From a Prospective Study of Chronic Cough

Diagnostic and Therapeutic Aspects in Older Adults

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Background: Cough is the most common complaint for which adults see a physician in the ambulatory setting in the United States. An anatomical diagnostic protocol has been used since 1981 to evaluate patients with chronic cough. It has been shown to be effective in diagnosing the cause of cough and leading to specific treatment in a variety of adult populations but has never been evaluated specifically in a population of older adults.

Objectives: To question whether the spectrum and frequency of causes of chronic cough and the response to therapy would be different in older adults.

Methods: Thirty patients at least 64 years of age with a history of cough lasting at least 3 weeks were prospectively evaluated with a protocol designed to detect diseases that stimulate the afferent limb of the cough reflex. The final diagnosis of the cause of chronic cough required fulfillment of pretreatment criteria and having cough disappear with specific therapy. When more than one disease fulfilled pretreatment diagnostic criteria, therapy was instituted in the order that these were fulfilled. Probability statistics were used to describe the testing characteristics of individual components of the diagnostic protocol in terms of sensitivity, specificity, positive predictive value, and negative predictive value as they applied to chronic cough.

Results: Forty causes of chronic cough were identified in all 30 patients. Postnasal drip syndrome, gastroesophageal reflux disease, and asthma were the most common causes of chronic cough, accounting for 85% of all causes found. Among patients with normal chest radiograph findings who were not cigarette smokers and not taking an angiotensin-converting enzyme inhibitor, postnasal drip syndrome, gastroesophageal reflux disease, and asthma accounted for 100% of all causes found. Specific therapy was successful in eliminating chronic cough in 100% of the patients studied. Except for barium esophagography, all laboratory tests for which information was available had sensitivities and negative predictive values of 100%.

Conclusions: Postnasal drip syndrome, gastroesophageal reflux disease, and asthma accounted for 85% of all causes of chronic cough in older adults. Chronic cough caused substantial physical and emotional morbidity among older patients. The major value of performing objective testing in evaluating chronic cough is its ability to rule out specific diseases as a diagnostic possibility. The following clinical profile consistently predicts patients with cough attributable to gastroesophageal reflux disease: the patient has cough that has been persistently troublesome for at least 3 weeks; does not smoke cigarettes; does not take an angiotensin-converting enzyme inhibitor; does not have or has not responded to therapy for postnasal drip syndrome and asthma; and has normal or nearly normal findings and stable chest radiograph. The differences between what we observed regarding chronic cough in older adults and observations by ourselves and others regarding chronic cough in general are minor.

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PATIENTS AND METHODS

An anatomical diagnostic protocol has been used since 1981 to evaluate patients with chronic cough. It has been shown to be effective in diagnosing the cause of chronic cough and leading to effective specific therapy in an adult population in a tertiary care center, in children in a tertiary care setting, in adults in the community hospital setting, and in adults with chronic cough productive of an excessive amount of phlegm. For this study, the subjects consisted of individuals at least 64 years of age who presented to the Pulmonary Clinic at the University of Massachusetts Medical Center in Worcester with a complaint of cough of at least 3 weeks' duration and were evaluated by one of us (R.S.I.). These patients were a subgroup of a larger group of patients of all ages with chronic cough presented previously. All patients were prospectively evaluated in the following manner:

- For all patients, a medical history taking and a physical examination were performed, concentrating on the anatomical locations of the afferent limb of the cough reflex.
- A chest radiograph was ordered in almost all patients.
- For patients who were active cigarette smokers or exposed to environmental irritants, no further studies were ordered until an attempt was made to remove the patient from the source of irritation for at least 4 weeks.
- If findings of the medical history and physical examination suggested PNDS, sinus radiographs and an allergy evaluation were obtained.
- If findings of the medical history, physical examination, and the chest radiograph did not suggest a cause, a nonspecific pharmacological bronchoprovocation challenge with methacholine chloride was performed.
- If the chest radiograph showed an abnormality, consistent with either infection or malignancy, expectorated sputum studies, fiberoptic bronchoscopy, or both were performed.
- If a cause still had not been discovered, tests for GERD were ordered. If results of a barium esophagography were nondiagnostic, 24-hour esophageal pH probe monitoring was performed.
- Fiberoptic bronchoscopy and cardiac studies were performed as a last resort when the cause of cough had not been determined after all the above-mentioned maneuvers were carried out.
- If the evaluation suggested more than one possible cause of cough, therapies were initiated in the same sequence that the abnormalities were discovered. A favorable response to a specific therapy was considered diagnostic of the primary cause if cough disappeared.
- Pulmonary function studies consisted of spirometry before and after the inhalation of albuterol or methacholine.

