask for a cough linctus containing the drug dextromethorphan. At least 60 mg of this drug is required for effective relief in adults
- In adults a moderate amount of alcohol will help to suppress the cough, particularly at night
- In both children and adults menthol, again available from the pharmacy, will help prevent bouts of coughing
- Simple cough/cold does not require treatment from your doctor. The most effective medicines are available at the pharmacy. Consult your doctor if you have additional unusual symptoms such as persistent chest pain or coughing up of blood, or if you cough goes on for longer than six weeks

Flow diagram

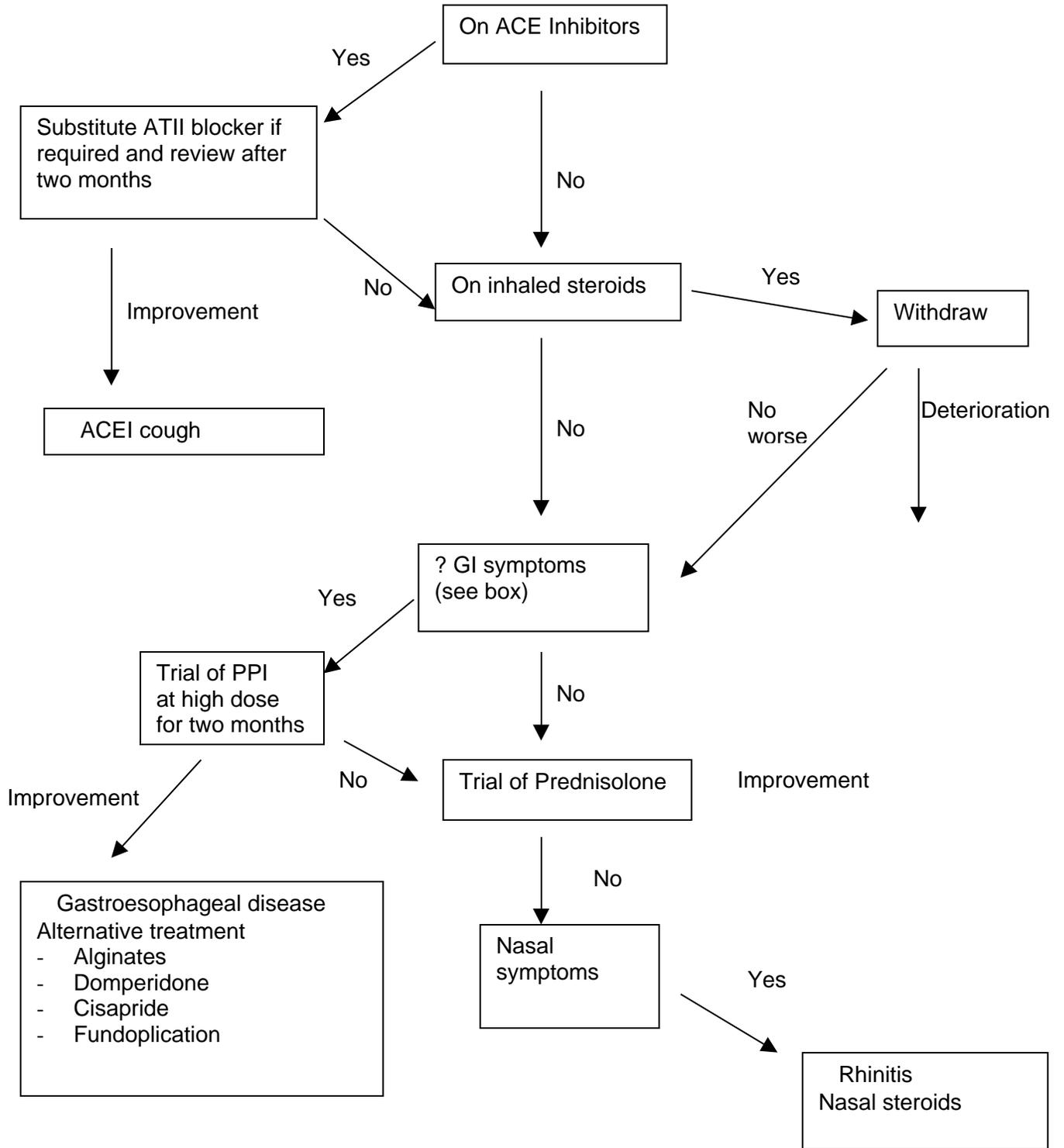


Table ? – The most frequent causes of chronic cough presenting to cough clinics with normal chest Xray

1. Asthma syndromes <ul style="list-style-type: none"><li>• Cough variant asthma</li><li>• Eosinophilic bronchitis</li><li>• Classic bronchoconstricting asthma</li></ul>
2. Oesophageal disease <ul style="list-style-type: none"><li>• Gastroesophageal reflux</li><li>• Oesophageal dysmotility</li><li>• 'Volume' reflux</li><li>• Weak lower oesophageal sphincter</li></ul>
3. Upper airways disease <ul style="list-style-type: none"><li>• Rhinitis</li><li>• Post nasal drip syndrome</li></ul>
4. ACE inhibitor cough
5. Post viral cough

Table ? – The most common causes of cough presenting to cough clinic with abnormal chest Xray

1. Bronchiectasis <ul style="list-style-type: none"><li>• Post infective</li><li>• Allergic broncho pulmonary aspergillosis</li><li>• Foreign body</li></ul>
2. Alveolitis <ul style="list-style-type: none"><li>• Cryptogenic fibrosing alveolitis</li><li>• Extrinsic allergic alveolitis</li></ul>
3. Lung cancer
4. Non infective pneumonias <ul style="list-style-type: none"><li>• Cryptogenic organising pneumonitis (COP)</li><li>• Bronchiolitis obliterans organising pneumonia (BOOP)</li><li>• Wegner's granulomatosis</li></ul>

Table ? – Basic investigations in the diagnosis of chronic cough

1. <ul style="list-style-type: none"><li>• Chest Xray</li><li>• Reversibility Inhalation of salbutamol (peak flow or FEV<sub>1</sub>)</li><li>• Home peak flow monitoring (one month)</li><li>• Sputum culture and sensitivity (when applicable)</li></ul>
--