



The difficult-to-treat, therapy-resistant cough: Why are current cough treatments not working and what can we do?



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ABSTRACT

Cough can persist despite exhaustive diagnostic and therapeutic effort and has been termed 'idiopathic' or 'unexplained' but perhaps 'difficult to treat' cough is a more appropriate description. In this article the reasons for poor treatment response are discussed. These include a lack of physician fidelity to management guidelines, patient non-adherence and the lack of effective medicines. A number of randomized controlled trials have been undertaken including low dose opiate therapy, the use of a speech pathology intervention, oral antibiotics and antidepressants. The success or otherwise of such interventions will be discussed. A number of approaches to deal with the problem of 'difficult to treat cough' will be considered.

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1. Introduction

For the vast majority of people a troublesome cough settles down almost as quickly as it starts. Despite this 'self limiting' characteristic, the volume of 'over the counter' cough preparations purchased annually suggest large numbers of people are sufficiently disturbed by their cough to seek relief with medicines [1]. Annual healthcare statistics continue to place cough as the most common reason for patients seeking medical help [2]. Patients with a chronic cough as the sole or primary problem account for up to 40% of all referrals to a respiratory clinic [3]. In general the recommended approach in both adult and paediatric settings is to undertake a systematic, integrated evaluation of the patient beginning with history and physical examination, baseline investigations followed by a combination of diagnostic tests and therapeutic trials based on a suspected cause(s) [4–6]. Using this approach which is based on the original work by Irwin and colleagues and first reported almost 40 years ago, a significant proportion of patients the cause for the cough can be successfully identified and treated [7]. This highly cited work detailing the rationale for using an 'anatomic diagnostic protocol' which has now become embedded in clinical practice and as a consequence there is a broad appreciation at least in adult practice that asthma, gastro-oesophageal reflux and upper airway disease commonly cause cough [8]. The initial experience of clinicians managing patients

attending specialist cough clinics was that fairly simple interventions such as prescribing a course of inhaled corticosteroids or a trial of acid suppression or just stopping an ACE-inhibitor produced very satisfying results [8]. However, it quickly became clear that an increasing number of patients referred did not respond at all to this approach or that some gained initial benefit from the various trials of therapy before relapsing. The terms 'idiopathic' or 'unexplained' cough have generally been used to describe this clinical scenario [9,10] but perhaps 'difficult to treat' or 'therapy-resistant' cough are more appropriate terms. These patients represent a significant clinical challenge and the purpose of this article is to consider the reasons why current treatments don't appear to work and to provide some suggestions as to what can be done. In addition to the text a flow chart detailing the series of steps to be considered when assessing a patient with persistent cough has been provided (see Fig. 1).

2. Why are current treatments not working?

2.1. Physician non-concurrence with treatment recommendations

Some take the view that the problem of 'difficult to treat' cough is almost entirely a consequence of inadequate evaluation and treatment [11]. This is often the case and typical reasons for treatment failure include a reluctance to prescribe inhaled steroids to patients with normal spirometry, or to consider non-acid reflux as a trigger for cough. Failure to consider less well recognized associations such as sleep apnoea [12], tonsillar enlargement [13] and chronic fungal infection [14] are also possibilities. The consequence

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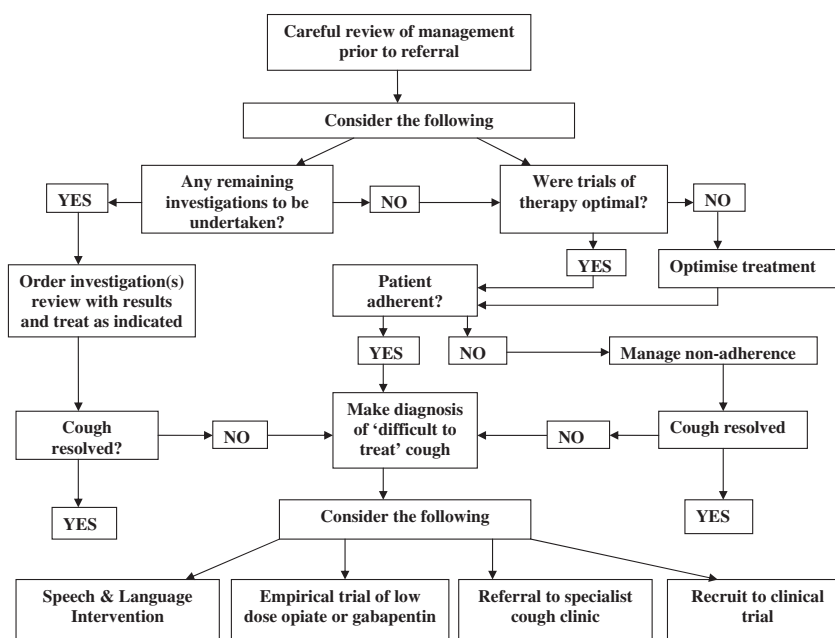


