

DIAGNOSIS IN GENERAL PRACTICE

Chronic cough in adults

Kevin Barraclough

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Hoyland House, Painswick, Stroud
GL6 6RD

k.barraclough@btinternet.com

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This case is an example of how “test of treatment” can be used when the diagnosis is uncertain

Case scenario

A 42 year old non-smoking woman presents with a three month history of cough after a coryzal illness. The cough is worse in the morning and rarely produces sputum. She is not short of breath, and she has been taking an angiotensin converting enzyme (ACE) inhibitor for two years for hypertension.

The diagnostic dilemma

Chronic cough is somewhat arbitrarily defined as any cough with a duration of eight weeks.¹ It is common in primary care. In one postal survey of 11 000 patients registered with four general practices, 14% of men and 10% of women reported coughing on more than half the days in the year.² In practice, smokers rarely consult about their cough because they assume (usually correctly) that smoking is the cause.

The problem in diagnosis is differentiating between the common causes of chronic cough—asthma, chronic obstructive pulmonary disease, postnasal drip, gastro-oesophageal reflux disease (GORD), and drug (ACE inhibitor) induced—and not missing rare but more serious causes.

In primary care the cause of chronic cough is often uncertain, and asthma is a common diagnosis. In a study in secondary care of 78 adult non-smokers with chronic cough and a normal chest x ray, in 73 (94%) the cough was considered to be caused by one or more of the “pathogenic triad” of asthma, gastro-oesophageal reflux, and postnasal drip syndrome. In 48 patients (62%) there was more than one cause.³ Studies from specialist cough clinics found that the cause of chronic cough can be established in 89-100% of cases, making the previously popular diagnosis of “psychogenic cough” redundant.⁴ In smokers, chronic cough is common and can also be the presenting feature of chronic obstructive pulmonary disease or bronchogenic carcinoma.

“Red flag” symptoms

In both smokers and non-smokers, certain features require early investigation:

- Copious production of sputum (indicating bronchiectasis)
- Fever, sweats, weight loss, haemoptysis (indicating tuberculosis, lymphoma, bronchial carcinoma)
- Considerable breathlessness with the cough (indicating heart failure, obstructive airways disease, fibrotic lung disease).

The approach to diagnosis: the test of treatment

If there are no red flags, “test of treatment” can be a useful approach in primary care⁵—a formal diagnosis may be less important if the patient is satisfied with their response to the treatment, and if no serious conditions are missed. If the patient relapses on stopping treatment, the putative diagnosis is more likely to be correct and a second “therapeutic challenge” may be justified.⁵ In a secondary care series of 131 patients with unexplained chronic cough, this approach was more cost effective than expensive investigations such as bronchial challenge or bronchoscopy.⁶

Assessment should initially elicit the information outlined in the box. The figure outlines a plan for establishing the diagnosis using a pragmatic test of treatment, based on the *European Respiratory Journal's* guideline on chronic cough.⁷

Stopping smoking

Although this does not apply in our case scenario, several longitudinal studies show that stopping smoking leads to a reduction in the cough (but often not resolution) by two months.⁸ Smokers are clearly at high risk for chronic obstructive pulmonary disease and cancer, and chest x ray and spirometry are needed to determine whether these conditions are the cause of chronic cough in smokers.

