CHEST

Original Research

COUGH

Evaluation of Chronic Cough in Children*

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Chronic cough in children is among the problems that lead to frequent consultations with a doctor. In this study, we attempted to research the reasons for chronic cough by an evaluation method using the guidelines that were suggested for children by the American College of Chest Physicians (ACCP) in 2006. We studied 108 children between 6 and 14 years of age who had a cough that lasted for > 4 weeks. The patients were reevaluated during the second to fourth weeks, and until either the cough terminated or resolved. Twenty-five percent of the patients received diagnoses of asthma and asthma-like symptoms, 23.4% received diagnoses of protracted bronchitis, 20.3% received diagnoses of upper airway cough syndrome (UACS), and 4.6% received diagnoses of gastroesophageal reflux disease. Asthma and asthma-like symptoms, protracted bronchitis, and UACS were detected in order of frequency as the reason for chronic cough in children. We concluded that the 2006 ACCP guidelines for the management of chronic cough in children are effective and can be successfully utilized in a nonaffluent study setting.

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Key words: children; chronic cough

Abbreviations: ACCP = American College of Chest Physicians; GERD = gastroesophageal reflux disease; HRCT = high-resolution CT; PPD = purified protein derivative; UACS = upper airway cough syndrome

Cough is one of the most common health problems in children that makes parents concerned and compels them to take their children to see a doctor.[1,2] In a multicentric study[3] of children 7 to 11 years of age, it was found that 9% of children in this age group complained of chronic cough. Although the phenomenon is observed frequently, only a few studies[4,5] have addressed the reasons for chronic cough. If findings leading to a specific diagnosis exist, the etiologic causes are detected and appropriate treatments are administered. Most children have a nonspecific cough that is the result of a nonserious condition; in some cases, spontaneous recovery occurs.[4,5] However, sometimes the reasons for specific and nonspecific cough are integrated. Hence, all children experiencing chronic cough should be evaluated carefully.

Etiologic studies[6] of chronic cough in adults have shown that an algorithmic approach successfully facilitates the diagnosis of cough in up to 99% of cases. In these studies, postnasal drip syndrome, gastroesophageal reflux disease (GERD) and asthma were found to be the three most common reasons forchronic cough. In 1998, the American College of Chest Physicians (ACCP) also recommended[7] a similar algorithm for children.

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In studies conducted by Holinger[8] and Callahan,[9] asthma was cited as the most common reason for chronic cough in children. On the other hand, Thomson et al[10] and Seear and Wensley[11] have observed that asthma alone does not cause cough.

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Although GERD is one of the most common reasons for chronic cough in adults, cough due to GERD is not so common in children.[10,12,13] In addition, Marchant et al[14] reported that protracted bacterial bronchitis was the most common etiologic cause of chronic cough in young children.

Children differ from adults in certain aspects. Since a growing child responds to therapy in a different manner than adults,[15,16] the evaluation of coughing children should be different from that of coughing adults. Hence, it was recommended that coughing children should be evaluated in accordance with the ACCP guidelines.[17] This study aimed to evaluate children with cough in accordance with the 2006 ACCP guidelines.[17]

Materials and Methods

Patients presenting to Dr. Behcet Uz Child Disease and Surgery Education and Research Hospital with chronic cough between November 2006 and May 2007 were included in the study. Chronic cough was defined as cough lasting > 4 weeks. Initially, a detailed medical history of the patient was obtained and a physical examination was completed. The duration and characteristics of the cough, wheezing, allergy, sinusitis and respiratory tract infection, and the presence of smoking exposure, atopy, and asthma in the family were investigated. Symptoms of deformed chest, clubbing, and cardiac abnormality were examined. Patients with premature birth, known lung disease, neuromotor growth deficiency, cardiac disease, growth deficiency, and deformed chest, as well as those with an acute respiratory tract infection within the last 4 weeks were excluded from the study. Permission was obtained from the parents and the local ethics committee for participating of the children in the study.

