Prevalence of Gastroesophageal Reflux in Difficult Asthma*

Relationship to Asthma Outcome

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Study objectives: To determine the prevalence of gastroesophageal reflux disease (GERD)—both symptoms and objective evidence—using 24-h dual-probe pH monitoring in difficult asthma, and the relationship between the presence and treatment of GERD to clinical outcome.

Design and setting: As part of a systematic evaluation protocol, 68 subjects with difficult-to-control asthma attending a difficult asthma clinic were referred for dual-probe ambulatory pH esophageal monitoring.

Results: Esophageal probe data were available in 52 patients (76%) with difficult asthma. The prevalence of GERD/GERD-associated asthma symptoms was 75% (39 of 52 patients; 95% confidence interval [CI], 63 to 84.7%). The prevalence of GERD as evidenced by an abnormal pH profile at the distal esophageal probe was 55% (29 of 52 patients; 95% CI, 40 to 69%). The prevalence of GERD at the proximal probe was 34.6% (18 of 52 patients; 95% CI, 23.6 to 51%). The prevalence of GERD was similar in asthmatic subjects who responded to intervention and those who remained difficult to control (therapy resistant). Asymptomatic GERD was present in 9.6% (5 of 52 patients); 16% of cough episodes correlated with acid reflux.

Conclusions: In difficult-to-control asthma, GERD is common, but identification and treatment of GERD do not appear to relate to improvement in asthma control in this population.

Key words: difficult asthma; gastroesophageal reflux disease; therapy-resistant asthma

Abbreviations: CI = confidence interval; GERD = gastroesophageal reflux disease

The relationship between gastroesophageal reflux disease (GERD) and asthma has remained controversial since Sir William Osler first described their association in 1892.1 A number of studies2–4 have demonstrated a GERD prevalence ranging from 15 to 82% using pH monitoring in asthma. Distal esophageal stimulation with acid may cause bronchoconstriction5 or may increase bronchial reactivity6 via vagal mechanisms. In an animal model, proximal esophageal reflux has been shown to cause microaspiration of gastric acid contents and lead to bronchoconstriction.7 Thus, potential mechanisms exist for GERD to cause asthma symptoms; however, it is unclear whether or not there is a true causal relationship between reflux episodes and asthma symptoms.8 It has been proposed that GERD is particularly likely to be an exacerbating factor in the subgroup of patients with “difficult-to-control” asthma.9 In one study10 of patients with difficult-to-control asthma, GERD was identified as the most common identifiable exacerbating factor; however, subjects were not receiving inhaled steroids but were maintained on oral steroids, and the diagnosis of GERD was based solely on clinical grounds in a proportion of study patients. The aims of this study were to determine the following in a population with difficult-to-control asthma: (1) the prevalence of GERD, based on symptoms and measured objectively using 24-h dual-probe pH monitoring; (2) the relationship between the presence and treatment of GERD and clinical outcome; and (3) the correlation between symptoms of cough and reflux episodes.

METHODS AND MATERIALS

Study Design

Subjects with difficult-to-control asthma referred to the Difficult Asthma Service in the Regional Respiratory Centre, Belfast City Hospital were recruited between 1999 and 2002.
Study Patients

On entry to the investigative protocol, all patients fulfilled the criteria for difficult-to-control asthma, i.e., all had persistent refractory symptoms, were receiving minimal maintenance therapy of long-acting β₂-agonist and inhaled steroids (≥800 μg beclomethasone dipropionate or equivalent), and had received at least one course of systemic steroids in the preceding 12 months. Asthma was defined on the basis of symptoms together with documented reversible airflow obstruction (FEV₁ > 12% either spontaneously or with medication).11 Asthma was managed according to British Thoracic Society guidelines with treatment being stepped up and down as appropriate. The lowest dose of inhaled corticosteroid required to control asthma symptoms during the period of evaluation was recorded.

Study Methods

All patients underwent a detailed systematic evaluation to identify exacerbating factors. At the first consultation, the following tests were performed: skin-prick testing to 12 inhalant allergens, chest radiography and spirometric testing with reversibility to nebulized β₂-agonist, urinalysis, and a standardized battery of blood tests. A previously validated asthma-related quality-of-life questionnaire12 was completed at the initial visit and when discharged (if asthma control achieved) or 12 to 18 months after the initial evaluation.

