

An Algorithmic Approach To The Treatment Of Chronic Cough

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Abstract

Background : Chronic cough is a common disorder. Although its exact mechanism has not been clarified, most of cases are successfully treated, whatever the causative disorders are. Therefore, the confirmative diagnosis may not be essential for the management of chronic cough.

Objectives : To develop an algorithmic approach according to common presumptive diagnosis and its treatment, and to investigate its applicability.

Methods : An algorithm was designed by the literature review, doctor's experiences, and local medical appliances. Patients with the chief complaint of cough persisting more than 4 weeks were enrolled. Diagnostic and therapeutic trials were performed following the algorithm. The subjective grade of cough severity was measured by visual analogue scale (VAS) from 1 (no cough at all) to 10 (same cough severity as the first visit). Successful responder (SR) was defined that VAS was reported less than 3. The therapeutic response period was measured.

Results : Among 378 enrolled patients, 343 patients (92%) were categorized as SR after the algorithmic approach. As presumptive diagnoses, postnasal drip syndrome was the most frequent and overlapped pathologies were shown in 82 patients (21.7%). Therapeutic response periods were 5 days in half of the patients and 12 days in 85%. Thirty-two patients (8.5%) received other diagnostic investigation than those in the algorithm.

Conclusion : This algorithmic approach is a useful diagnostic and therapeutic option for the treatment of chronic cough.

ABBREVIATION

PC₂₀; the provocative concentration of agonist causing a 20% fall in FEV₁

INTRODUCTION

Chronic cough is defined as a cough lasting more than four or more than eight weeks, depending on the authors. ¹ It is one of the common respiratory complaints of patients visiting outpatient clinics. Although some cases are intractable or termed idiopathic cough, most specialists reports high success rates in the treatment of patients with chronic cough. ² Its successful management can be achieved by the accurate treatment of the causative disorders.

It is well known that most patients with chronic cough have one or more than one of three disease categories, that is, asthma, reflux and rhinitis, each of which arises from

different anatomic sites. Therefore, in a specialized and divisional clinic, a specialist in one form may have little experience in the other causes of chronic cough. Moreover, there may be rare disease conditions causing the condition, which may not be readily detected using routine diagnostic procedures.

There are two general approaches to the diagnosis and management of patients with chronic cough. One is "test all at first visit, then treat", which is the most expensive option, but which might also decrease the duration of treatment. In contrast, one can use sequential diagnosis and treatment starting from one of the most common causes according to frequency: that is, an algorithmic approach. ³

Most previous algorithmic approaches have been based on a confirmative diagnosis and its management. ⁴ The three

major confirmative diagnoses are well known as postnasal drip syndrome, asthma, and gastroesophageal reflux disorder.^{2,3,6} In addition to these major diagnoses, there are some minor confirmative diagnoses such as chronic bronchitis, postinfectious cough, bronchiectasis, and psychogenic cough. To make a confirmative diagnosis, medical expenses will not only be increased, but treatment will also be delayed. In most patients with chronic cough, this approach may not be essential for treatment, because most of the confirmative diagnoses are not of acutely debilitating and rapidly progressive disorders, so even misdiagnosis yields little risk to patients from any delayed treatment. We suggest that the management of patients with chronic cough has to depend on the presumptive diagnosis, which allows the diagnostic algorithm to be simplified, offers earlier treatment and is cost-effective.

We developed an algorithm focused on the treatment of patients with chronic cough, with minimal diagnostic investigations, regardless of the confirmative diagnosis. We tried to evaluate the algorithmic approach from the perspective of the presumptive diagnosis and the therapeutic response period.

METHODS

DESIGN OF THE TREATMENT ALGORITHM

The algorithm was designed initially based on a review of the literature on the treatment of patients with chronic cough. It was simplified and modified by the experiences of doctors who had been running a hospital pulmonology clinic for more than a year in Jeju, Korea, considering local patient characteristics and locally available medical appliances and resources.

SUBJECTS

Patients were included who had visited the clinic of internal medicine in Cheju National University Hospital for a year (from January 1 to December 31, 2005), with the chief complaint of cough persisting more than four weeks and who had normal initial examinations. Initial examinations involved auscultation by a physician, chest radiography (posterior–anterior view and left lateral view), and complete blood cell counts. Current users of angiotensin converting enzyme (ACE) inhibitors were excluded. The enrolled patients received information on the algorithmic approach to the treatment of chronic cough. The enrolled patients were encouraged to follow the algorithmic approach during a telephone notification of the next visit.