Gastroesophageal reflux disease (GERD) are the most common causes of chronic cough. Cough can be the sole presenting manifestation of asthma and GERD. Although chronic cough can be treated either specifically or nonspecifically, specific treatment is effective in most cases.

Among the challenges still remaining is to determine whether what we have learned about cough in general applies to different groups of patients, particularly older adults.

Our equipment and the techniques for performing these tests have been previously reported. A positive response to methacholine consistent with symptomatic asthma was defined as a decrease in forced expiratory volume in 1 second from the postsaline baseline of 20% or greater after the inhalation of 10 µmol of methacholine or less. The cumulative provocative dose was reported as the PD20. Gastroesophageal reflux disease was evaluated by barium esophagography, 24-hour esophageal pH monitoring, or both. Our technique for prolonged esophageal pH monitoring has also been reported previously. In this study, 2.1-mm-diameter electrode catheters (Synectics Med Inc, Irvine, Calif) and Mark II gold digitrappers (Synectics Med Inc) were used.

PRETREATMENT DIAGNOSTIC CRITERIA

Prospective criteria were established for the presumptive diagnoses of PNDS, asthma, GERD, chronic bronchitis, and bronchiectasis as the cause of chronic cough in older adults.

Postnasal drip syndrome was considered when patients described the sensation of having something drip down into their throats, nasal discharge, or the frequent need to clear their throats, or physical examination of the nasopharynx and oropharynx revealed mucoid or mucopurulent secretions or a cobblestone appearance of the mucosa. Rhinosinusitis was considered as a potential cause of PNDS when sinus radiographs demonstrated more than 6 mm of mucosal thickening, air-fluid levels, or opacification of any sinus; or when cough was associated with nasal congestion and a purulent discharge was seen on examination of the nasal cavities or posterior oropharynx in the absence of abnormal radiograph findings.

Asthma was considered when patients complained of episodic wheezing, shortness of breath and cough, and were heard to wheeze; reversible airflow obstruction was demonstrated by pulmonary function testing (forced expiratory volume in 1 second increased at least 15% from baseline and approached normal after inhalation of albuterol even in the absence of wheeze); or methacholine inhalation challenge results were positive in the presence of normal results of routine spirometry and absence of wheeze. The diagnosis of asthma was not made in any patient who had experienced an obvious respiratory tract infection within 2 months before examination.

Gastroesophageal reflux disease was considered when patients complained of heartburn and sour taste in their mouths more frequently than every 3 weeks; barium esophagography demonstrated reflux of barium to the middle of the esophagus or higher; or 24-hour esophageal pH monitoring showed an abnormality in the absence of upper gastrointestinal tract complaints.

In this article, we describe our experience with a group of 30 patients aged 64 years or older with chronic cough. We examined the usefulness in older patients of an anatomical, diagnostic protocol that was originally developed for use in a population of adults of all ages. Finally, we describe the effectiveness of treatment of chronic cough in older adults, giving attention to the difficulties of drug treatment in this unique group of patients.
Chronic bronchitis was considered when a patient met the criteria set forth by the British Medical Research Council: (1) a patient expectorates phlegm on most days during periods spanning at least 3 consecutive months, and such periods have occurred for more than 2 consecutive years; (2) alternative cough-phlegm syndromes have been ruled out; and (3) the patient is known to be exposed to irritating dust, fumes, or smoke. When pulmonary function tests were performed in these patients for other clinical reasons (ie, coexisting dyspnea) and they demonstrated airflow obstruction, they must have failed to demonstrate enough reversibility to be suspected of having asthma as described above (in patients with suspected asthma, forced expiratory volume in 1 second increased at least 15% from baseline and approached normal after inhalation of albuterol even in the absence of wheeze).

