Chronic Cough and Gastroesophageal Reflux Disease*

Experience With Specific Therapy for Diagnosis and Treatment

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Study objective: To evaluate experience using a therapeutic trial of proton-pump inhibitor therapy with or without a prokinetic agent in diagnosis and treatment of gastroesophageal reflux disease (GERD)-related cough.

Design: A review of experience with 214 patients with cough of ≥ 3 weeks referred over 3.5 years. An anatomic diagnostic protocol was used to identify and treat those with GERD-related cough.

Setting: A pulmonary specialty practice affiliated with the University of Rochester School of Medicine and Dentistry.

Patients: One hundred eighty-three patients were identified with chronic cough and were included in the study. Thirty-one patients were disqualified because of abnormal chest radiographic findings, inadequate follow-up, or cough being not the primary complaint. Fifty-six patients were identified as having GERD-related cough.

Interventions: A once-daily dose of a proton-pump inhibitor was prescribed. A prokinetic agent was added if esophageal dysfunction was suspected or response was inadequate. Those who did not respond underwent 24-h esophageal pH monitoring.

Results: GERD was the single cause of cough in 24 patients (43%). Twenty-nine patients (52%) had GERD plus another cause, and 3 patients (5%) had GERD with more than two causes. Twenty-four patients (43%) had cough only, while 32 patients (57%) had other symptoms of GERD. Proton-pump therapy was successful in 42 patients (79%). Twenty-four patients responded to proton-pump inhibitor therapy, and 18 patients responded when metoclopramide or cisapride was added. The remaining two patients responded to a histamine type-2 blocker or cisapride alone. The cough was eliminated or markedly improved in 38 patients (86%) after 4 weeks and by 8 weeks in the remaining 6 patients. Six of the nonresponders had aspiration diagnosed by bronchoscopy. Four patients had fundoplication recommended, and two patients responded to alternative interventions.

Conclusions: Four to 6 weeks of a proton-pump inhibitor alone or in combination with a prokinetic agent successfully diagnoses and treats four of five patients with GERD-related cough. Twenty-four-hour esophageal pH monitoring will confirm the diagnosis in the others. These patients may be candidates for fundoplication. Nonresponders often aspirate as an additional aggravating factor.

(CHEST 2003; 123:679–684)

Key words: cough; gastroesophageal reflux; proton-pump inhibitor

Abbreviations: GERD = gastroesophageal reflux disease; PNDS = postnasal drip syndrome

Gastroesophageal reflux disease (GERD) has been identified as one of the most common causes of chronic cough.1–4 A vagally mediated esophageal-tracheal-bronchial reflex triggered by acid reflux into the lower esophagus and aspiration are believed to be

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Manuscript received October 12, 2001; revision accepted July 29, 2002.
the usual mechanisms. GERD as the cause of the cough may not be readily apparent, as cough may be the sole presenting symptom of GERD.

It has been estimated that up to 75% of persons with reflux-induced cough may have no other symptoms of reflux or experience symptoms only following cough. Persons with microaspiration are most likely to have hoarseness, dysphagia, sore throat, and the usual symptoms associated with GERD. GERD may occur primarily during the day and in the upright position. It may have been present for years. Chronic cough due to other causes may precipitate GERD and, by a cough reflex self-perpetuating cycle, contribute to persistence of the symptom, even when the other specific causes have been identified and treated.

The diagnosis of GERD-induced cough can be made for certain only when the cough responds to specific therapy. The 24-h ambulatory esophageal pH monitoring study is the most sensitive and specific test for GERD-induced cough either identifying pathologic reflux or showing a temporal relationship between cough and reflux even when the other parameters are normal. Unfortunately, this test is relatively expensive, not always available, may be poorly tolerated by some patients, and may not include monitoring of the temporal relationship between reflux and cough episodes unless specifically requested of the laboratory performing the test. Others report success with diagnosis with high-dose omeprazole. We report the results of a practical approach for both diagnosing and treating GERD-related cough in a relatively large number of patients referred for pulmonary consultation because of their persistent cough. Our study differs from previous reports in that we employed a therapeutic trial of once-daily proton-pump inhibitor therapy to both diagnose and treat chronic cough when the cough was believed related to GERD. We added a prokinetic agent when response was incomplete or esophageal dysfunction was suspected, and resorted to 24-h pH monitoring only when the approach failed to achieve the goals.