Study Protocol

The study was conducted using the algorithm suggested by the 2006 ACCP guidelines for chronic cough in children.[17] Patients were reevaluated, and physical examinations were performed at intervals of 2 to 4 weeks until the cough had either terminated or resolved. All patients underwent respiratory function testing, and chest radiographs were obtained. The respiratory function test was performed using spirometry. In patients with variable air flow limitation, an increase in FEV_1 of ≥ 12% predicted after the administration of a bronchodilator (two puffs of albuterol administered via a mask) indicated the presence of reversible air flow limitation consistent with asthma. A retest of respiratory function was performed, and a chest radiograph was obtained when necessary. A high-resolution CT (HRCT) scan of the thorax, a sweat test, Ig level measurement, purified protein derivative (PPD) skin test, gastroesophageal scintigraphy, *Mycoplasma pneumoniae* IgM and IgG antibody tests, bronchoscopy, and BAL were performed in some cases.

Definition of the Diagnostic Categories

A diagnostic classification designed in response to the treatment and definitions made according to the results of research was used, as follows:

1. Asthma and asthma-like symptoms: cough with variable air flow limitation demonstrated by bronchodilator responsiveness and/or response to inhaled steroid (budesonide, 400 μg/d) within 2 to 4 weeks;
2. Protracted bronchitis: a history of chronic moist cough and a response to antibiotic therapy (clarithromycin, 15 mg/kg/d for 10 days) with resolution of cough within 2 to 4 weeks;
3. GERD: detection of reflux via gastroesophageal scintigraphy in children with cough and responding to treatment (lansoprazole, 15 mg/d) within 2 to 4 weeks;
4. Upper airway cough syndrome (UACS): a medical history matching the diagnosis, the detection of postnasal discharge during a physical examination, and/or nasal mucosal edema, hyperemia, faintness, response to antihistamine, nasal saline solution, and/or nasal steroid therapy in 2 to 4 weeks;
5. Natural recovery: remission of cough under medical observation, without treatment;
6. Bronchiectasis: demonstrating bronchiectasis via an HRCT scan of the thorax in patients with chronic wet cough and abnormal chest radiograph findings who did not respond to antibiotic therapy (clarithromycin, 15 mg/kg/d for 10 days) within 2 to 4 weeks;
7. Tuberculosis: medical history of chronic cough with consistent radiologic findings, positive PPD skin test result, and a response to antituberculosis treatment; and
8. *M pneumoniae* infection: chronic cough, the presence of *M pneumoniae* IgM antibodies via enzyme-linked immunosorbent assay and improvement of symptoms with a single clarithromycin treatment.

Statistical Analysis

Descriptive analyses were made using a statistical software package (SPSS, version 11.0; SPSS; Chicago, IL). The data were presented as the mean ± SD.

Results

One hundred eight patients between 6 and 14 years of age, 56 of whom were women, were included. Of all patients, 61 patients (56.4%) were passive smokers, 56 patients (51.8%) had wet cough, 52 patients (48.2%) had dry cough, and 32 patients (29.6%) had a family history of atopic disease (demographic data for the patients are presented in Table 1).

According to the 2006 ACCP guidelines,[17] after the physical examination and medical history a respiratory function test and chest radiograph were performed in all patients. A reversibility test was applied when necessary. Positive reversibility, which was evaluated as asthma, was detected in 20 cases; these patients inhaled 400 μg of budesonide daily as

Table 1—*Demographic Characteristics of the Patients

Characteristics	Values
Patients, No.	108
Male gender	56 (51.8)
Age, yr	8.44 ± 2.13
Length of cough, mo	4.16 ± 4.94
Presence of atopic disease	32 (29.4)
Passive smoking	61 (56.4)

*Values are given as No. (%) of mean ± SD, unless otherwise indicated.

treatment. Three patients with evident local peribronchial thickening and wet cough received therapy with clarithromycin (15 mg/kg/d for 10 days). Since no recovery was observed despite therapy, these patients were evaluated using an HRCT scan of the thorax; bronchiectasis was diagnosed thereafter. Levels of IgG, IgM, IgA, and IgE; sweat test results; and nasal mucosal transport time were examined in these three patients; however, no abnormality was found. In order to explain the etiologic causes, bronchoscopy was performed. A bronchoscopic investigation of these three patients did not reveal any structural difference in the bronchi either. Increases in polymorphonuclear leukocyte counts were observed in BAL fluid samples of these patients although the BAL fluid culture findings were negative.