Bronchiectasis was considered when chest radiographs demonstrated an increase in size or loss of definition of the markings in specific segmental areas of the lung; crowded markings and atelectasis; cystic spaces; honeycombing; signs of compensatory hyperinflation; or when purulent-appearing sputum was expectorated.

**POSTTREATMENT DIAGNOSTIC CRITERIA**

The final diagnosis of the cause of chronic cough required fulfillment of pretreatment criteria and having cough disappear with specific therapy.

**Cough Due to PNDS**

Patients with postnasal drip due to rhinosinusitis were initially treated with a combination of an antibiotic plus dexamethasone maleate and d-ephedrine for at least 3 weeks, and a decongestant nasal spray (oxymetazoline hydrochloride) for 5 days. Nasal corticosteroids were given for 3 months following a favorable response to initial therapy. Allergic, perennial nonallergic, postinfectious, environmental irritant, and vasomotor rhinitis were treated with intranasal beclomethasone dipropionate, and/or oral dexbrompheniramine maleate and d-ephedrine. Whenever possible, an allergic precipitating factor was avoided.

**Cough Due to Asthma**

Patients were treated initially with a regimen of inhaled β2-agonist bronchodilators with or without inhaled corticosteroids. Chronic maintenance therapy then included inhaled corticosteroids. When therapy with metered dose inhalers caused increased cough due to airway irritation by a constituent of the aerosol, oral β2-agonist therapy was substituted.

**Cough Due to GERD**

Medical therapy consisted of the following: (1) a high-protein, low-fat (<40 g/d) antireflux diet (ie, avoiding substances that have the potential of relaxing the lower esophageal sphincter); (2) metoclopramide and histamine2-blockers; (3) head of bed elevation; (4) eating 3 meals a day without snacking; and (5) not eating or drinking except for taking medicines for 2 to 3 hours prior to lying down.

**Chronic Bronchitis**

The specific therapy of cough due to chronic bronchitis was removal of an environmental irritant such as cigarette smoking.

**Miscellaneous**

Bronchiectasis was treated with β2-agonists, theophylline, antibiotics, and chest physiotherapy with postural drainage when necessary. Left ventricular failure was treated with diuresis, afterload reduction, anti-anginal medications, and digoxin. Angiotensin-converting enzyme inhibitor–induced cough was treated with cessation of the medication. Bronchogenic carcinoma and Zenker diverticulum were treated with surgery.

**STATISTICAL ANALYSIS**

Probability statistics were used to describe the testing characteristics of individual components of the diagnostic protocol in terms of sensitivity, specificity, positive predictive value, and negative predictive value as they applied to diagnosing the cause of chronic cough. A test result was deemed a true-positive or true-negative, or false-positive or false-negative, on the basis of the response of the cough to specific therapy directed against the condition detected by the test. If a test detected a condition and specific therapy was successful, it was determined to be a true-positive result. If therapy was unsuccessful, or if an alternative condition was discovered and therapy for that condition caused cough to resolve, the test result was considered false-negative. If a test failed to reveal a condition it might have detected, and the condition was ultimately detected by other means, and therapy for that condition was successful in resolving cough, the test result in question would be considered false-negative. Finally, if a test did not reveal a condition, and therapy for an alternate condition caused the cough to resolve, that test result would be considered true-negative. Differences between groups were compared with Student t test and χ² test analysis. The .05 level of significance (type I error rate) was used throughout. Usefulness percentage was defined as the number of true-positive test results divided by the number of patients (n = 30) undergoing evaluation for chronic cough.

### RESULTS

**CHARACTERISTICS OF THE STUDY GROUP**

Thirty patients at least 64 years of age who complained of cough lasting longer than 3 weeks were evaluated. There were 18 men and 12 women ranging in age from 64 to 83 years (mean ± SD, 70.4 ± 5 years). Mean (± SD) duration of cough was 77 ± 140 months (range, 1-600 months).