PARAMETERS FOR TREATMENT

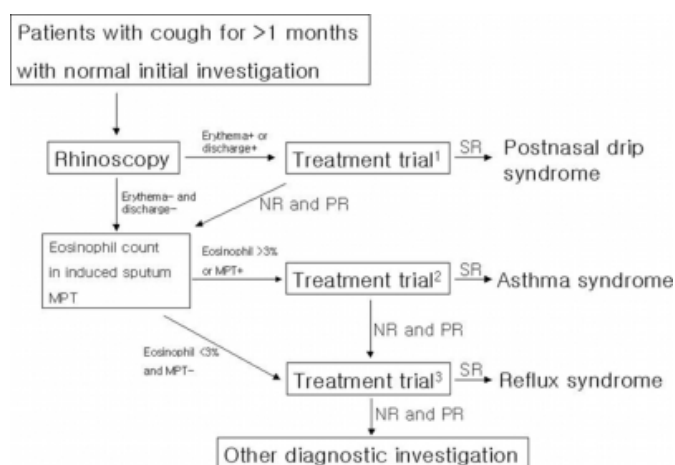
The subjective grade of cough severity was recorded using a questionnaire at each visit and measured using a visual analogue scale (VAS) from 1 (no cough at all) to 10 (same cough severity to that remembered from the first visit to the clinic). “Successful” responders were defined as patients reporting a subjective grade of cough severity of less than 3. “Partial” responders and “nonresponders” were defined as those reporting VAS scores from 3 to 6 and more than 6, respectively.

ALGORITHM

Diagnostic and therapeutic trials were performed following the algorithm outlined in Figure 1. Initially, patients were subjected to a rhinoscopic examination.

Figure 1

Figure 1: The algorithm for diagnostic and therapeutic trials.



Footnote: MPT, methacholine bronchial provocation test; SR, successful responder; PR, partial responder; NR, nonresponder; Treatment trial1, antihistamine + pseudoephedrine + intranasal corticosteroid for 5 days; Treatment trial2, inhaled corticosteroid + long acting beta agonist for 1 week; Treatment trial3, proton pump inhibitor for 2 weeks

When the clinician detected redness of nasal mucosa or abnormal discharge on the nasal mucosa, antihistamine (10 mg Ebastine p.o. q.d., Ebastel®, Boryung Pharmaceutical, Seoul, Korea), pseudoephedrine (30 mg, p.o. t.i.d.) and intranasal corticosteroid (triamcinolone acetonide 110 g b.i.d. intranasally, Nasacort nasal spray®, Aventis Pharma, UK) were prescribed for five days. Otherwise, patients were referred to the next diagnostic approach. After five-day trial of the prescribed medication, the grade of cough severity was evaluated by questionnaire as above at the next visit.

Each successful responder (SR) was asked to continue using the same medication for at least two weeks. Each partial responder (PR) was asked to continue the same medication and each nonresponder (NR) was asked to stop the medication. Patients in the SR and PR categories were referred with a presumptive diagnosis of “postnasal drip syndrome”. Patients classed as PR or NR were asked to enter the next diagnostic approach: a methacholine bronchial provocation test (MPT)₅ and eosinophil count with induced sputum.⁶ A positive MPT was defined as a PC₂₀ value of less than 10 mg/mL. Patients with more than 3% eosinophils in the induced sputum or with a positive MPT received a prescription of inhaled budesonide, 160 g b.i.d. and inhaled formoterol, 4.5 g b.i.d. (Symbicort®, AstraZeneca, Södertälje, Sweden) for one week. Otherwise, patients were referred to the next step. At this next visit, the grade of cough severity was re-evaluated. Patients classed as SR were asked to continue the same medication for at least two weeks. Whatever the responses to this therapeutic trial were, the patients with positive MPT tests were referred to a special clinic for asthma. Those classed as PR were asked to continue the same medication and those classed as NR were asked to stop their medication. Patients in the SR and PR categories received a presumptive diagnosis of “asthma syndrome”. As a next step, PR and NR patients received the prescription of a proton pump inhibitor, pantoprazole (40 mg p.o. q.d.; Pantoloc®, Pacific Pharmaceuticals, Seoul, Korea), for two weeks until the next visit.⁷ At that time, the grade of cough severity was re-evaluated. Patients classed as SR were asked to continue the same medication for at least six weeks; those in SR and PR categories were given a presumptive diagnosis of “reflux syndrome”. PR and NR patients received other diagnostic investigations following individual physician's decision, including high resolution computerized tomography (HRCT) of the lungs bronchoscopic examination, sputum smear and culture for acid fast bacilli (AFB), sputum culture for ordinary bacteria and fungi, and a serological test for human immunodeficiency virus (HIV).