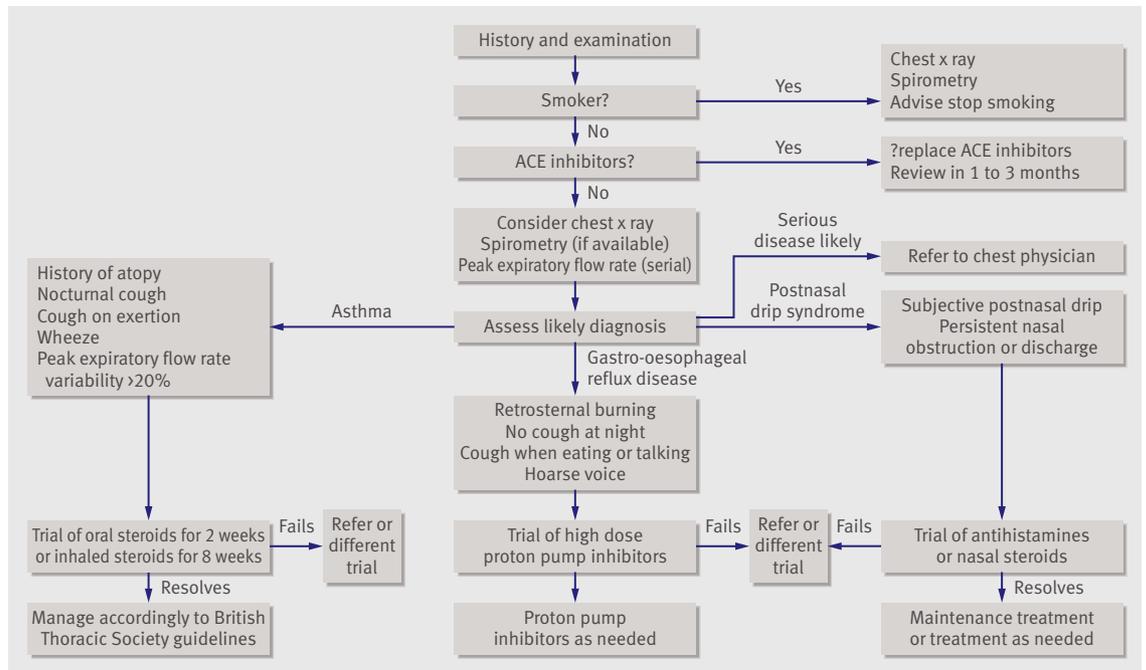
Stopping ACE inhibitors

Treatment with ACE inhibitors leads to chronic cough in up to 15% of patients, and the cough may start after some years of treatment. Cough usually stops with one to four weeks of stopping treatment but may persist for up to three months.⁹

Consider simple tests

Chest x ray, spirometry, and serial peak expiratory flow rate may not be required in all primary care

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Establishing a diagnosis by using “test of treatment”

patients with chronic cough, but consider them in non-smokers with “red flags”—possible asthma, work exposure to dusts or irritants, or recurrent cough—after a test of treatment.

Trial of treatment for asthma and its variants

Asthma is usually diagnosed on the basis of symptoms (cough, especially nocturnal or on exercise, and wheeze) and reversible airways obstruction. However, it may manifest solely as cough without airways reversibility (cough variant asthma).³ These patients have bronchial hyper-responsiveness on provocation testing with inhaled methacholine or histamine, but otherwise no variation in peak flow. Another group is described as having a cough with eosinophilic sputum but no hyper-responsiveness on challenge (non asthma eosinophilic bronchitis) (see table).¹ A pragmatic view would be that all these variants should respond to inhaled or oral corticosteroids.

Inhaled corticosteroids should be trialled for at least eight weeks. Some evidence shows that although classic asthma may respond within two weeks of treatment, cough variant asthma and eosinophilic bronchitis may take up to eight weeks.¹⁰

Asthma can be “ruled in” if serial peak expiratory flow rate or spirometry before and after bronchodilator treatment show >20% reversibility. However, a negative result does not rule out the diagnosis, as many patients with asthma do not manifest reversible airway obstruction at a given time. A retrospective review of 590 patients with asthma at a tertiary clinic showed that only 9% had >15% airways reversibility.¹¹ Moreover, patients with eosinophilic bronchitis do not show reversibility (table). Thus, reversibility on spirometry has 100% specificity for asthma but a low sensitivity (possibly only 9%).