**SPECTRUM AND FREQUENCY OF CAUSES OF CHRONIC COUGH**

Using posttreatment criteria, 40 causes of chronic cough were identified in 30 (100%) of 30 patients.
trum and frequency of causes is shown in Figure 1. Postnasal drip syndrome was the most common cause of cough, accounting for 19 (48%) of 40 of all causes found. Gastroesophageal reflux disease was the second most common cause, accounting for 8 (20%) of 40 causes. In 3 (37%) patients with GERD, chronic cough was the only presenting manifestation and the diagnosis was revealed with 24-hour esophageal pH monitoring. Asthma consisted of 7 (17%) of 40 cases. In 5 (71%) patients with asthma, chronic cough was the sole presenting manifestation and the diagnosis was revealed by positive results of methacholine inhalation challenge test. Miscellaneous causes, including one case each of bronchiectasis, chronic bronchitis, Zenker diverticulum with aspiration, use of angiotensin-converting enzyme inhibitor, left ventricular failure, and bronchogenic carcinoma, PNDS indicates postnasal drip syndrome; GERD, gastroesophageal reflux disease; and Misc, miscellaneous causes.

USEFULNESS OF THE DIAGNOSTIC PROTOCOL

The testing characteristics of various laboratory components of our diagnostic protocol are shown in the Table. All laboratory tests except for barium esophagography had sensitivities or negative predictive values of 100%. Of the 3 patients with GERD who had negative results of barium esophagography, all had pathologic gastroesophageal reflux detected by ambulatory 24-hour esophageal pH monitoring, accounting for a negative predictive value of barium esophagography of 0%. In addition, all 4 patients who underwent ambulatory esophageal pH monitoring had GERD, causing the negative predictive value of that test to be undeterminable.

The relative usefulness of each test performed is shown in Figure 3. Sinus radiography was found to be the most useful test in this group. Sinus radiography had a true-positive rate of 30%, usually detecting chronic rhinosinusitis causing PNDS. Methacholine inhalation challenge, spirometry, and barium esophagography all were useful in 5 (17%) patients.

OUTCOME OF SPECIFIC THERAPY

Specific therapy was successful in eliminating chronic cough in 30 (100%) of the patients studied. None of these
patients were given nonspecific antitussive therapy. On average it took 3.3 visits to the physician over 12 weeks before a specific diagnosis was made and successful specific therapy prescribed.

**CHRONIC COUGH AS A CAUSE OF MORBIDITY**

The reasons why our older patients sought medical attention for chronic cough are listed below. Each one of the following complaints was cited by more than half of all patients: something’s wrong (93%); urinary incontinence (56%); insomnia (53%); and exhaustion (53%). While 33% of all patients were concerned that their cough represented a symptom of cancer, only 1 of the 30 patients was actually diagnosed to have bronchogenic carcinoma.

<table>
<thead>
<tr>
<th>Reasons</th>
<th>No. (%)</th>
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<tbody>
<tr>
<td>Something’s wrong</td>
<td>28 (93)</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>17 (56)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>16 (53)</td>
</tr>
<tr>
<td>Exhaustion</td>
<td>16 (53)</td>
</tr>
<tr>
<td>Self-consciousness</td>
<td>13 (43)</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>11 (36)</td>
</tr>
<tr>
<td>Worried about cancer</td>
<td>10 (33)</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>10 (33)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>8 (26)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (26)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Changes in lifestyle</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Retching</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Syncope or near syncope</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

It has been known since 1981 that when adult patients present with a cough that persists for at least 3 weeks, the cause of the cough can be found and effective specific therapy can be instituted in the vast majority of patients when they are evaluated with a protocol that systematically evaluates the anatomical locations of the afferent limb of the cough reflex. While the success obtained using such an anatomical, diagnostic protocol has been shown for chronic cough in adults of all ages in a tertiary care setting, children in a tertiary care setting, adults of all ages in a community hospital setting, and adults of all ages with chronic cough with a history of excessive sputum production the spectrum and frequency of causes of chronic cough and the outcome of specific therapy have not been reported in older adults prior to this study. We have determined that the diagnostic and therapeutic aspects of chronic cough in older adults are similar to those features of chronic cough in adults of all ages.

