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Role of Gastroesophageal Reflux in Older Children With Persistent Asthma*

Vikram Khoshoo, MD, PhD; Thao Le; Robert M. Haydel, Jr., MD; Lisa Landry, LPN; and Carl Nelson, MS, RRT

**Background:** Gastroesophageal reflux (GER) plays a role in inducing or exacerbating asthma.

**Methods:** We evaluated asthma outcome before and after anti-GER treatment in older children (age range, 5 to 10.5 years) who had persistent moderate asthma and were being treated with short- and long-acting bronchodilators, inhaled corticosteroids, and leukotriene antagonists. Forty-six such consecutive children underwent extended esophageal pH monitoring. Of the 27 patients (59%) who had evidence of GER disease, 18 patients underwent medical treatment (lifestyle changes, proton pump inhibitors, and prokinetics) and 9 patients opted for surgical treatment (Nissen fundoplication) of GER. Of the 19 patients with normal pH study findings, 8 patients underwent empiric medical anti-GER treatment and the remaining 11 patients served as a control group. Data on all patients were collected from 6 months prior to performing the pH studies and for 12 months after initiation of anti-GER treatment. The frequency of oral and inhaled corticosteroids, short- and long-acting bronchodilators, and leukotriene antagonists was prospectively recorded.

**Results:** There was a significant reduction in the use of short- and long-acting bronchodilators as well as inhaled corticosteroids after anti-GER treatment was instituted in patients with GER disease (p < 0.05). Two patients (25%) without evidence of GER disease showed significant reduction in need for asthma medication after anti-GER treatment, but none of the patients without GER disease and no GER treatment showed any significant reduction in the need for asthma medications.

**Conclusions:** Anti-GER treatment in patients with GER disease and asthma results in a significant reduction in the requirement of asthma medications. (CHEST 2003; 123:1008–1013)

**Key words:** asthma; asthma medications; gastroesophageal reflux

**Abbreviation:** GER = gastroesophageal reflux

The relationship of gastroesophageal reflux (GER) and asthma is complex. It is not clear if GER is a concomitant finding in asthma, induces asthma, or exacerbates asthma. The prevalence of GER symptoms in adult patients with asthma is approximately 75%. The prevalence of GER disease as measured by extended esophageal pH monitoring in adults with asthma ranges from 55 to 83% and in children with asthma is approximately 50 to 63%. Despite methodologic weaknesses, several controlled trials in adult patients, with varied designs but using proton-pump inhibitors for GER disease, have shown improvement in asthma outcomes as measured by decrease in symptoms, reduction in medication usage, and improvement in pulmonary functions. Similar studies in the pediatric population are lacking. We therefore evaluated the effect of aggressive anti-GER therapy using proton-pump inhibitors on the requirement for asthma medications in older children with persistent moderate asthma before and after treatment of GER without the use of a placebo. The assessment of asthma severity and hence treatment rendered as well as the treatment for GER was uniform.