The following investigations were arranged as part of the systematic evaluation: formal psychiatric interview; ear, nose and throat examination; pulmonary function testing (inspiratory/expiratory flow volume loop, carbon monoxide transfer factor, and lung volumes by helium dilution), high-resolution CT scan of thorax, 24-h dual-probe ambulatory esophageal pH monitoring, and dual-emission radiograph absorptiometry scan. All subjects were offered the services of a social worker if an underlying contributory social issue was identified. Any identified exacerbating factor was treated or managed according to standard management guidelines, the results of which have been previously published.13 Subjects with reflux (see below) were treated with omeprazole, 40 mg/d. When administered as a single dose or as twice daily as in this study, omeprazole has been shown to provide significant suppression in distal esophageal acid exposure compared to baseline both in healthy control subjects and in Barrett esophagus (a condition also associated with excess esophageal acid exposure)14,15 and a significant reduction in duodenal contents delivered to the upper gastric body noted.16

In an attempt to identify patients with asthma-related reflux symptoms, the following questions were asked: (1) Do you have heartburn, waterbrash, or indigestion? (2) Is your asthma worse lying flat? (3) Is your asthma worse after stooping? (4) Is your asthma worse after eating? If patients answered “yes” to one or more of the questions, they were recorded as having symptoms suggestive of GERD/GERD-associated asthma.

Ambulatory 24-h dual probe esophageal pH monitoring was performed as previously described.17,18 In brief, after an overnight fast, a dual-probe antimony electrode (Synectics; Stockholm, Sweden) was placed transnasally such that the distal probe lay in the lower esophagus 5 cm above the upper border of the manometrically determined lower esophageal sphincter. The second probe lay in the proximal esophagus 15 cm above the distal probe. Patients were encouraged to eat their usual meals at breakfast, lunch, and dinner, and keep a diary of meal times, sleep times, and symptoms such as heartburn, chest pain, regurgitation, and cough. Patients were encouraged to remain ambulatory as normal during the day. Patients returned the following day for the data to be downloaded from the Digitrapper onto a computer. Significant reflux in the distal esophagus was present if the percentage of total time pH ≤ 4 was > 4.8% of total time (95th percentile of normal volunteers in our laboratory).18 Reflux at the proximal probe was significant if the percentage of total time pH ≤ 4 was > 0.9% of total time.19 An episode of cough (or other respiratory symptom) was regarded as associated with a reflux event if the cough occurred simultaneously with the esophageal pH dropping below 4 or within 5 min of the drop.

Patients underwent a systematic evaluation and follow-up for at least 12 months. This included the treatment of any identified exacerbating factors. Only after this was the designation of subjects into either therapy-resistant or therapy-responsive asthma made. Therapy-responsive asthma occurred when good asthma control was achieved, and the patient was discharged back to their primary care service. Therapy-resistant asthma was defined in accordance with the European Respiratory Society Task Force on Difficult Asthma:10 persisting symptoms due to asthma despite high-dose inhaled steroids (2,000 μg of beclomethasone, 1,600 μg of budesonide, 1,000 μg of fluticasone) plus long-acting β₂-agonist and the requirement for either maintenance systemic steroids or at least two rescue courses of steroids in a follow-up period of 12 months despite trials of add-on therapy, eg, leukotriene receptor antagonist or theophylline.

Statistical Analysis

Demographic data are presented as the mean, SEM, or absolute value. Differences in continuous variables were calculated using the unpaired t test. The difference in prevalence of GERD in the treatment groups was tested using the χ² test (with Yates correction or Fisher exact test as appropriate). Statistical differences in quality-of-life scores at the same point in time were calculated using the paired t test. Dichotomous variables were analyzed using the Fisher exact probability test. The level of significance was set at 5% (0.05). All statistics were performed using software (SPSS for Windows Version 11; SPSS; Chicago, IL).

Results

Of 68 evaluated asthmatic subjects, 34 were classified as therapy responsive and 34 as therapy resistant after evaluation. Demographic data for both groups are shown in Table 1. The dose of inhaled corticosteroid at presentation and discharge was significantly higher in the therapy-resistant group. The clinical assignment was supported by the asthma-related quality-of-life scores, which improved significantly only in the therapy-responsive group with a mean change > 0.5 (which has been previously determined to represent the minimal clinical significant change30) [Table 1].