Asthma, and its variants, are the final diagnosis in 20-30% of patients referred to chest clinics with chronic cough.¹⁰ Limited evidence suggests that chronic cough is ascribed to asthma far more commonly in primary care,⁹ although this may represent overdiagnosis of asthma and a failure to recognise other causes, such as gastro-oesophageal reflux disease.¹²

Trial of proton pump inhibitors for gastro-oesophageal reflux

Chronic cough may be the only manifestation of gastro-oesophageal reflux, which may be the diagnosis in 10-40% of individuals with chronic cough.¹³ This cough rarely occurs during sleep, is more common on waking or sitting up, and may be associated with hoarseness, whereas the cough associated with asthma is typically described as being worse at night. Other suggestive clinical features include retrosternal

Clinical features to be elicited

- Duration and frequency of cough
- Pattern of cough: productive or dry, nocturnal, postural, or associated with food
- Haemoptysis or chest pain
- Smoking history and exposure to dust
- Use of ACE inhibitors
- Red flags—for example, breathlessness, sweats, weight loss
- Absence of focal chest signs (including normal heart sounds)
- Results of spirometry or serial peak expiratory flow rate if asthma or chronic obstructive pulmonary disease is likely or if a first test of treatment fails
- Chest x ray if patient smokes or red flag is present; consider also if first test of treatment fails

Cough syndromes responsive to corticosteroids

Diagnosis	Peak flow variability	Bronchial hyper-responsiveness on challenge	Sputum eosinophilia
Classical asthma	Yes	Yes	Yes
Cough variant asthma	No	Yes	Yes
Eosinophilic bronchitis	No	No	Yes

“burning” chest pain, which is often positional or occurs hours after food, and coughing while eating or talking.

A meta-analysis of 15 studies showed that response or non-response of symptoms to a trial of proton pump inhibitors had a sensitivity of 78% and a specificity of 54%, measured against 24 hour pH monitoring.¹⁴ Thus about 20% of patients with proved gastro-oesophageal reflux do not respond to proton pump inhibitors—but most of the studies in the meta-analysis assessed symptoms after only two weeks. Little evidence exists to guide treatment duration, and high dose proton pump inhibitors may take one to three months to stop chronic cough.¹

Treatment of rhinitis, sinusitis, and postnasal drip

Clarity declines somewhat with the last condition of the triad: postnasal drip syndrome. This lacks an objective standard for diagnosis, and is suggested clinically if the patient is aware of something dripping down the back of their throat or has a recurrent desire to clear their throat.³ The diagnosis is strengthened if symptoms respond to antihistamines, decongestants, or nasal corticosteroids. How commonly this causes chronic cough is disputed, as is the required duration and dose of treatment.^{14 17 15}

Consideration of pertussis infection

Bordetella pertussis infection is now said to be an unrecognised cause of chronic cough in adolescents and adults, with serological evidence of recent pertussis infection in 13-32% of adults with prolonged cough.^{16 17} In primary care, however, the importance of this diagnosis in chronic cough is questionable. A test of treatment is not feasible: antibiotics do not affect the course of the disease if they are given more than seven days into the illness, and 27% of infected adults

LEARNING POINTS

Chronic cough is usually defined as cough lasting more than eight weeks

Cough should improve appreciably within eight weeks of smokers stopping smoking; a cough caused by ACE inhibitors usually resolves one to four weeks after the patient stops taking the drug

Unexplained chronic cough in adults is usually due to one of the “pathogenic triad”: asthma, gastro-oesophageal reflux, or postnasal drip syndrome

Empirical trial of treatment for at least eight weeks is usually a more appropriate initial intervention than is specialist investigation

will still be coughing at 90 days,¹⁸ with no evidence that intervention alters this.