**Materials and Methods**

Predetermined entry criteria allowed inclusion of only those children who: (1) had no family history of asthma; (2) had no personal or family history of atopic disease; (3) had been receiving treatment for asthma for at least 2 years; (4) had parents...
who did not smoke; (5) had at least three emergency visits or hospital admissions per year in the preceding 1 year; (6) required a combination of short- and long-acting bronchodilators, leukotriene antagonists, and inhaled or oral corticosteroids for the management of asthma; (7) did not have a history of respiratory syncytial virus bronchiolitis; and (8) could swallow a tablet or capsule. All the patients were derived from a geographically distinct region where all children with asthma, who are deemed to require care by a specialist, are referred to the only one specialist, and all the patients with GI problems are referred to the only pediatric gastroenterologist in that region. All consecutive children with asthma fulfilling these entry criteria and referred to the gastroenterologist for ruling out GER disease underwent extended esophageal pH monitoring (20 to 24 h) using a dual-channel (10 cm apart) pH probe with the distal channel placed and confirmed radiologically at approximately 3 cm proximal to the gastroesophageal junction. All asthma medications were continued uninterrupted. No advice regarding diet or positioning was given. Care was taken to ensure that no antacids were consumed during or up to 3 days before the study. Those children who had an abnormal pH study finding (pH < 4 in the distal esophagus for > 5% of the time) underwent aggressive anti-GER treatment with lifestyle changes, a prokinetic, and a proton-pump inhibitor. At the initial visit, extensive counseling was provided about the different components of anti-GER treatment as well as the role of anti-GER surgery. These children then underwent regular follow-up at intervals of 4 weeks for asthma management based on symptoms in the preceding 4 weeks. Medications were added or deleted based on this assessment. Patients were also seen for acute exacerbation, and medications were adjusted accordingly. Every 4 weeks, the dose of the prokinetic was adjusted based on current weight. Medications were continued or deleted based on current weight. The proton-pump inhibitor was lansoprazole, 30 mg/d, as a single dose early in the morning. The inhaled corticosteroids used were either budesonide, 200 to 400 µg bid, or fluticasone, 110 to 220 µg bid. The only leukotriene inhibitor used was montelukast administered as a capsule. All the patients were derived from a geographically distinct region where all children with asthma, who are deemed to require care by a specialist, are referred to the only pediatric gastroenterologist in that region. All consecutive children with asthma fulfilling these entry criteria and referred to the gastroenterologist for ruling out GER disease underwent extended esophageal pH monitoring (20 to 24 h) using a dual-channel (10 cm apart) pH probe with the distal channel placed and confirmed radiologically at approximately 3 cm proximal to the gastroesophageal junction. All asthma medications were continued uninterrupted. No advice regarding diet or positioning was given. Care was taken to ensure that no antacids were consumed during or up to 3 days before the study. Those children who had an abnormal pH study finding (pH < 4 in the distal esophagus for > 5% of the time) underwent aggressive anti-GER treatment with lifestyle changes, a prokinetic, and a proton-pump inhibitor. At the initial visit, extensive counseling was provided about the different components of anti-GER treatment as well as the role of anti-GER surgery. These children then underwent regular follow-up at intervals of 4 weeks for asthma management based on symptoms in the preceding 4 weeks. Medications were added or deleted based on this assessment. Patients were also seen for acute exacerbation, and medications were adjusted accordingly. Every 4 weeks, the dose of the prokinetic was adjusted based on current weight. The prokinetics used were either cisapride, 1 mg/kg/d divided in three doses, or metoclopramide, 0.15 mg/kg per dose tid administered before meals. The proton-pump inhibitor used was lansoprazole, 30 mg/d, as a single dose early in the morning. The inhaled corticosteroids used were either budesonide, 200 to 400 µg bid, or fluticasone, 110 to 220 µg bid. The only leukotriene inhibitor used was montelukast administered as a 10-mg tablet once a day. The short-acting bronchodilators used were either albuterol, 2.5 mg per dose, or levalbuterol, 0.63 mg per dose, administered as directed, depending on the severity of the symptoms. Salmeterol, 50 µg bid, was the only long-acting bronchodilator used. Mometasone, 50 µg once or twice daily, or budesonide, 32 µg once or twice daily, were the two corticosteroid preparations used as a nasal spray.

Data on asthma medications used was collected from the parents’ daily log and corroborated by the patients’ medical records in the asthma clinic. Data were gathered for a 6-month period prior to referral for GER workup and for 12 months after initiation of anti-GER treatment. An initial 6-month period of the anti-GER treatment phase was regarded as a washout period, and these data were not used in the analysis. The washout period was introduced to allow the anti-GER management to take effect and be able to produce a discernable improvement in asthma outcomes. Similarly, data on patients opting for anti-GER surgery (Nissen fundoplication) were collected only after a 6-month washout period after the surgery. The same pediatric surgeon performed all surgeries.