First, with respect to the spectrum and frequency of causes of chronic cough, PNDS, GERD, and asthma accounted for 85% of all causes of chronic cough in older adults. Among patients with normal chest radiograph findings who were not cigarette smokers and not taking an angiotensin-converting enzyme inhibitor, PNDS, GERD, and asthma accounted for 100% of all causes found. A substantial number of patients (8 [27%]) had more than one cause of cough detected. In those cases, cough did not disappear until all causes were treated specifically. In almost all studies of chronic cough in adults published to date, the use of an anatomical diagnostic protocol similar to ours led to determining the cause of cough in between 88% and 100% of cases and to successful specific treatment 84% to 98% of the time. The consistency of these findings is probably a reflection of how common those diseases are in general and how frequently they are associated with chronic cough. In the 2 studies that found lower rates of success, different diagnostic and therapeutic protocols were followed. For example, one of those studies used intranasal beclometasone dipropionate and ipratropium bromide and a nonselecting oral histamine, antagonist to treat postnasal drip and failed to use a prokinetic agent to treat GERD. These are potentially inferior treatment regimens because of the lack of the drying anticholinergic activity in an antihistamine preparation being used to treat nonhistamine-mediated PNDS, and the absence of the lower esophageal sphincter tone-enhancing activity of the prokinetic agent. The other study failed to acknowledge the potential for cough to be the sole presenting manifestation of GERD. It has previously been reported that when GERD is the cause of cough, cough may be the sole or presenting manifestation from 43% to 75% of the time. These are significant differences that minimize the conclusions that may be drawn from these 2 studies.

Second, chronic cough causes substantial physical and emotional morbidity among older adults. The average patient studied in this group was 70 years of age and had been coughing for more than 6 years. At the time of presentation patients averaged more than 5 separate physical or emotional complaints attributable to their cough. While some of those complaints were concrete physical symptoms (eg, urinary incontinence, musculoskeletal pain, or hoarseness), others were more indicative of the psychological impact of having such an outwardly obvious chronic symptom (eg, something’s wrong, changes in lifestyle, or worried about cancer). The reasons why our older patients sought medical attention were similar to those reported in a group of adults of all ages studied by French et al. Using the Sickness Impact Profile and the Adverse Cough Outcome Survey, their study determined that chronic cough significantly affected the quality of life of patients in an adverse manner. Therapy directed at the specific cause of chronic cough was effective in reducing the adverse effect of cough on quality of life.

Third, the major value of performing objective testing in evaluating chronic cough is its ability to rule out specific diseases as a diagnostic possibility. Specifically, the sensitivity and negative predictive values of chest radiography, sinus radiography, and methacholine inhalation challenge approached 100%, as has been shown in adults of all ages. In this study, normal chest radiograph findings were uniformly effective in initially ruling out any disease other than PNDS, asthma, and GERD as a cause of chronic cough in older adults. Standard 4-view sinus radiography was able to detect all ultimately
diagnosed cases of chronic rhinosinusitis, and methacholine inhalation challenge was able to diagnose all cases of asthma in those patients without significant abnormalities of pulmonary function at baseline.

Because of the small number of tests performed, it is difficult to draw conclusions about the value of barium esophagography, 24-hour esophageal pH monitoring, bronchoscopy, and spirometry before and after the administration of inhaled bronchodilator. However, previous studies have shown that of these tests, 24-hour esophageal pH monitoring is the most useful and barium swallow is the least useful. Previous studies of adult subjects with chronic cough also have shown that all patients who were not cigarette smokers or taking an angiotensin-converting enzyme inhibitor, and had a normal chest radiograph, and either did not have or did not fully respond to treatment for PNDS or asthma, were ultimately found to have GERD. Therefore, the excellent results of the use of our 24-hour esophageal pH monitoring is not surprising. Perhaps consideration should be given to treating patients with this clinical profile empirically for GERD. If such an approach is adopted, the clinician should be aware that the full effect of intensive medical therapy for cough induced by GERD may not be seen on average for 5.5 to 6 months.