Materials and Methods

We evaluated our experience with 214 persons referred to a university-affiliated pulmonary specialty practice over 3.5 years to diagnose and treat their chronic cough. We used chart review of prospectively coded charts to include all patients seen with a chronic cough. All patients had been evaluated and treated by one of two physicians. We utilized an anatomic diagnostic protocol as originally described by Irwin et al to determine the cause of the cough. This protocol systematically evaluates persons with a chronic cough (lasting ≥ 3 weeks) who have normal chest radiographic findings and are not receiving an angiotensin-converting enzyme inhibitor initially for the three most common causes of cough (postnasal drip syndrome [PNDS], asthma, and GERD), based on the afferent limb of the cough reflex. We used symptoms, if present, to determine the initial approach. If no symptoms suggested a cause for the cough, we first used an esophageal challenge test and an empiric trial of an antihistamine/decongestant to diagnose asthma or PNDS, respectively, before considering GERD. If asthma appeared to be the cause, we initially treated with an inhaled corticosteroid followed by a long-acting β-agonist if needed. Resolution of the cough defined success. We followed up the patients until the cough cleared or for a minimum of 3 months of therapy if the cough persisted.

When reviewing the records, we tried to contact the patient or the referring physician whenever the outcome was not apparent. All qualified persons had normal chest radiographic findings. We disqualified 31 of the 214 patients because of abnormal chest radiographic findings (n = 21), inadequate investigation or follow-up (n = 7), or cough being not the primary complaint (n = 3). One hundred eighty-three persons qualified for the study. Of these, 56 patients were identified eventually by response to therapy or 24-h esophageal pH monitoring as having GERD either as the cause of or contributing to their cough. If not instituted previously by the referring physician, conservative measures, eg, weight reduction, high-protein antireflux diet, elevation of the head of the bed, and avoiding coffee and smoking were recommended as appropriate for all patients. The referring physician had often treated patients with a histamine type-2 blocker without success prior to consultation. We used a proton-pump inhibitor with or without a prokinetic agent, to confirm the diagnosis. Two months of therapy was employed before defining the patient as a nonresponder. We routinely employed 40 mg of omeprazole, or 30 mg of lanosoprazole each morning before breakfast. Two patients received 20 mg of rabeprazole daily. When the patient had dysphagia or other suspicion of esophageal dysfunction, or the response to the proton-pump inhibitor was less than expected, we added a prokinetic agent, either 10 mg of metoclopramide or cisapride four times daily, before meals and at bedtime. Eighteen patients had been treated with a histamine type-2 blocker prior to referral by the referring physician. Seventeen patients had not achieved relief from the cough. We continued a histamine type-2 blocker in one patient who appeared to be responding at the time of consultation, and another patient was treated with cisapride alone due to previously encountered intolerance of a proton-pump inhibitor.

Patients not responding to a trial of therapy and in whom an alternative diagnosis (eg, asthma, PNDS, chronic bronchitis) was not diagnosed underwent a 24-h esophageal pH study for further confirmation of the diagnosis. We used either a single or dual probe, used the pull-through method or manometry to determine the lower esophageal sphincter, and fluoroscoped if necessary to ensure accurate placement of the probe. The patient recorded respiratory and reflux events by diary. We routinely tested patients off medication for a minimum of 72 h. We defined a diagnostic study as one with frequent sustained episodes of a pH < 4 with a definite temporal relationship to the recorded event. We did not rely solely on an abnormal DeMeester score. If the diagnosis was confirmed but therapy proved ineffective, gastroenterology consultation was recommended. Some of these patients were later retested on medication. We relied on the recommendations of the gastroenterologist and did not routinely perform other tests ourselves.
Results

Figure 1 shows the results of using the anatomic diagnostic protocol in the 214 patients identified as having chronic cough. The 56 persons identified as having a GERD-related cough constituted 31% of persons with chronic cough. GERD was the single cause for cough in 24 persons (43%). Twenty-nine persons (52%) had GERD plus an additional cause responsible for the cough. This was most commonly cough-variant asthma or PNDS. Smoking was a contributing cause in three cases. Three persons (5%) had three or more causes for their cough.

Demographics did not distinguish GERD from non-GERD patients. Table 1 lists the characteristics of the two groups. Twenty-four of the 56 persons (43%) with GERD-related cough had no symptoms of GERD other than the cough. Thirty-two patients (57%) had other symptoms of GERD suggesting the diagnosis. Heartburn was universal in this subgroup; sour taste, regurgitation, hoarseness, dysphonia, and sore throat were encountered in a minority of patients. Chest pain was unusual and was usually the result of the cough.