The pediatric pulmonologist treating asthma was aware of the anti-GER treatment. This would in no way compromise standard of care. The diagnosis and management strategy for asthma was according to the National Institute of Health guidelines. All patients were receiving inhaled corticosteroids and the long-acting bronchodilator on a daily basis for maintenance. The short-acting bronchodilators were used on an as-needed basis for wheezing. Oral corticosteroids and the leukotriene antagonist were used for breakthrough symptoms. Nasal steroids were used if and when needed for rhinorrhea.

The use of short- and long-acting bronchodilators and inhaled corticosteroids (days of use over the second 6-month period after initiation of anti-GER treatment) were used as the outcome variables. Each patient served as his/her own control. All results from the pretreatment phase for a particular patient were compared to those for the same patient in the posttreatment phase using a paired t test and two-way analysis of variance for repeated measures. None of the patients received a placebo.

Table 1—Patient Characteristics

<table>
<thead>
<tr>
<th>Groups</th>
<th>Patients, No.</th>
<th>Mean Age (SD), yr</th>
<th>Male/Female Gender, No.</th>
<th>pH Probe Evidence of GER Disease</th>
<th>Treatment of GER Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>18</td>
<td>8.5 (1.3)</td>
<td>10/8</td>
<td>Yes</td>
<td>Medical</td>
</tr>
<tr>
<td>B</td>
<td>9</td>
<td>8.6 (0.9)</td>
<td>6/3</td>
<td>Yes</td>
<td>Surgical</td>
</tr>
<tr>
<td>C</td>
<td>8</td>
<td>8.2 (1.3)</td>
<td>5/3</td>
<td>No</td>
<td>Medical</td>
</tr>
<tr>
<td>D</td>
<td>11</td>
<td>8.0 (1.7)</td>
<td>6/5</td>
<td>No</td>
<td>None</td>
</tr>
</tbody>
</table>

Table 1 outlines the patient characteristics and treatment groups. Over a 2.5-year period, 482 patients with asthma of > 2 years duration were screened. A total of 46 consecutive patients with persistent moderate asthma referred to the pediatric gastroenterologist for ruling out GER disease and fulfilling all the entry criteria were enrolled in the study. All patients underwent extended esophageal pH monitoring. Twenty-seven of the 46 patients (59%) had abnormal pH study findings, defined as total duration of pH < 4 in the distal esophagus > 5% of the time. Eighteen of these 27 patients underwent medical anti-GER treatment (group A), and the remaining 9 patients opted for surgical treatment (Nissen fundoplication, laparoscopic [n = 7] and open [n = 2]) within 1 to 6 months of diagnosis of GER disease (group B). Nineteen patients (41%) had normal pH study findings. Eight of these 19 patients opted for a therapeutic trial of...
anti-GER treatment (group C), and the remaining 11 patients did not receive any anti-GER treatment (group D). The age and sex distribution in the different groups was comparable (p > 0.05). No long-term complications of surgery were seen in any patients. None of the anti-GER medications were associated with a clinically obvious side effect. Frequent ECGs in patients receiving cisapride did not show any arrhythmias or prolongation of ST segment.

Table 2 outlines the results of the pH monitoring in the different groups. All the patients in groups A and B had duration of acid pH in the distal esophagus for > 10% of the time. All patients in groups C and D had duration of acid pH in the distal esophagus for < 5% of the time.

Table 3 shows the number of days of the short-acting bronchodilator use before and after treatment for GER in different groups. In groups A and B, there was a significant reduction in the days of bronchodilator use following medical or surgical treatment for GER, respectively (p < 0.05). The mean use of short-acting bronchodilators, though lesser, was not statistically significant in group C before and after treatment for GER (p > 0.05). In group D, there was no difference in the use of bronchodilators in the two 6-month observation periods (p > 0.05). In group B, 78% of the patients did not require any bronchodilators in the second 6 months of the 12-month observation period following treatment for GER, which was comparable to 67% in group A (p > 0.05). All patients in groups A and B had > 50% reduction in the bronchodilator use over the 6-month posttreatment period as compared to pretreatment period. None of the patients in group D and two of eight patients in group C showed > 50% reduction in bronchodilator use following treatment for GER.