Other than the cases that were diagnosed in this step, gastroesophageal scintigraphy was performed in 55 patients, and serologic surveys were performed to obtain *M pneumoniae* IgM and IgG levels in 41 cases. Additionally, parents were informed about passive smoking and diet, and patients were reevaluated 2 to 4 weeks later. Cough was found to be resolved in two patients during this reevaluation. Scintigraphy revealed gastroesophageal reflux in 5 of 55 patients, who then received therapy with a proton pump inhibitor (lansoprazole, 15 mg/d), were placed on a special diet, and were rescheduled for a checkup. Cough was also found to be resolved in these patients. Algorithmic monitoring of our patients is shown in Figure 1.

A nasal saline solution, a steroid, and an oral antihistamine were administered to 31 patients in whom UACS was considered to be present after a physical examination was performed and a medical history was obtained. When patients were reevaluated after 2 to 4 weeks, cough was found to persist in 12 of them. Four of these 12 patients received therapy with clarithromycin (15 mg/kg/d for 10 days) after clinical findings were obtained that were consistent with sinusitis. Since eight patients had dry cough, they were evaluated as asthma-like symptoms and received therapy with an inhaled steroid (budesonide, 400 μg/d) by inhalation. On examination after 2 to 4 weeks, it was seen that cough was resolved completely in five patients, while three patients still were experiencing a cough with some improvement. The evaluation of our patients with UACS is shown in Figure 2.

Of the patients with no specific diagnosis until this step, 39 patients had wet cough and started receiving therapy with clarithromycin. Two weeks after treatment onset, cough was improved in 25 patients, whereas in 14 patients wet cough turned to dry cough. Ten patients with dry cough who started receiving therapy with an inhaled steroid recovered completely from cough. However, in four patients cough resumed upon the cessation of inhaled steroid therapy. Reversible obstruction was detected in a controlled respiratory function test in three of these patients, and they received a diagnosis of asthma. In the fourth patient, pneumonia was detected in a repeat chest radiograph, which was performed as a result of auscultation findings and the development of fever and malaise. Since a thoracic CT scan revealed pneumonia and lymphadenopathy in the left lower lobe and there was no response to nonspecific treatment, the PPD test was evaluated. Acid-resistant bacteria were not detected in the mucus culture, but PPD test response wheal was 17 mm in size, and the antituberculosis treatment was successful.

Because eight patients in the group without a specific diagnosis had dry cough, they received a diagnosis of asthma-like symptoms and received therapy with an inhaled steroid. Cough improved with inhaled steroid therapy in these patients. However, since the cough recurred 2 to 4 weeks after treatment cessation, a thoracic CT scan was performed in three patients. A bronchogenic cyst was detected in one patient, and surgery was recommended. The findings of a thoracic CT scan was normal in the other two patients. The evaluation of our patients with wet and dry cough has been shown in Figure 3.

Forty-one patients were examined for *M pneumoniae* IgM and IgG antibodies. Seventeen patients were positive for IgM and/or IgG antibodies. Seven patients were positive for IgM antibodies, three patients were positive for both IgM and IgG antibodies, and seven patients were positive for IgG antibodies. Of the patients who were positive for IgM antibodies, one received a diagnosis of *M pneumoniae* infection because only this patient had responded to monotherapy with clarithromycin. Of the other six patients, one received a diagnosis of protracted bronchitis and asthma-like symptoms, two received a diagnosis of asthma-like symptoms, and three received a diagnosis of UACS.

Cough was resolved in all patients except for six (5.5%). Thoracic HRCT scans and Ig tests were examined in these six patients, but no pathologic results were found. We recommended bronchoscopy to these patients, but their families did not agree. The diagnostic distribution of the patients is shown in Table 2.