All 56 persons were treated for GERD. Table 2 summarizes the results. Of the 18 patients treated with a histamine type-2 blocking agent (ranitidine, famotidine, or nizatidine) prior to consultation, the cough had persisted in 17 patients. The cough responded in 12 patients when a proton-pump inhibitor alone substituted the histamine type-2 blocker. The remaining five persons were eventually classified in the group of nonresponders.

Table 1—Demographic Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>GERD</th>
<th>No GERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No.</td>
<td>56</td>
<td>127</td>
</tr>
<tr>
<td>Age, yr (range)</td>
<td>57 (20–93)</td>
<td>54 (18–85)</td>
</tr>
<tr>
<td>Female/male sex, No. (%)</td>
<td>36/20 (64)</td>
<td>76/51 (60)</td>
</tr>
<tr>
<td>Cough lasting &gt; 1 yr, No. (%)</td>
<td>19 (34)</td>
<td>36 (28)</td>
</tr>
<tr>
<td>Smoking, No.</td>
<td>3</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 2—Results of Therapy in Treating Cough due to GERD

<table>
<thead>
<tr>
<th>Variables</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful trial</td>
<td>44</td>
</tr>
<tr>
<td>Proton-pump inhibitor* alone</td>
<td>24</td>
</tr>
<tr>
<td>Proton-pump inhibitor with a prokinetic agent†</td>
<td>18</td>
</tr>
<tr>
<td>Histamine type-2 (ranitidine)</td>
<td>1</td>
</tr>
<tr>
<td>Prokinetic agent (cisapride)</td>
<td>1</td>
</tr>
<tr>
<td>Therapy not successful (two agents)</td>
<td>12</td>
</tr>
<tr>
<td>Aspiration confirmed by bronchoscopy</td>
<td>6</td>
</tr>
<tr>
<td>Response to fundoplication</td>
<td>2</td>
</tr>
<tr>
<td>Surgery declined or not possible</td>
<td>2</td>
</tr>
<tr>
<td>Responded to therapy only after withdrawal of losartan</td>
<td>1</td>
</tr>
<tr>
<td>Responded to addition of oral anticholinergic</td>
<td>1</td>
</tr>
</tbody>
</table>

*Omeprazole, Lansoprazole, rabeprazole.
†Metoclopramide, cisapride.
Forty-two of the 44 responders experienced resolution of their cough when a proton-pump inhibitor alone or combined with a prokinetic agent was prescribed. One patient responded with continuation of the histamine type-2 blocker alone, and another patient responded to cisapride alone. The latter patient had severe dysphagia. Fifteen of the 24 persons who had no symptoms of GERD other than cough responded to a proton-pump inhibitor alone. A prokinetic drug had to be added for complete clearing of cough in the other nine patients. Table 3 shows the cumulative response over time to proton-pump therapy in responders. Overall, sixteen of the 42 patients receiving the proton-pump inhibitor with or without the prokinetic agent responded within 2 weeks of initiating therapy. Another 20 patients required a month for a meaningful response. Five patients required between 6 weeks and 8 weeks of treatment for a satisfactory result. One patient, initially thought to be a nonresponder, required 3 months for a satisfactory response. The cough in the two patients receiving only a histamine type-2 blocker and the prokinetic drug respectively responded within 2 weeks of therapy. We found that the cough returned in eight patients when therapy was stopped requiring resumption. We also know of three other patients who were able to stop therapy but required retreatment at a later date. We do not have late follow-up on all patients; hence, others may have relapsed when treatment was stopped and were treated by their primary physician.

The 12 nonresponders were evaluated by 24-h esophageal pH monitoring. Four of the patients clearly had cough during reflux events. Three of the four patients also had sustained reflux associated with a pH < 4 and a positive DeMeester score (> 14.7). Another five patients had some cough episodes associated with reflux events, of which three patients had a positive DeMeester score. The remaining three patients had reflux believed to be abnormal but did not meet DeMeester criteria, and the relationship between reflux events and their cough was unclear. The pH study demonstrated that the majority of reflux episodes occurred during the day in an upright posture in 10 of the 12 nonresponders. Six patients had reflux only when upright but not in supine position. Four had reflux both upright and in supine position. Only one patient had reflux when in supine position only, and the remaining patient's study was so equivocal it could not be definitively interpreted. After gastroenterology consultation, four patients eventually responded to prolonged high-dose proton-pump inhibitor therapy (40 mg of omeprazole or 30 mg of lansoprazole twice daily) combined with a prokinetic agent. Two patients had success with fundoplication. In two others, fundoplication was recommended but either was refused or could not be done. Two responded to alternative interventions (extended-release hyoscymamine sulfate, and discontinuation of losartan, thought initially not to be the offending agent, respectively). Two patients continued to cough despite maximal therapy. GERD could not be excluded, but no definitive diagnosis as to the cause of the cough was ever made. Habit or psychogenic cough was suspected. Six nonresponders had aspiration confirmed by bronchoscopy. Recovery of food particles in BAL fluid was considered diagnostic. The other nonresponders had negative procedure results.