All the patients were using the long-acting bronchodilator on a daily basis prior to institution of anti-GER treatment. During the second 6-month observation period, none of the patients in groups A or B, 4 of 8 patients in group C, and all 11 patients in group D were still using the long-acting bronchodilator for alleviation of asthma symptoms.

Table 4 outlines data in a similar fashion as in Table 3 but for the use of inhaled corticosteroids. There was a significant reduction in the use of inhaled corticosteroids in groups A and B following treatment for GER (p < 0.05). In the second 6-month observation period, 16 of 18 patients (89%) in group A and 8 of 9 patients (89%) in group B required no treatment with inhaled corticosteroids. The difference between groups A and B was not significant (p > 0.05). There was a reduction in the mean use of inhaled corticosteroids in group C following GER treatment, but this difference was not statistically significant (p > 0.05). However, two of eight patients in group C had a dramatic reduction in the use of inhaled corticosteroids from 180 days in the pretreatment phase to 24 and 59 days in the 6 months of the posttreatment phase. The same patients had a similar dramatic reduction in the use of bronchodilators as well.

All the 46 patients required leukotriene antagonists for alleviation of their asthma symptoms prior to

<table>
<thead>
<tr>
<th>Groups</th>
<th>Percentage of Time pH Was &lt; 4 in the Proximal Esophagus</th>
<th>Percentage of Time pH Was &lt; 4 in the Distal Esophagus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) Range</td>
<td>Mean (SD) Range</td>
</tr>
<tr>
<td>A</td>
<td>5.0 (1.7) 2.3–9.2</td>
<td>13.5 (3.5) 10.2–23.1</td>
</tr>
<tr>
<td>B</td>
<td>4.3 (1.1) 2.8–5.6</td>
<td>14.2 (3.9) 10.1–22.2</td>
</tr>
<tr>
<td>C</td>
<td>0.8 (0.9) 0.1–2.3</td>
<td>2.7 (1.3) 0.9–4.2</td>
</tr>
<tr>
<td>D</td>
<td>0.3 (0.2) 0.1–0.6</td>
<td>2.5 (0.9) 1.2–3.9</td>
</tr>
</tbody>
</table>

Table 3—Days of Short-Acting Bronchodilator Use Before and After Treatment of GER

<table>
<thead>
<tr>
<th>Pretreatment (6 mo)</th>
<th>Posttreatment (6–12 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups</td>
<td>Days of Use</td>
</tr>
<tr>
<td></td>
<td>Mean (SD) Range</td>
</tr>
<tr>
<td>A (n = 18)</td>
<td>66.4 (25.6) 34–118</td>
</tr>
<tr>
<td>B (n = 9)</td>
<td>72.8 (20.4) 49–102</td>
</tr>
<tr>
<td>C (n = 8)</td>
<td>64.4 (28.6) 34–106</td>
</tr>
<tr>
<td>D (n = 11)</td>
<td>68.3 (25.8) 34–112</td>
</tr>
</tbody>
</table>

*p < 0.05.
initiation of anti-GER treatment or diagnosis. None of the patients in groups A or B required the use of leukotriene antagonists during the second 6-month observation period following GER treatment. Four patients in group C and two patients in group D did not require leukotriene antagonists in the second 6-month posttreatment observation period.