Discussion

This is the first study that has aimed to evaluate children with chronic cough according to the 2006 ACCP guidelines.[17] We have detected that asthma, asthma-like symptoms, protracted bronchitis, and

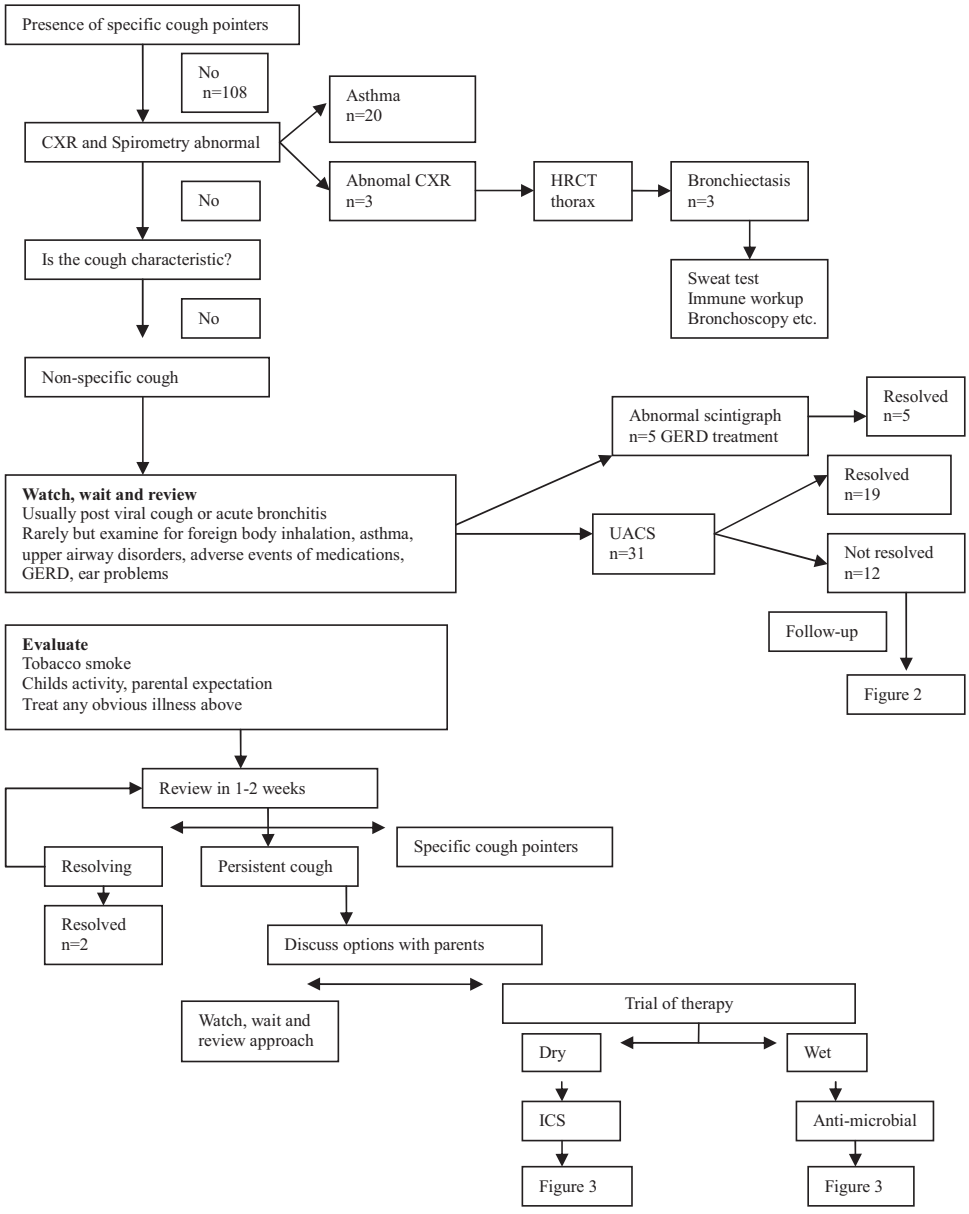

FIGURE 1. Monitoring algorithm for the treatment of our patients. CXR = chest radiograph; ICS = inhaled corticosteroid therapy.