Fourth, we have reconfirmed that there is a clinical profile that consistently predicts that chronic cough is due to PNDS, asthma, or GERD. That profile is characterized by the following attributes. The patient: (1) has cough that has been persistently troublesome for at least 3 weeks; (2) does not smoke cigarettes; (3) does not take an angiotensin-converting enzyme inhibitor; and (4) has normal or nearly normal and stable chest radiograph findings. This profile was 100% accurate in predicting that these diseases would be the cause of cough. Similar findings have been consistently reported by others.

Fifth, the differences between what we have observed regarding chronic cough in older adults and observations by ourselves and others regarding chronic cough in general are minor. Gastroesophageal reflux was the second most common cause of chronic cough in older adults, in contrast to its position as the third most common cause of chronic cough in the general adult population. This finding should not be surprising given what we already know about GERD in older adults. More than 20% of older patients seen in the outpatient setting may have acid or alkaline GERD, determined by 24-hour esophageal pH monitoring. Since esophageal function in healthy older adults is thought to be extremely well preserved, we can only speculate that the factors that predispose people to develop GERD, including ethanol use, obesity, and poor diet, are common among older adults. However, there are no objective data to support this speculation. In addition, medications that predispose to GERD, such as theophylline, narcotics, and calcium-channel antagonists, are used commonly by older adults. Patients in this study had complained of cough for longer than those presented in previous studies. While it is possible that older adults may have been more willing to tolerate this symptom longer as a consequence of aging, we have no data on this. Sinus radiography had a 30% true-positive rate, and was found to be the most useful test in this regard, in contrast to previous studies that showed pulmonary function testing to be the most useful test. This is probably because rhinosinusitis made up a greater percentage of patients with PNDS in this older group (9 [47%] of 19) than in previous studies of chronic cough. Older patients with asthma seem to include a high percentage of cases of cough-variant asthma. In other words, a high percentage of older patients with asthma (5 [71%] of 7) had chronic cough as the sole presenting manifestation of their disease. A comparative figure for our most recent study of adults of all ages was 32%. The overall prevalence of asthma in older adults has been estimated to be between 2.9% and 7.5%.

In conclusion, the syndrome of chronic cough in older adults shares many characteristics with the syndrome of chronic cough in adult patients of other ages. Using the same anatomical diagnostic protocol as with patients of all ages, the causes of chronic cough can be diagnosed with a high degree of accuracy. Postnasal drip syndrome, GERD, and asthma consist of 85% of all causes of chronic cough and 100% of all causes in patients who have normal or nearly normal and stable chest radiograph findings who do not smoke cigarettes or take an angiotensin-converting enzyme inhibitor. Twenty-seven percent of patients have more than one cause of chronic cough. Cough should be effectively treated in the vast majority of patients using treatment directed specifically at the causes or operant pathophysiological mechanisms causing the cough. Treatment must be directed at all causes detected to be effective. Chronic cough causes tremendous physical and emotional morbidity among older adults. On average, patients had 5 separate physical or emotional complaints attributable to their cough. The value of objective testing remains in its ability to rule out specific diseases as a diagnostic possibility because the sensitivity and negative predictive values of chest radiography, sinus radiography, and methacholine inhalation challenge are excellent. While there are some differences in comparison with the diagnostic and therapeutic aspects of other adult patients, we believe these differences are minor. Chronic cough in older patients should be evaluated in the same manner as it is in other groups, using a diagnostic protocol that focuses on diseases that may stimulate the afferent limb of the cough reflex. The same excellent results of specific therapy should be expected. Nonspecific therapy has the potential to cause a higher frequency and severity of adverse reactions and should be avoided unless no specific therapy is found to be available.

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Correction

Error in Figure Legends. In the original investigation titled “Estimating the Benefits of Modifying Risk Factors of Cardiovascular Disease,” published in the March 23 issue of the ARCHIVES (1998;158:655-662), the legends for Figure 2 and Figure 3 were accidentally reversed during processing for publication. The journal apologizes for the error.