### Table 3—Cumulative Response to GERD Therapy

<table>
<thead>
<tr>
<th>Weeks of Antireflux Therapy, No.</th>
<th>Patients Responding, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>16 (41)</td>
</tr>
<tr>
<td>4</td>
<td>38 (86)</td>
</tr>
<tr>
<td>6</td>
<td>42 (95)</td>
</tr>
<tr>
<td>8</td>
<td>43 (99)</td>
</tr>
<tr>
<td>12</td>
<td>44 (100)</td>
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**Discussion**

Evaluation of the patient with chronic cough is best accomplished using an anatomic diagnostic protocol. GERD has been so identified as one of the most common causes of chronic cough. It has also been found to be difficult to treat. In our study, GERD alone accounted for cough in 24 of 183 patients (13.1%). Adding those patients in whom GERD was a contributing factor to persistence of the cough increased the number to 56 or 31%. Twenty-one percent is the prevalence often quoted in previous studies. Thirty-two percent was recorded in one study when the diagnosis was by 24-h esophageal pH monitoring. The prevalence of GERD-related cough in our study is comparable.

Many physicians do not realize that cough resulting from reflux can occur during the day and in the upright posture. This is believed to be the result of preservation of normal esophageal function suppressing transient lower esophageal sphincter relaxation in the supine position. We found the cough in GERD patients to occur at any time of the day. We note that 10 of the 12 patients who failed the therapeutic trial and underwent 24-h esophageal pH monitoring had upright reflux. This also implies that conventional conservative measures may be ineffective in controlling cough due to reflux. At times, the cough is nocturnal and intensified by lying down or occurs after a gain in weight. Therefore, we agree with the recommendation that conservative measures, eg, weight reduction, a high-
protein antireflux diet, elevation of the head of the bed, and avoiding coffee and smoking, should be advocated for all patients.\textsuperscript{3,7} When cough is not the only symptom of GERD, the diagnosis is more frequently suspected. However, GERD as a cause of a persistent cough may not be readily apparent if there are no other symptoms. Up to 75% of patients may have no typical symptoms.\textsuperscript{5} Forty-three percent of our patients had no other symptoms of GERD. The premise of the current analysis is that the diagnosis of GERD as the cause of cough is made with certainty only when the cough resolves in response to specific therapy. We believe a therapeutic trial of a proton-pump inhibitor with or without a prokinetic agent is an effective way of diagnosing GERD-related cough. Twenty-four–hour ambulatory pH monitoring has been stated to be the most sensitive and specific test for GERD in patients with typical symptoms with up to 96% sensitivity and specificity.\textsuperscript{16,17} Even in patients with reflux in whom cough is the only symptom, positive and negative predictive values of 89% and 100%, respectively, have been obtained in diagnosing GERD as the cause of the cough.\textsuperscript{3,7} One study, however, found the test to be specific but not as sensitive (35%), and recommended instead 2 weeks of high-dose omeprazole, 40 mg bid, for 2 weeks in diagnosing and treating the cough.\textsuperscript{11} The apparent discrepancy in the sensitivity of 24-h esophageal pH monitoring might be explained by a multiple mediator pathogenesis concept with acid perhaps not being the sole or primary mediator of GERD-induced cough. GERD induced cough may respond to a once-daily dose of a proton-pump inhibitor between 1 week and 12 weeks of therapy.\textsuperscript{4,18} Our study suggests that a morning dose of omeprazole or similar drug, with the addition of a prokinetic drug when symptoms of esophageal dysfunction are present, works in four of five patients by 4 weeks. A few patients may need 8 weeks but rarely longer to obtain a complete response.

The cough appears to return in some patients when therapy is stopped, or may reoccur sometime later requiring retreatment. We observed this in our study, but unfortunately do not have follow-up on all patients once their cough had initially resolved. The pathophysiology of GERD would favor the need for long-term therapy in patients unless the precipitating factors had been corrected.