UACS are the most common reasons for chronic cough in children 6 to 14 years of age.

In adults, it was shown that diagnoses could be made in > 90% of patients and > 85% of patients could be treated successfully using an algorithmic approach.[13] In 1998, the ACCP recommended[7] a similar protocol for children. In a study based on this protocol,[7] the most frequent reason found for chronic cough in young children was bacterial bronchitis. The reason why asthma and asthma-like symptoms were found to be the primary cause in our study could be that the mean age of the study group was older. Moreover, this could be due to the fact that asthma is an uncertain diagnosis in very young children. Persistent bacterial bronchitis was found to be the second most frequent cause. The diagnosis of protracted bacterial bronchitis was based on the history of wet cough and a positive response to antibiotic therapy, as defined by Chang et al.[18] In our study, the diagnosis was never confirmed with BAL or airway secretions, but cough was resolved with therapy. The response to antimicrobial therapy was variable in fact, but we could not evaluate this response due to the lack of a placebo control. We think that bronchoscopy should not necessarily be performed in all patients with wet cough. If patients

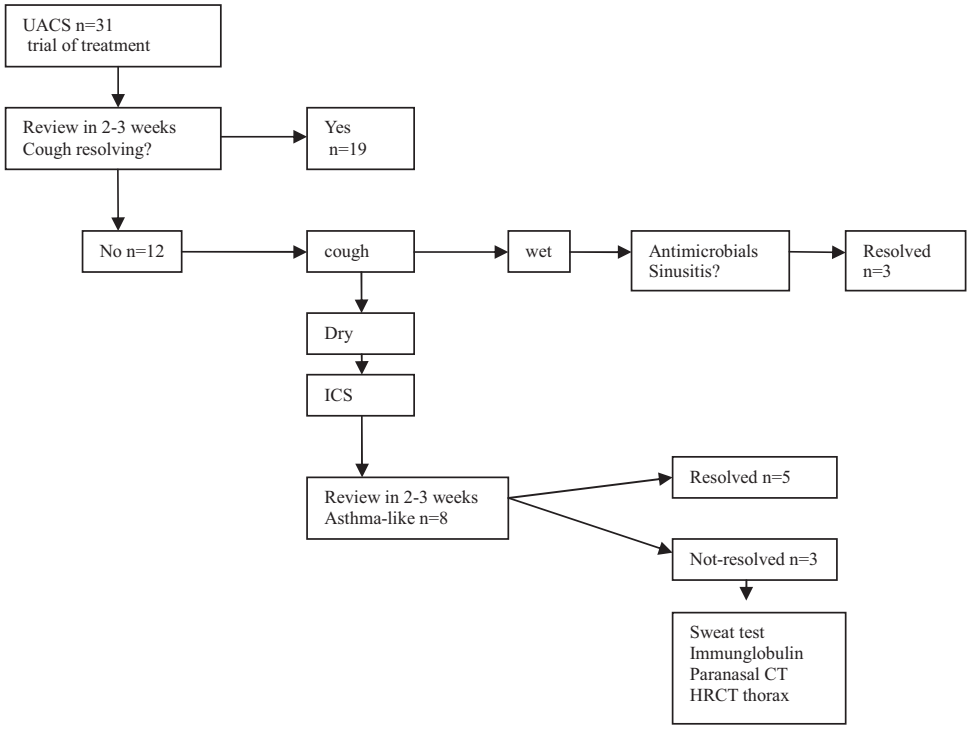

FIGURE 2. Evaluation of our patients with UACS. See the legend of Figure 1 for abbreviations not used in text.

do not respond to antibiotic therapy, they should be reevaluated for etiologic causes.

The "watch, wait, and review" step of the 2006 ACCP guidelines[17] is very important for evaluating children with cough. When therapy was initiated, the response to the treatment should absolutely be evaluated at intervals of 2 to 4 weeks. Unresponsive patients have to be reevaluated for different causes of chronic cough. This way, the unnecessary evaluation of all patients can be prevented. In our study, reevaluation steps helped us to find an airway anomaly in a patient in whom asthma-like symptoms were diagnosed and to detect tuberculosis in a patient in whom we had previously diagnosed protracted bronchitis. Furthermore, we noticed that there could be more than one reason for chronic cough.