A 24-h esophageal pH profile was not available in 16 subjects (23.5%). Of these, 9 subjects (13%) failed to attend for the procedure despite several appointments, 6 subjects (9%) were unable to tolerate the probe, and 1 subject (1.5%) had a failed recording. Of those who failed to attend, only three were in the therapy-resistant group. Esophageal probe data were available in 28 of therapy-resistant patients (82.3%) and 24 of therapy-responsive patients (70.6%) [Table 2].
Of those who underwent pH testing symptoms suggestive of GERD or GERD-associated asthma were present in 75% (39 of 52 patients; 95% confidence interval [CI], 63 to 83.5%). The prevalence of these symptoms in the therapy-responsive group was 70.6% (95% CI, 52.5 to 84.9%) vs 79.4% (95% CI, 62.1 to 91.3%) in the therapy-resistant group (p = 0.58). The positive and negative predictive values of reflux symptoms in predicting significant GERD at the distal probe were 65% and 71%, respectively. Asymptomatic GERD was present in 9.6% (5 of 52 patients).

Using pH monitoring, the overall prevalence of GERD at the distal probe was 55% (29 of 52 patients; 95% CI, 40 to 69%), with no difference between groups: therapy-responsive group, 50% (95% CI, 29.1 to 70.9%); therapy-resistant group, 57.1% (95% CI, 37.2 to 75.5%). The overall prevalence of GERD at the proximal probe was 34.6% (18 of 52 patients; 95% CI, 22.4 to 49.9%); therapy-responsive group, 39.1% (95% CI, 19.7 to 61.5%); therapy-resistant group, 32.1% (95% CI, 15.9 to 52.4%).

Table 2—Twenty-four Hour Ambulatory Dual-Probe pH Profiles in Subjects With Therapy-Responsive and Therapy-resistant Asthma*

<table>
<thead>
<tr>
<th>Asthma</th>
<th>Proximal Probe</th>
<th>Distal Probe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy Responsive (n = 24)</td>
<td>0.3 (0.0–1.4)</td>
<td>4.8 (1.33–10.8)</td>
</tr>
<tr>
<td>Therapy resistant (n = 28)</td>
<td>0.35 (0.0–1.2)</td>
<td>6.05 (2.05–10.7)</td>
</tr>
</tbody>
</table>

*Data are presented as median (IQR).

Discussion

This represents the largest group of patients with difficult-to-control asthma to have been systematically evaluated using 24-h esophageal pH monitoring. While we cannot exclude the possibility that antireflux therapy contributed to asthma control in individual subjects of the responsive group, the identification and treatment of GERD failed to improve asthma outcome in the group as a whole. This finding questions the importance currently attached to GERD in difficult asthma.

Studies2–4 that have attempted to quantify the prevalence of GERD in asthma have examined heterogeneous asthma populations with a range of disease severity. Using a comprehensive diagnostic protocol that has previously been published,13 we were able to identify and manage other factors that
can exacerbate or mimic asthma. We are confident that the 34 patients defined as having therapy-resistant asthma after evaluation did have severe asthma, which was poorly responsive to high-dose maintenance therapy. This observation is supported by the lack of change in asthma-related quality-of-life scores in this group.

All patients were receiving long-acting β-agonists and high-dose inhaled corticosteroids. The dose of inhaled corticosteroids was greater in the therapy-resistant group; however, we feel it is unlikely that this could be responsible for more refractory GERD in the therapy-resistant group since no difference in reflux prevalence was noted between the two groups.

The prevalence figure of 75% for symptoms suggestive of GERD in our study may be high because of our broad definition of GERD-related asthma symptoms. However, this prevalence figure is similar to that of other, less severe asthma populations. Field et al quoted prevalence figures for symptoms of heartburn and regurgitation of 77% and 55% of asthmatics, respectively Harding et al retrospectively examined 199 asthmatics, of whom one third were classified as severe, and found 164 subjects (82%) with symptoms of GERD. O’Connell et al found 72% of consecutive asthma patients had heartburn (136 of 189 patients). Although studies vary in their criteria for diagnosing what level of symptoms is pathologic, symptoms of GERD appear to be more common among asthma populations compared to 35 to 40% reported for the general population.

