Long-term Antireflux Medication Use Following Pediatric Nissen Fundoplication

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Hypothesis: Nissen fundoplication decreases the use of antireflux medications.

Design: Retrospective cohort study using discharge abstract data and pharmacy data.

Setting: Twelve regional Kaiser Permanente hospitals in southern California.

Patients: Three hundred forty-two patients underwent Nissen fundoplication.

Intervention: Nissen fundoplication.

Main Outcome Measure: Use of antireflux medications.

Results: The number of patients requiring antireflux medications decreased from 233 patients (68.1%) before Nissen fundoplication to 197 (57.6%) after Nissen fundoplication. Of the 233 patients, 176 (75.6%) were restarted on antireflux medications within 1 year after Nissen fundoplication. Use of antireflux medication decreased in neurologically healthy patients but was unchanged in neurologically impaired children.

Conclusions: Use of antireflux medication decreased after Nissen fundoplication. Neurologically healthy children showed the biggest decrease in antireflux medication use after Nissen fundoplication.

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Gastroesophageal reflux, or physiological reflux, is common in infants and children. Although the natural history of gastroesophageal reflux is not well understood, most children will outgrow their symptoms by 12 to 18 months of age.1 Gastroesophageal reflux disease (GERD), on the other hand, is pathological and requires treatment to prevent associated complications of reflux esophagitis, Barrett esophagus, and esophageal stricture. Medical management remains the mainstay of treatment for GERD and is successful in most patients. Gastroesophageal reflux disease may also be associated with pulmonary complications, apnea, and failure to thrive, and this is when antireflux operations are generally considered. With the introduction of minimally invasive techniques, laparoscopic Nissen fundoplication (NF) has been performed with increased frequency during the last decade and is now one of the most common operations performed by pediatric surgeons, with more than 30,000 antireflux operations performed annually.2 Successful NF may also obviate the inconvenience and expense of lifelong medical management. The long-term effect of NF remains controversial. Excellent symptomatic results following NF have been shown in large retrospective studies.3,4 However, objective long-term data following NF in children are not available. Furthermore, studies in adults have shown a high rate of relapse in patients with severe GERD following NF, with a significant number of patients requiring antireflux medications.5 The purpose of this study is to determine whether NF decreases the use of antireflux medications in children.

Methods

The Southern California Kaiser Permanente Discharge Abstract Database was used to identify pediatric patients (aged <19 years) hospitalized in 12 acute care hospitals for NF for GERD between January 1, 1996, and December 31, 2005. Surgical therapy was determined according to the Current Procedural Terminology, 4th Edition procedure code for NF. This study was approved by the institutional review board of Kaiser Permanente Southern California, protocol numbers 3934 and 3040.

Data of patients were then analyzed using the Southern California Kaiser Permanente Pharmacy Database for use of antireflux medications. Specifically, use of H2-blockers and proton pump inhibitors was analyzed. The pre-NF period was defined as birth to the first NF, and...
the post-NF period was defined as the time from the first NF to death or to the end of the study, whichever came first. The number of patients using antireflux medications was recorded before and after NF. The data from the Southern California Kaiser Permanente Discharge Abstract Database were exported to SAS version 9.13 statistical software (SAS Institute Inc, Cary, North Carolina) for subsequent analyses. Use of antireflux medication before and after NF was analyzed using the McNemar test. Odds ratios were calculated using logistic regression. In addition to NF, underlying neurological disorder was also included in the regression model. Estimates were considered statistically significant if the 95% confidence interval did not overlap 1.00 and if \( P < .05 \).

### RESULTS

A total of 342 patients were identified as having an NF during the study period. The mean (SD) age at the time of NF was 3.9 (4.8) years (median age, 1 year; age range, 0-17 years). The male to female ratio was 1.19 to 1. The mean follow-up was 4.5 years. A total of 154 patients (45.0%) had an associated neurological disorder. Twenty-six patients (7.6%) had more than 1 NF performed.