With GERD being a frequent cause of or contributor to chronic cough, we believe a trial of an effective proton-pump inhibitor is a good initial approach in the patient without clues to the cause of the cough when postnasal drip and asthma have been excluded or treated. We employed a single morning dose for 2 months (one responder required 3 months). When compared to 24-h esophageal pH monitoring, this is a cost-effective approach, although with a relatively expensive drug, and although we utilized 2 months to define responders, most (36 of 42 patients) actually responded within a month if not sooner. The Consensus Panel Report by the American College of Chest Physicians acknowledges the empiric trial of medical therapy is appropriate when 24-h esophageal pH monitoring cannot be done or is not available.\textsuperscript{19} We agree, but suggest a trial of medication should also be considered even if pH testing is available, since it is a lesser expensive alternative. We were able to diagnose 79% (44 of 56 patients) with cough due to GERD by the empiric trial of therapy. Forty-two patients received a proton-pump inhibitor either alone or in combination. With a majority of patients responding within 4 weeks of initiating therapy, a therapeutic trial is feasible without undue patient dissatisfaction from continued cough. Other investigators have reported that up to 6 months of treatment may be required for complete resolution of GERD-induced cough.\textsuperscript{3,7,20} These studies used a histamine type-2 blocker sometimes with a prokinetic agent. The shorter time to respond seen in the majority of our patients favors the proton-pump inhibitor to be the superior therapy. Five of our patients required up to 8 weeks, and one patient needed 12 weeks to achieve significant results, confirming that prolonged therapy may occasionally be required to resolve GERD-induced cough. Ours et al\textsuperscript{11} recommended 2 weeks of twice-daily omeprazole for diagnosis and treatment of GERD-induced cough. The results of the current study indicate a slightly longer course of once-daily therapy may be required for diagnosis, but continued therapy is necessary anyway to prevent relapse. We also note that Ours et al\textsuperscript{11} indicated that treatment was recommended for up to a year.

Our previous clinical experience with histamine type-2 blockers in treating cough due to GERD was confirmed in this study. Many of our consultations were the result of failure of the patient to respond to histamine type-2 blocker therapy in treating their cough. Only one patient responded when the drug was continued on the suspicion of a partial response observed at the time of consultation. We believe that histamine type-2 blockers are no longer the standard of care for esophageal reflux disease.

A vagally mediated distal esophageal-tracheobronchial reflux mechanism is believed responsible mechanism for cough in the majority of patients with GERD who have cough and no other symptoms.\textsuperscript{9} Cough is believed to result from gastric contents stimulating receptors in the distal esophagus in the absence of aspiration or proximal esophageal reflux.\textsuperscript{5,10} It seems logical that most of these patients should respond to effective proton-pump inhibitor
therapy and would explain why we achieved a favorable response in the 24 patients in our study. However, patients with an esophageal motility disturbance or microaspiration might not respond to a proton-pump inhibitor alone. This would account for why some patients, particularly those with other symptoms, need a prokinetic agent added before the desired result is achieved. We utilized 24-h esophageal pH monitoring when patients did not respond to treatment to confirm the diagnosis. A few patients responded eventually to enhanced therapy. We found that when the cough did not respond to therapy as expected, aspiration and/or severe esophageal disease was present. Gastroenterology referral was recommended for such patients. We confirmed aspiration by bronchoscopy with BAL in six of these patients. Surgery was recommended by the gastroenterology consultant for four of the nonresponders because of severe esophageal disease. The lack of response to standard medical therapy in such patients would be expected.

**CONCLUSION**

We conclude that a systematic approach with an anatomic-based protocol should be followed in diagnosing the cause of chronic cough. When patients have either reflux symptoms or present no clues as to the cause of their cough, and postnasal drip and asthma have been excluded or treated, we believe a trial of a proton-pump inhibitor is in order on the assumption that the problem may be due to GERD. Patients with dysphagia or other symptoms of esophageal dysfunction should have a prokinetic drug added from the onset. We have found 6 to 8 weeks of treatment to be a reasonable time to determine if it works. Many respond in 4 weeks, but a few may require a longer course. We would reserve 24-h esophageal monitoring for those patients in whom GERD is still suspected and treatment does not eliminate the cough. Such testing is often done with the patient receiving therapy.

**REFERENCES**


8 Sontag S, O’Connell S, Khandelwal S, et al. Most asthmatics have gastroesophageal reflux with or without bronchodilator therapy. Gastroenterology 1990; 99:613–620

9 Ing AJ. How to investigate the patient with chronic cough. Mod Med Aust 1993; 36:56–61


13 Irwin RS, Zawacki JK. Accurately diagnosing and successfully treating chronic cough due to gastroesophageal reflux disease can be difficult. Am J Gastroenterol 1989; 84:3095–3098