Ambulatory pH monitoring has been reported to have a higher sensitivity and specificity than any other single clinical test in the diagnosis of GERD. Using pH studies and analyzing receiver operating characteristics to generate pH threshold values, Sontag et al showed evidence of excessive acid reflux in > 80% of an asthma population. This is higher than our 55% and those of 34% and 15% published by Nagel et al and Compte et al, respectively. One possible explanation for this is different patient populations. Additional contributory factors include the male predominance (95% male) and higher percentage of current smokers (39.4%) in the group of Sontag et al.

Using a systematic protocol, Irwin et al examined 42 patients with difficult asthma and found that GERD was the most common factor making asthma difficult to treat. However, their definition of GERD included the presence of prominent symptoms, positive esophagography findings, or an abnormal pH probe profile. All patients recruited into their study had to have received at least 10 mg of oral prednisolone every other day for at least 3 consecutive months per year and were not receiving inhaled steroids or long-acting β-agonists, which reflected asthma treatment at that time. Systemic steroids have been shown to increase both proximal and distal GERD in asthma patients and may have potentiated reflux disease. This, combined with a diagnosis based on symptoms, may have contributed to their high prevalence of reflux. These factors make this study difficult to compare directly with our findings.

The reported prevalence of clinically silent GERD defined by pH monitoring varies between 29% and 62%. In our study, only 9.6% (5 of 52 patients) with significant reflux on pH monitoring had clinically silent disease. This difference may relate to the use of a broader set of screening questions. We sought to identify those with “silent” disease in terms of specific reflux symptoms but who may still have had asthma symptom exacerbation related to posture or food. The addition of questions to highlight potential asthma symptom exacerbation was intentional and sought to minimize patients labeled as “silent” when appropriate questioning might demonstrate a link between their asthma symptoms and reflux. This approach appears to have been justified by reducing the prevalence of silent reflux to 9.6%, although this method needs to be validated.

Using a time window of 5 min, we found that cough correlated poorly with reflux episodes. This is in marked contrast with Harding et al, who, using the same time association, found 90.5% (76 of 84 coughs) were associated with acid in the esophagus. However, our result is more in keeping with the study by Laukka et al, who found that 80.9% (182 of 221 cough episodes) did not correlate with acid reflux. Avidan et al found that half of all coughs in 128 asthmatics were associated with acid reflux into the esophagus.

The analysis of cough and its correlation to reflux episodes remains problematic. Patients underreport cough, and the timing of coughs can be misreported. Paterson et al suggested that combining ambulatory esophageal manometry and pH monitoring may provide an objective measure of the temporal relationship between cough episodes and reflux that is superior to relying on patient reporting. They found that if single coughs and cough bursts were considered; patients reported a mean of 4.4 coughs per study out of 36.9 recorded manometrically (p = 0.001).

One possible criticism of our study is the failure to repeat esophageal pH monitoring on patients unresponsive to medical antireflux therapy to ensure GERD had indeed settled with treatment. However, these patients did have a symptomatic improvement in GERD symptoms; despite this, their asthma remained difficult to control. In addition, twice-daily dosing of 20 mg of omeprazole has been shown to provide successful acid suppression in 22 of 23
patients (96%) with Barrett esophagus, a condition similarly associated with excess esophageal acid exposure, as well as in healthy control subjects.14,15

Ongoing nonacid reflux when receiving a proton pump inhibitor could be cited as an alternative potential explanation for the negative result of our study. However, Champion et al32 demonstrated that omeprazole, 40 mg, reduces bile reflux by 90% as well as controlling acid reflux.

A further potential explanation for the negative findings could be that the patients had received treatment for refractory asthma symptoms by primary care and general physicians for some time prior to referral. Such treatments may have included a trial of antireflux therapy. Therefore, when finally referred for specialist investigation, it is possible that our patients represent a phenotype least likely to respond to intervention with antireflux therapy.

The most important finding from this study is the similar prevalence of GERD in therapy-responsive and therapy-resistant difficult asthmatics. This suggests that while GERD is common in difficult asthma, proactive identification and treatment of GERD using high-dose proton pump inhibitors does not relate to asthma outcome, at least in this population. Our findings question the previous prominence afforded to GERD therapy in the management of patients with difficult asthma and raises the possibility they may be two common conditions coinciding in the same patients.

References
3 Soutaj SJ, O'Connell S, Khandelwal T, et al. Most asthmatic patients have gastroesophageal reflux with or without bronchodilator therapy. Gastroenterology 1990; 99:613–620