Medication data were available in 336 patients. A total of 233 patients were administered antireflux medication prior to NF and 197 patients were administered antireflux medication after NF (Table 1) (odds ratio = 0.63; 95% confidence interval, 0.47-0.84; \( P = .002 \)). Of the 233 patients receiving antireflux medication prior to NF, 150 were restarted on antireflux medication after NF. An additional 47 patients with no history of antireflux medication use were started on antireflux medication after NF. Of the 233 patients, 176 (75.6%) were restarted on antireflux medications within 1 year after NF. Use of antireflux medication decreased in neurologically healthy patients, but there was no significant change in neurologically impaired children (Table 2).

### COMMENT

The goals of an antireflux operation are to relieve reflux symptoms, decrease GERD-related complications and hospitalizations, and halt the use of antireflux medications. Previous studies have shown that antireflux procedures are successful in relieving reflux symptoms in children. In a multi-institutional review of 7467 patients, Fonkalsrud et al reported good to excellent resolution of symptoms in 95% of neurologically healthy children and 85% resolution in neurologically impaired children after NF. However, these subjective outcomes were not clearly defined and there were no objective outcome measures in this study. Furthermore, follow-up was based on a questionnaire filled out by each of the participating institutions rather than on objective evaluation of the patient. For these reasons, the methods and results of this study have been questioned.

In the experience of 1050 pediatric NFs by a single surgeon at a single institution, the recurrence rate after laparoscopic NF was reported to be 3.1%. This remarkable study showed that laparoscopic NF can be safely performed in children as young as 5 days and as small as 1.2 kg. This study, however, did not provide details of the follow-up; it appears that the only objective follow-up was reoperation. Thus, this study showed that laparoscopic NF can be done in children but did not answer the questions of whether NF should be done and in whom NF should be done.

Few studies have documented objective end points following NF in children. Conversely, in adult patients, long-term follow-up comparing medical and surgical management of GERD showed no difference in grade of esophagitis, frequency of treatment of esophageal stricture, 36-Item Short Form Health Survey scores, and overall satisfaction with antireflux therapy. Such end points following NF are difficult to reproduce in children. Not all children being treated for GERD routinely undergo endoscopy to document esophagitis or stricture. Furthermore, existing quality-of-life surveys used in adults are not applicable to children. Currently, quality-of-life tools are being developed and validated specifically for caregivers of children with GERD and may be more accurate than symptoms and perceived satisfaction following NF. Finally, the preoperative evaluation for children undergoing NF is inconsistent, making it difficult to accurately assess the effect following NF. One reason for such an inconsistent preoperative workup is that the diagnosis of GERD and current indications for NF are mostly based on clinical factors. Nissen fundoplication is often performed in pediatric patients with associated pulmonary symptoms such as pneumonia, respiratory distress, and apnea. It has also been advocated for children with failure to thrive despite medical management. Many believe that NF is warranted in children with such significant GERD-related complications and that an extensive preoperative evaluation would only delay and not change management.

### Table 1. Antireflux Medication Use Before and After Nissen Fundoplication

<table>
<thead>
<tr>
<th>Patients, No.</th>
<th>Antireflux Medication Use</th>
<th>Pre-NF</th>
<th>Post-NF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients (n=336)</td>
<td>233</td>
<td>197</td>
<td></td>
</tr>
<tr>
<td>Antireflux medication use prior to NF</td>
<td>233</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>No antireflux medication use prior to NF</td>
<td>0</td>
<td>47</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviation: NF, Nissen fundoplication.**

### Table 2. Antireflux Medication Use in Neurologically Healthy and Neurologically Impaired Children Before and After Nissen Fundoplication