Case review

In this case it was appropriate to stop the ACE inhibitor and review the patient in a month. The cough improved but did not stop. As a non-smoker, and in the absence of “red flags,” the patient was unlikely to have serious underlying disease. The likely cause of her cough was one (or more) of the “pathogenic triad”: asthma, gastro-oesophageal reflux, or postnasal drip syndrome. Some features suggested gastro-oesophageal reflux (cough when talking on the telephone), and a trial of a proton pump inhibitor twice daily for eight weeks resolved the cough. One pitfall with a trial of treatment is that the positive result may have been due to spontaneous remission. Withdrawing treatment and reintroducing it if the cough recurs should improve the accuracy of the diagnosis.⁵

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DIAGNOSIS IN GENERAL PRACTICE

Diagnosis using “test of treatment”

Paul Glasziou, Peter Rose, Carl Heneghan, John Balla

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Centre for Evidence Based Medicine, Department of Primary Health Care, University of Oxford, Oxford OX3 7LF

Correspondence to: P Glasziou paul.glasziou@dphpc.ox.ac.uk

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Tests of treatment are commonly used when the diagnosis is uncertain, but can have pitfalls. The accompanying article gives an example of how test of treatment can be used

What is test of treatment?

Though ideally we should have a clear diagnosis before starting treatment, such certainty is not always possible. Sometimes this uncertainty can be resolved by using the treatment as the test that confirms the diagnosis.¹ For example, if we are unsure if a patient's airway obstruction has a reversible element, a trial of steroids can test this: a sufficient response is then considered evidence of reversibility. At other times the test of treatment is not planned, but the failure to respond to treatment as expected leads to a rethink of the diagnosis. In this brief review we discuss different uses of the “test of treatment,” its reliability as a diagnostic tool, and how its use might be improved (for a specific example of its use, see the accompanying article on chronic cough²).

When is it used?

As illustrated in the figure, a “test of treatment” is one strategy for the final stage of arriving at a diagnosis. It is appropriate when a single diagnosis is highly probable but not certain, when an available treatment works for most patients if the diagnosis is correct, and when there is a measurable short term outcome or surrogate. Such tests are more common and more useful in chronic or recurrent conditions rather than in acute conditions.

A test of treatment is likely to be useful:

- To make a diagnosis when the clinical features are atypical—for example, using glyceryl trinitrate for atypical chest pain or prednisone for suspected polymyalgia rheumatica in patients with a low or normal erythrocyte sedimentation rate
- To make a definitive diagnosis when various differential diagnoses are possible—for example, chronic cough²
- To see if a particular treatment—for example, switching antihypertensive drugs to minimise adverse effects—is appropriate in someone with the diagnosis.

One early example of a test of treatment is the physostigmine test for myasthenia gravis,³ used since 1937. The treatment used for testing is not always the treatment used in the long term: short acting edrophonium

(Tensilon) has become the standard agent to test for myasthenia gravis, although it is not suitable for long term treatment.⁴ Similarly with the trial of steroids (in several conditions): we usually won't plan to continue long term oral steroids but will switch to other long term treatments. In the examples of tests of treatment in the table, the focus is a single condition, but sometimes a sequence of treatments can be used.

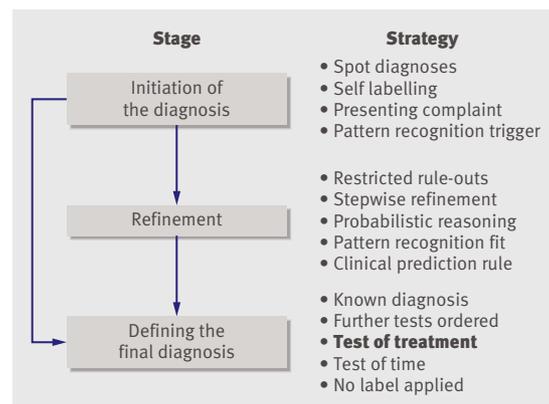
How does a test of treatment go wrong?