THERAPEUTIC RESPONSE PERIOD

The therapeutic response period was accessed. This was defined as the number of days from the enrollment until the patient's visit when they first reported a VAS score of cough severity less than 3.

RESULTS

CHARACTERISTICS OF ENROLLED PATIENTS

Three hundred seventy eight patients with a mean age of 51.2 years were enrolled in the algorithmic approach. All were Korean adults living in Jeju, Korea. One hundred eighty six (49%) were men. The median reported cough duration was two months (range, 1–36 months) (Table 1).

Figure 2

Table 1: Characteristics of the 378 enrolled patients

Men/women	186/192 (49/51%)
Age, years	51.2 ± 16.12
Cough duration in months, median (range)	2 (1–36)

PRESUMPTIVE DIAGNOSIS

Among 378 patients, 346 (91%) showed erythematous mucosa or abnormal discharge in rhinoscopic examinations and received empirical medication for five days. The SR category included 176 patients (47%); 79 (21%) were classed as PR, and 255 (67%) received the presumptive diagnosis of “postnasal drip syndrome”. Among the 346 treated patients, 91 (24% of those enrolled, or 26% of treated) showed no response.

Thirty-two patients with normal rhinoscopic findings and 170 categorized as PR or NR in the previous step underwent MPT and eosinophil count of induced sputum. One hundred forty four showed positive results and had empirical treatment for one week. Among these, 141 were classed SR (37% of enrolled, or 98% of treated), three as PR (1% of enrolled, or 2% of treated), and none were classed as NR.

In all, 61 patients had empirical treatment for two weeks for “reflux syndrome”: 58 patients had normal findings for both the MPT and sputum eosinophil count and three were classed as PR. Twenty-nine patients (8% of enrolled, or 47% of treated) were classed as SR after the two weeks (Table 2).

Figure 3

Table 2: The presumptive diagnoses of the 378 enrolled patients

Diagnosis	No. of patients (%)
Postnasal drip syndrome	255(67.5)
Asthma syndrome	144 (38.1)
Reflux syndrome	29 (7.7)
Overlapped pathologies	82 (21.7)
Postnasal drip syndrome and asthma syndrome	52 (13.8)
Postnasal drip syndrome and reflux syndrome	7 (1.9)
Postnasal drip syndrome and other diagnosis	20 (5.3)
Asthma syndrome and other diagnosis	3 (0.8)

THERAPEUTIC RESPONSE PERIOD

The chronic cough of 176 patients classed as SR (47%) with only “postnasal drip syndrome” was successfully controlled in five days. Another 141 of the SR patients (37%) diagnosed with “asthma syndrome” with or without “postnasal drip syndrome” were reported with successful treatment in between seven and 12 days of treatment. Another 29 SR patients (8%) with “reflux syndrome” were successfully treated by between 14 and 26 days.

TREATMENT OF CHRONIC COUGH BY THE ALGORITHM

After application of the therapeutic algorithm, the chronic cough of 343 patients (92%) was treated successfully and the others of 32 patients (8.5%) had other diagnostic investigations.

Final diagnosis of patients who underwent other diagnostic investigations

Ten patients reported that they stopped coughing spontaneously while waiting for diagnostic investigations. Seven patients were confirmed as having mycobacterial infections by AFB smears or culture of sputum or bronchoscopic washings. Six patients were diagnosed as having localized or diffuse bronchiectasis by HRCT, which was used retrogradely to review normal or equivocal findings in the initial diagnostic investigations. Twelve patients were finally regarded as having idiopathic or psychogenic cough using other diagnostic investigations.

DISCUSSION

Chronic cough is a common complaint in outpatient clinics.