<table>
<thead>
<tr>
<th>Patients, No.</th>
<th>Neurological Status and Antireflux Medication Use</th>
<th>Pre-NF</th>
<th>Post-NF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologically healthy (n=186)</td>
<td>140</td>
<td>101</td>
<td></td>
</tr>
<tr>
<td>Antireflux medication use prior to NF</td>
<td>140</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Neurologically impaired (n=150)</td>
<td>93</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Antireflux medication use prior to NF</td>
<td>93</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>No antireflux medication use prior to NF</td>
<td>0</td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviation: NF, Nissen fundoplication.**
We previously looked at the number of hospitalizations for GERD-related complications to determine long-term effectiveness following NF. There was no change in the frequency of hospitalizations, the number of hospitalizations, or the number of patients hospitalized for pulmonary symptoms and failure to thrive before and after NF. One surprising finding was that there were a significant number of patients requiring hospitalization for GERD-related complications who had no history of hospitalization prior to NF. However, in those patients with a well-documented GERD-related complication prior to NF, it appears that NF may decrease future hospitalizations for that specific complication. This finding emphasizes the need for a standard preoperative evaluation for GERD. This may help to identify which children are at risk for developing recurrent symptoms or postoperative hospitalizations for GERD-related complications and would benefit most from NF. Goldin et al recently demonstrated mixed results in a population-based study looking at the frequency of hospitalizations for GERD-related complications. The frequency of hospitalizations decreased in children younger than 4 years, did not change in older children, and increased in older children with developmental delay.

To our knowledge, no studies have compared medical management with surgical management of GERD in children. Furthermore, long-term outcomes studies following medical management of GERD in children are not available. Proton pump inhibitors are highly efficacious in treating GERD in children. However, long-term safety data for children do not exist. To date, the longest-term safety and efficacy data in children for continuous use of proton pump inhibitors are for 2 years. One potential benefit of NF may be to eliminate the use of antireflux medications. Our study showed that long-term use of antireflux medication following NF decreased by 37.0%. Most children (176 of 233 children [75.6%]) required readministration of antireflux medications within 1 year of NF. Thus, NF should not be performed with the expectation that patients will no longer need antireflux medications. An unexpected finding of our study is that only 233 patients (68.1%) were receiving antireflux medications. Since implementing a more thorough preoperative workup for GERD, we have noticed a significant decrease in the number of NFs performed at our institution. Finally, to prevent overprescribing acid suppression medication after NF, the diagnosis of GERD should be confirmed when restarting medical management.

Our study has several limitations. Our data come from a discharge abstract database, and the *International Classification of Diseases, Ninth Revision or Current Procedural Terminology*, 4th Edition coding of each diagnosis and procedure was not independently validated. Thus, we were not able to determine the exact indications for NF. Some patients with underlying neurological or cardiac anomalies had NF performed based on their perceived risk of developing GERD. Also, technical details of the NF such as the length of wrap, crural approximation, or open vs laparoscopic were not available. Another limitation of this study is that indications for administration of antireflux medications were not reviewed and are not known. Previous studies have shown that antireflux medications may be overprescribed in children. Antireflux medications were prescribed without adequate workup and documented GERD. In adult studies, up to 80% of patients were still receiving antireflux medication following NF. However, other adult studies have shown that only one-fourth of patients receiving acid suppression medication after NF had abnormal pH study results. In our study, we do not know who (pediatricians, pediatric surgeons, pediatric gastroenterologists, etc) restarted the patients on antireflux medications, nor do we know whether such medications were actually discontinued following NF. It has been our practice, however, to wean patients off of all antireflux medications starting 3 to 4 weeks after NF. Lastly, we do not know how compliant patients were in using the antireflux medications. Our pharmacy database represents dispensed medications, so we cannot be sure that the patients were using what was prescribed.

Overall, the findings of this study demonstrated a slight decrease in antireflux medication use after NF. In children with neurological impairment, there was no decrease in antireflux medication use after NF. We strongly advocate standardizing the preoperative evaluation prior to any antireflux procedure as this may better select which children are at highest risk for recurrent GERD requiring antireflux medications. Since implementing a more thorough preoperative workup for GERD, we have noticed a significant decrease in the number of NFs performed at our institution. Finally, to prevent overprescribing acid suppression medication after NF, the diagnosis of GERD should be confirmed when restarting medical management.