As with every diagnostic test, the test of treatment can have both false negative and false positive results. If a test of treatment has been assessed against a diagnostic “gold standard” it is possible to quantify the accuracy of the test (table).¹ For example, the combined results of five randomised trials of using proton pump inhibitors to “test” for gastro-oesophageal reflux showed an average sensitivity of 78% and a specificity of 54% in comparison to 24 hour monitoring of pH.⁶ However, such accuracy has not been assessed for most tests of treatment.

How can we improve?

Since tests of treatment can easily lead to an inappropriate diagnosis, assessment of response to treatment should be more rigorous than in treatments where diagnosis is “certain.” A test of treatment has several potentially remediable problems. False positives can arise because of spontaneous remission of the condition or from placebo effects. False negatives can arise with an insufficient dose or duration of treatment, or if the patient is resistant to the particular treatment. Several things can reduce the influence of chance fluctuations in the condition or bias in evaluating response to treatment:

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Stages and strategies in arriving at a diagnosis

Some common tests of treatment and their accuracy

Condition	Treatment	Accuracy
Myasthenia gravis	Edrophonium	High sensitivity (92% for ocular disease and 88% for generalised myasthenia) and high specificity (97% for both forms of myasthenia) ⁵
Oesophageal reflux	Proton pump inhibitors	Sensitivity 78%, specificity 54% compared with 24 hour pH monitoring ⁶
Angina	Nitroglycerin	Response within 5 minutes, sensitivity 53-63% and specificity 69-71% ⁷
Gout	Colchicine	2/3 patients respond within 48 hours (sensitivity 67%) ⁸
Obstructive sleep apnoea	2 week trial of positive airway pressure	Sensitivity 80% and specificity 97% compared with blinded polysomnography ⁹
Polymyalgia rheumatica	Low dose corticosteroids (15 mg prednisone)	Patient reported global improvement of at least 70% within a week of starting steroids, and normalisation of inflammatory markers within 4 weeks. (Accuracy is not definable as treatment response is part of the definition) ¹⁰

LEARNING POINTS

Tests of treatment are common but imperfect
 Clinicians should be aware of the accuracy of different tests of treatment
 The accuracy may be improved by use of better measurements or more treatment crossovers

- *Use multiple measurements*—if the measurements for an individual vary from occasion to occasion, getting several pretreatment measurements is helpful
- *Use multiple treatment periods*—sometimes it is necessary and reasonable to withdraw and then reintroduce the treatment to provide convincing evidence of response. Using crossover periods (no treatment, treatment, no treatment, treatment, etc) provides more solid evidence; formally, this is the “n of 1” trial. For example, Guyatt reported that a patient thought their asthma was worse when they were taking theophylline. An n of 1 trial with six periods (three of theophylline, three of placebo) verified the patient’s impression. Also, for polymyalgia rheumatica some doctors use the “steroid sandwich”: patients keep a diary of symptoms for 21 days, during which they are given seven days of three tablets of Vitamin C, seven days of three tablets of non-enteric coated prednisone 5 mg, then seven days of three tablets of Vitamin C (the tablets resembled each other as nearly as possible). Sometimes such replication can be done in parallel—for example, in a test of treatment for yellow nail syndrome, Vitamin E was put on some of a patient’s fingernails, while that patient’s other fingernails were used as “controls”.¹²
- *Use blinded measurements or supplementary objective measurements*—since we all often see what we hope to see, either blinded or objective assessment measures are needed to reduce bias.
- *Use objective measurements*—if you don’t know what response you are looking for at the outset

then it will be difficult to ascertain whether the patient has responded to the treatment at all. For example, a man with prostate obstruction may report that he has not improved, but by using the international prostate symptom score you can show him whether he has responded.

In clinical practice, tests of treatment, whether formal or informal, are commonly used. In a sense every time we use a treatment, we are testing whether it works in a given patient. However, a false response may also lead to an incorrect diagnosis. By recognising and researching tests of treatment as a legitimate diagnostic test, we will be able to improve the accuracy and safety of their use.

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