The prevalence varies according to the studied populations and the defined duration of the complaint.⁸ The proportions of underlying disorders are also diverse in most studies, even though all studies agree on the three most common disorders. There have been few reports on the prevalence of chronic cough or the frequency of etiologies in Korean subjects. Cho et al.⁹ reported that among 93 Korean patients with chronic cough, postnasal drip syndrome was the most common etiology (52%) and bronchitis the second (16%). Only three (4%) patients were diagnosed with gastroesophageal reflux disease using 24 h ambulatory esophageal pH monitoring and half of these patients reported improvement after treatment. Among other Korean patients with a chronic cough, asthma (22%) and eosinophilic bronchitis (7%) were found in more than a quarter. The authors suggested that an empirical one-week prednisolone administration (0.5 mg/kg) with basic diagnostic investigations was cost-effective for the diagnosis of asthma.¹⁰ However, the empirical trial of systemic glucocorticoid in chronic cough is not advocated because it may confuse the diagnosis among inflammatory disorders including asthma, rhinitis, and eosinophilic bronchitis in addition to the increasing risk of infection. Recently, Bordetella pertussis infection was referred as one of the differential diagnoses.¹¹ In Korean adults with a chronic cough, 2.9% were positive to B. pertussis by polymerase chain reaction amplification.¹² As a first diagnostic investigational trial, we chose rhinoscopic examination, for previous studies in Korea showed postnasal drip was the most frequent cause. No professional rhinoscopic description on nasal mucosa was used but patients with any abnormality were enrolled for the treatment trial for postnasal drip syndrome. The proportion of abnormal finding showed higher, however, considering the treatment response, the proportion of presumptive diagnosis of postnasal drip met that of previous investigations.

Cough itself is a subjective symptom, which can hardly be measured objectively. The severity of cough has been measured by daily cough diary and visual analogue scale in previous studies, although these are not the objective measuring tools. We used the visual analogue scale to measure the severity and the treatment response to each treatment trial. We made a presumptive diagnosis confirmed by the symptomatic improvement by the each patient's report on the change of cough severity.

Current smoking status was not considered in this algorithmic approach, which is designed for practical clinical

use. Although some investigators mentioned current smoking might contribute chronic cough, we experienced little smokers consider quitting smoking because of chronic cough itself. On the contrary, patients with chronic cough who are taking ACE inhibitors easily accepted the trials of changing antihypertensive medication.

This algorithmic approach was focused not on the definite diagnosis of chronic cough, but on its treatment with presumptive diagnosis. More than ninety percent of patients were successfully treated at the outset. The overall treatment rate reached those reported by previous studies, most of which revealed no assessment during the therapeutic response period.¹³ In the present study, half of all patients received successful treatment in five days and more than 80%, in 12 days.

As a presumptive diagnosis, “postnasal drip syndrome” was the most common cause, but roughly one-third of these patients proved to have another presumptive disorder. Previous investigations have also reported dual or multiple pathologies in patients with a chronic cough.¹⁴

After successful treatment, patients were asked to stop medication except for those with a positive methacholine bronchial provocation test. Asthma is a chronic inflammatory disorder of airways that needs persistent antiinflammatory therapy to prevent exacerbation and declining lung function.¹⁵ Challenge studies with methacholine or histamine are sensitive tests and provide high negative predictive values for the diagnosis of asthma and cough variant asthma.¹⁶

The natural course of a chronic cough is still in question. It has been poorly investigated because of the heterogeneity of final diagnosis. Although some common disease entities have been investigated during the natural course of the disorder, most studies were not focused on the symptoms. Park et al.¹⁷ investigated the natural course of eosinophilic bronchitis, which is one of the common underlying disorders in chronic coughers. In 48 months follow up with 36 patients diagnosed with eosinophilic bronc, 14% experienced recurrence after treatment and the patients with higher percentage of eosinophils in the sputum had a risk for developing airway hyperresponsiveness.

Ours et al.⁹ reported that an empirical two-week treatment trial using high dose proton pump inhibitors was more reliable and more cost saving in the treatment of chronic cough than treatment after esophageal manometry or 24

hours dual probe pH monitoring in patients without asthma or postnasal drip. Beside the medical expenses involved, both manometry and pH monitoring are invasive approaches and were not available in our locality. This algorithm adopted an empirical therapeutic approach, considering local medical appliances.

Chronic cough is a common disorder and the algorithmic approach outlined here proved a useful diagnostic and therapeutic option for decreasing medical expenses and therapeutic response periods. Any such algorithm should be designed considering the literature and needs to be modified by the local doctors' experiences and the available medical appliances and options.

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