Fig. 1. A proposed algorithm detailing a management approach to the patient with 'difficult to treat' cough.

of failing to consider current recommendations may result in one of the following scenarios: the patient may be prescribed the correct drug but at a suboptimal dose or duration of treatment or be given the wrong drug entirely. The scale of clinician non-concordance with cough management guidelines has not been reported. However in a recent study the recommendations on antibiotic prescribing and antibiotic choice for acute cough/lower respiratory tract infections were followed by clinicians in less than half of cases [15]. Clinicians may reasonably argue that the recommended systematic approach to managing cough patients is time consuming, demands a lot of clinician input and is not proven to be more effective. In one study it was reported to be more expensive but this was offset by a shorter time to treatment success [16]. Subsequently it has been reported that management protocols can be designed to be followed by non-clinicians with comparable response outcomes but with important cost savings [17]. However, the argument that the systematic approach may not be superior to alternative management strategies is a valid one. Results from a recent multicentre randomized controlled study suggest improved clinical outcomes when children with chronic are managed with a standardized algorithm compared to usual care [18].

2.2. Patient non-compliance

The issue of non-compliance with prescribed treatment is complex and not fully understood [19]. It is a well recognized factor responsible for poor symptom control in asthma and reflux disease [20,21]. In a study of mild asthmatics more than two-thirds of those with poor asthma control were identified as non-adherent with their inhaled corticosteroids [20]. It may be useful to consider a trial of oral steroids in those patients who are non-adherent with their inhaled corticosteroids. More than 40% of patients attending an otolaryngologist and diagnosed with reflux disease as the cause for laryngeal symptoms including cough failed to follow instructions regarding timing of their acid suppression therapy [21]. Inhalers and acid suppression are commonly prescribed for the treatment of cough and yet to date no study has specifically addressed the issue of non-adherence among patients with chronic cough. There is no

reason to suspect that cough patients are any more likely to be compliant with their medicines. Addressing non-compliance has been shown to be of benefit in effective in management of asthma [22], and therefore a proactive approach to identifying non-compliance in cough patients and taking measures to manage it should be adopted.

2.3. The right treatment but the wrong patient

Despite the limited evidence, empirical trials of asthma and anti-reflux medicines continue to be used by physicians and quite reasonably they justify this because they have all at one time or other encountered patients that respond well to this approach. Identifying which patients are likely to respond is difficult and the notion of being able to 'phenotype' cough patients has not gained much momentum. For example there are no characteristics on 24-h oesophageal pH monitoring that reliably identify the patients most likely to respond to acid suppression [23]. Although demonstration of an elevated fractional exhaled NO in a patient with chronic cough should logically prompt a trial of inhaled or oral corticosteroids there is little agreement on the levels likely to predict a treatment response [24,25].

2.4. Side effects and safety concerns

Patients may decide not to take their medication because they have quickly worked out that it hasn't helped. Alternatively they may feel that any possible therapeutic benefit is offset by side effects or safety concerns. Patients will obviously stop their medication if it makes the cough worse. Cough triggered by inhaled corticosteroids is a common complaint [26] and this can greatly limit therapeutic options for patients with asthma/eosinophilic cough syndromes. Concerns over the safety of some medications have led to their withdrawal and this has had an impact on treatment options available for cough patients. The withdrawal of cisapride because of cardiac concerns and the lack of alternative prokinetic agents at least in the United States has limited the range of medical treatments available for patients with reflux associated

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