Figure 1 summarizes the results of diagnosis and treatment. Of the 46 patients with persistent moderate asthma who underwent esophageal pH monitoring, 27 patients (59%) had abnormal study findings compatible with GER disease. These 27 patients underwent medical or surgical treatment for GER. Of these 27 patients, all showed a major reduction (>50%) in the amount of asthma medications used. Of the 19 patients with normal pH study findings, the 11 patients who did not receive any treatment for GER did not show any change in the requirement for asthma medications in any of the pretreatment or posttreatment 6-month observation periods over the course of 18 months (ie, 6 months pretreatment and 12 months posttreatment). However, two of eight patients (25%) with normal pH study findings showed a 70% reduction in the requirement of both bronchodilators and inhaled corticosteroids following empiric treatment for GER. Therefore, in patients with abnormal pH study findings, the probability of a significant reduction in the requirement for asthma medications following anti-GER treatment was 100%, and in those with normal pH study findings the similar probability was 25%.

**Discussion**

Our study shows that in children with persistent moderate asthma and GER, following anti-GER...

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**Table 4—Days of Inhaled Corticosteroid Use Before and After Treatment of GER**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Pretreatment (6 mo)</th>
<th>Posttreatment (6–12 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Days of Use Mean (SD)</td>
<td>Range</td>
</tr>
<tr>
<td>A (n=18)</td>
<td>180 (0)</td>
<td>180–180</td>
</tr>
<tr>
<td>B (n=9)</td>
<td>180 (0)</td>
<td>180–180</td>
</tr>
<tr>
<td>C (n=8)</td>
<td>180 (0)</td>
<td>180–180</td>
</tr>
<tr>
<td>D (n=11)</td>
<td>180 (0)</td>
<td>180–180</td>
</tr>
</tbody>
</table>

*p < 0.05.
treatment there is a significant improvement in asthma, as measured by reduction in the amount of medication required for alleviation of symptoms. While there are no comparable published studies in children, our results are comparable to those reported in a similar adult population.8–10

In two double-blind, randomized, cross-over, placebo trials of ranitidine in adults12,13 and one in children14 with GER disease and asthma, only slight or no improvement in asthma symptoms was noted. Several uncontrolled studies using nonobjective parameters have shown a dramatic improvement in asthma symptoms following anti-reflux surgery in adults15–17 and children.18,19 Unlike results of intervention with ranitidine and more like improvement noted after surgical treatment of GER, recent controlled studies with omeprazole have shown improvement in asthma symptoms, quality of life, and pulmonary functions in adults with GER and asthma.8–10 This trend clearly suggests that for improving the asthma symptoms in adults with GER and asthma one requires more than just treatment with ranitidine such as treatment with a proton-pump inhibitor or surgery. There are no studies in children with GER and asthma using a proton-pump inhibitor. This provided the rationale for doing our study.