UACS (formerly defined as postnasal drip syndrome) is one of the reasons for cough in adults.[19–21] On the other hand, Marchant and colleagues[14] found protracted bacterial bronchitis to be the most common cause of cough in children, but their population was composed of younger children < 2 years of age. This could be due to asthma being an uncertain diagnosis in very young children and to incomplete sinus development leading to a lower frequency of UACS. In our study, asthma and UACS are the most common causes of cough based on what has been observed in adults. This difference may be related to the older age of the group of patients participating in our study.

UACS could be diagnosed by obtaining a medical history and performing physical and radiologic examinations, if necessary, in patients with chronic cough. Antihistamines, decongestants, and nasal steroids are recommended as empirical treatment. A detailed investigation should be made in patients who do not respond to such treatment. We applied therapy with antihistamines, nasal saline solutions, and nasal steroids to patients in who we had diagnosed UACS after eliminating the reasons for anatomic obstruction. During the reevaluation of the same patients in terms of their responses to the treatment, we detected wet or dry cough in some.

It has been reported in different studies[22,23] that esophageal diseases could trigger cough in children. It has been alleged[22,24] that GERD could cause persistent cough, also that cough could provoke the GERD episodes. However, the relation between reflux and cough in children has not been established completely.[25] Only a few prospective studies have reported reflux in children suffering from isolated chronic cough. In studies of adults,[12,13] GERD is one of the most common reasons for chronic cough. In our study, episodes of gastroesophageal reflux were evaluated by scintigraphy. We have detected an episode of gastroesophageal reflux in five of our patients, all of whom responded to treatment with lansoprazole and diet. We thought that GERD developed in these five patients as a result of chronic cough.