There are several shortcomings of previously published similar intervention studies done in adults: (1) there are personal bias and differences in the assessment of severity and treatment strategy of asthma by different treating physicians, so the quality and quantity of medication used by different physicians may not be comparable; (2) the efficacy of anti-GER therapy has not been defined and the degree of acid suppression required for response, and that achieved by the treatment rendered, has not been defined; (3) the optimal duration of the intervention to produce discernable asthma response has not been determined; (4) appropriate control groups have not been included; (5) the potential order and carry-over effects have not been eliminated in blind cross-over trials; (6) the severity of asthma, an important variable, has not been controlled as an inclusion criteria, since patients with different severities may respond differently; and (7) multiple risk factors for asthma have not been controlled. In our study, we tried to control for the different confounding variables that could affect the results as well as including only those patients who had no obvious risk factors for asthma. As part of the entry criteria, we preselected patients with a similar severity of disease as well as the lack of risk factors such as atopy, family history, and smoking. All patients had a long follow-up history, so their present treatment for asthma was stable and had evolved over an extended period of time that was at least 2 years. All patients were treated by the same physician using a standard pre-established protocol, thus eliminating physician-to-physician differences in diagnosis and treatment. The diagnostic methodology and criteria for GER were uniform. The same physician treated all patients for GER in a uniform manner. Patients served as their own controls, eliminating the individual and patient-to-patient differences in severity and risk factors. A sufficiently long time was used for follow-up, thus minimizing the effects of month-to-month variations in the disease activity. Our follow-up of 12 months was much longer than the 1- to 3-month follow-up used in the adult studies.8–10 Further, we allowed an initial 6-month period just for the anti-GER treatment to take effect. Based on some studies, it seems that a discernable improvement in asthma outcomes should not be expected in a short time.9 Accordingly, we believed that data collected during the initial 6 months may not show the full impact of anti-GER treatment on asthma, as well as merely reflect the variation in disease status seen from month to month. For ethical reasons, we did not include a placebo group. We did not have a crossover design; therefore, there was no order or carry-over effect. We included a group of patients (group D) who had a comparable asthma severity but did not have GER and were not treated for GER. This group served as a good control to show that the variation in the asthma medication used was not significant in 6-month periods over the course of 18 months, and that the significant differences observed in groups A and B pre-GER treatment and post-GER treatment were far greater than in group D and were true differences. Despite the above-mentioned strengths, some shortcomings of our study also need to be mentioned. Though uniform anti-GER therapy was provided, the efficacy was presumed and not proven. The lack of response to anti-GER treatment could have been due to lack of adequate acid suppression. Further, though all patients were treated for asthma along a standard protocol and by the same physician, the physician was indeed aware of the anti-GER treatment. This could have influenced him to be more attentive to smaller changes in the severity of asthma during anti-GER treatment phase as compared to before anti-GER treatment was instituted. This bias could have led to a lesser or greater use of asthma medications following anti-GER treatment. However, this bias would have been uniform for all the patients and less likely to affect the overall trend. Nevertheless, the fact that a majority of patients did not require either inhaled corticosteroids or short-acting bronchodilators following 6 months of anti-GER treatment is in itself a significant finding. Furthermore, following 6 months of anti-GER medical or surgical treatment, none of the patients required the use of leukotriene antago-
nists or long-acting bronchodilators. None of these patients had ever been off any asthma medication for a continuous 3-month period prior to anti-GER treatment. It is needless to mention that inhaled corticosteroids and long-acting bronchodilators are regarded as the maintenance medications for patients with persistent moderate asthma. Alleviation of the need for the use of these maintenance medications is yet another indicator of significant improvement in the status of the patients’ asthma.

Based on our data, we found that an abnormal pH study finding was a good predictor of response to anti-GER treatment in our patients. Our data also show that in patients with persistent asthma and GER, one may have to use anti-GER treatment for a period of 6 months to see an appreciable response in asthma outcomes.

While our study helps answer some questions, it generates many more questions: (1) How long should aggressive anti-GER treatment be continued specially with a proton-pump inhibitor? (2) What is an appropriate step-down strategy once remission has been attained? Can high-dose histamine type 2 receptor antagonists help maintain remission? Does one really need a prokinetic? (3) How long will the airway reactivity last? Will airway reactivity diminish over time with effective and prolonged anti-GER treatment? (4) How much improvement in pulmonary function can one expect? (5) Would anti-GER treatment change the long-term outcome of asthma? What is the role of anti-GER surgery? When should surgery be recommended? Should one first document a good response to aggressive medical treatment before opting for surgery? Will the long-term outcome of surgery outweigh that of prolonged medical treatment especially since we do not know if patients will reverse the airway reactivity with prolonged medical treatment? (6) What would predict a good response to anti-GER treatment? (7) Finally, the major question is how can one diagnose GER-induced asthma?

In conclusion, we believe that even though our study raises more questions than it answers, our data are the first of their kind in the pediatric population and will thus provide the basis for future studies to help answer some of the questions. Based on current knowledge, some modality of long-term and high degree of acid suppression or acid exclusion seems to be the most effective treatment strategy. Preselecting children with an abnormal extended pH monitoring finding and a favorable response to a therapeutic trial of aggressive anti-GER therapy seems to be the best way to implicate GER in inducing or exacerbating asthma.

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