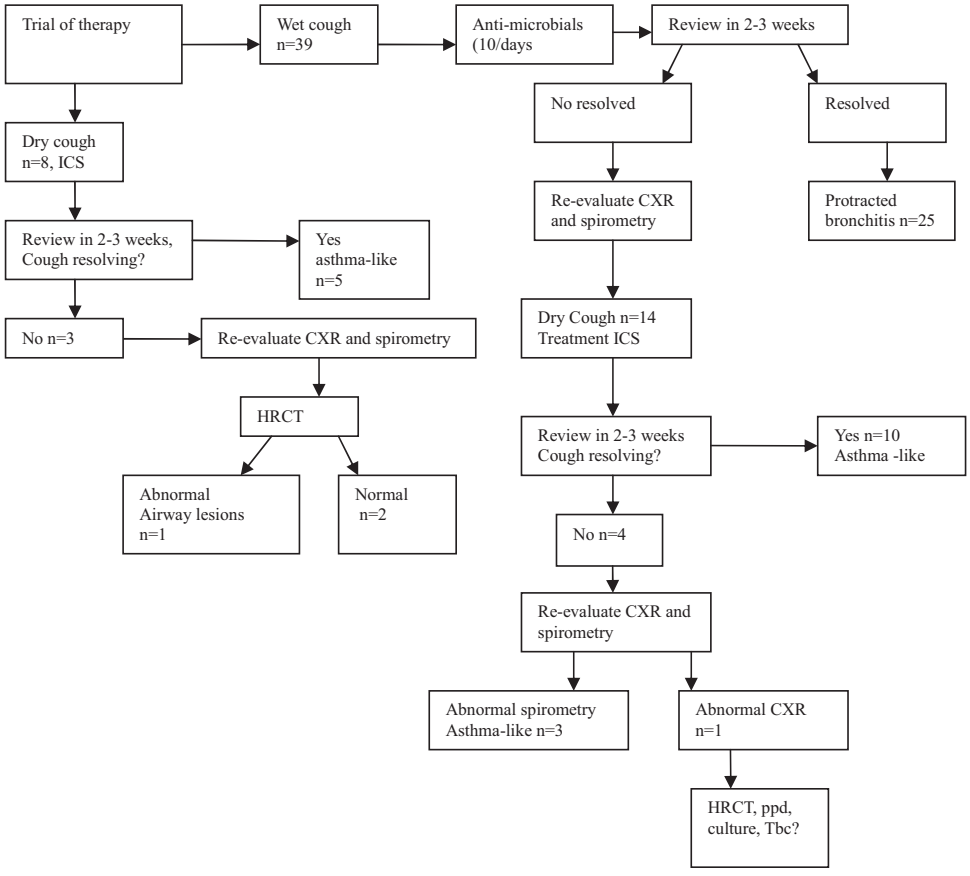

FIGURE 3. Evaluation of our patients with wet and dry cough. Tbc = tuberculosis. See the legend of Figure 1 for abbreviations not used in the text.

Postinfectious cough is one of the most common reasons for chronic cough in children. Diagnostic errors are frequently made, and it may be treated like asthma.[26] A specific infection that causes chronic cough is mostly unknown. Frequently, the infections diagnosed include respiratory syncytial virus, parainfluenza virus, *M pneumoniae*, *Chlamydia pneumoniae*, and *Bordetella pertussis*. Possible mechanisms include transient airway hyperactivity and persistent airway inflammation that occur after the infections.[27] In such cases, the disease limits itself in general, and the patient may recover without treatment. Studies[28] in adults that were carried out using therapy with ipratropium bromide were unsuccessful, hence, therapy with inhaled steroids or even short-term therapy with oral steroids was suggested for trial. We detected positive IgM and/or IgG antibodies in 17 of 41 patients in the evaluation of our patients with *M pneumoniae*. Although only part of these results suggests an acute infection, such factors may lead to chronic cough. Although we have been informed that postinfectious cough can last 3 to 8 weeks, we believe that some patients may have had protracted bronchitis due to persistent inflammation and reactive airways; however, we were unable to isolate any evident etiologic agent.

Although the wet and dry characteristics of cough can be well defined by families, it should be taken into consideration that these two different types of cough can be concurrent most of the time.[16] The same cough may be classified differently by the

Table 2—*Diagnostic Distribution of the Patients**

Diagnosis	Values
Asthma plus asthma-like symptoms	27 (25)
Protracted bronchitis	25 (23.4)
UACS	22 (20.3)
Protracted bronchitis plus asthma-like symptoms	13 (12)
UACS plus asthma-like symptoms	8 (7.4)
GERD	5 (4.6)
Bronchiectasis	3 (2.7)
Natural recovery	2 (1.8)
Tuberculosis	1 (0.9)
Congenital malformation	1 (0.9)
Mycoplasma infection	1 (0.9)

*Values are given as No. (%).

physician and can change over time. There have been no published studies on the etiology of dry cough vs wet cough in children. A wet cough represents excess airway secretions. Even in children with wet cough, a specific pediatric diagnostic category may not be found. On the other hand, a chronic dry cough may represent a dry phase of an otherwise usually wet cough. We saw that dry cough developed in some of the patients with wet cough in the beginning, or vice versa. This led us to conclude that cough does not always exhibit a wet or dry character; such characteristics can exist concurrently. The detection of a wet cough does not lead to a specific diagnosis, which should be considered when the physician decides on the treatment.

It was reported in a study by Hutton et al[29] that children whose parents asked for drug treatment for their kids recovered better regardless of the treatment administered. This means that the family's belief in treatment may affect recovery. In our study, most of the patients were administered a drug treatment and a response was detected. Since our study did not have any placebo control, we think that the evaluation of the response to treatment may not reflect the actual event. In most of our patients, when we suggested a drug treatment, we observed that the family had waited long enough and sought treatment immediately. Such a willingness to be treated may have led to a successful result.

As a result, when our patients were evaluated according to the ACCP 2006 guidelines,[17] asthma plus asthma-like symptoms, protracted bronchitis, and UACS were detected in the order they were mentioned. We concluded that the ACCP guidelines for the management of chronic cough in children is effective and can be successfully utilized in a nonaffluent study setting. We found that the "watch, wait, and review" step is particularly beneficial. The 2006 ACCP recommendations for the management of chronic cough in children should be supported with randomized controlled trials.

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