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**Author Contributions:** Study concept and design: Lee and Applebaum. Acquisition of data: Lee. Analysis and interpretation of data: Lee, Sydorak, Chiu, Hsu, Applebaum, and Haigh. Drafting of the manuscript: Lee. Critical revision of the manuscript for important intellectual content: Lee, Sydorak, Chiu, Hsu, Applebaum, and Haigh. Statistical analysis: Sydorak, Chiu, Hsu, and Haigh. Administrative, technical, and material support: Applebaum. Study supervision: Lee and Sydorak.

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DISCUSSION

Diana L. Farmer, MD, San Francisco, California: This is a retrospective cohort study using the Southern California Kaiser database to determine the effect of antireflux medications. The authors identified 342 patients under the age of 18 years who had Nissen fundoplication in the pediatric population. The authors found that the overall incidence of antireflux medications significantly decreased after antireflux surgery. For example, the odds of prescribed antireflux medications decreased by 0.63 (P value of .002). However, approximately 75% of the patients were restarted on antireflux medications within the first year after the operation. When the cohort was stratified by neurological disorders, the authors found that the benefit of antireflux medications was unchanged for patients with neurological disorders, while there was a decrease in use for patients without neurological disorders.

The results of this study in conjunction with the recently published article in the Journal of Pediatric Surgery (where the same authors demonstrated that the incidence of subsequent hospitalization for pulmonary complications after Nissen fundoplication did not change) make me question what the benefits are of antireflux operation in children with neurological disorders. Was the change in antireflux medications before or after the operation statistically significant or not in the strata of neurologically impaired and neurologically normal patients? In addition, I ask the authors if the use of antireflux medications after fundoplication is a time-dependent event? If so, the follow-up time for each patient becomes very important in the study, and a survival analysis may be the most appropriate statistical analysis. I suspect that the patients who were found not on antireflux medications after fundoplication may not have been followed up long enough.

Dr Applebaum: It was a great surprise for us to find such a high level of antireflux medication usage so soon after what we thought was technically successful procedures, but in fact, in our neurologically normal children, a 60% incidence of return to medication is relatively close to the 50% incidence reported in neurologically impaired patients.

As far as the statistical significance of our data, there was statistical significance for neurologically normal children. There was no significance for neurologically impaired children.

With regard to the use of antireflux medications being a time-dependent event, it probably is, but the large majority of patients going back on medications do so within a few months to a year of fundoplication, so a survival analysis likely would not change the results of the study. I would like to briefly touch upon why kids might appear to have more problems than adults. Growth is likely an important predisposing factor in children that may lead to complete or partial disruption of wraps and a return to symptoms. In many neurologically devastated children, growth is marked asymmetrical and is often accompanied by an increasing degree of scoliosis and respiratory compromise. Enlargement and shifting of tissues can result in a great deal of strain on sutures. In our practice, it is not uncommon for even neurologically normal children to return every 7 or 8 years, usually following growth spurts with a relatively sudden return of symptoms.

The other major factor for a return of antireflux medications in children as well as in adults is a lack of diagnostic sophistication on the part of primary care physicians. Any abdominal or pulmonary symptom, be it related to proven acid reflux or not, can become an indication. Children with neurological disabilities may have additional nasopharyngeal reflux, and all may have dysmotility of 1 or more parts of the GI [gastrointestinal] tract. While a fundoplication usually improves the overall sense of well-being, it will obviously fail to resolve symptoms related to these problems. The critical question, as was brought up earlier, is will we continue to recommend fundoplications in children either with or without neurological symptoms? We have witnessed a dramatic decrease in referrals for this procedure in the past several years as medical therapy becomes more potent. Those who are eventually referred have the most incapacitating problems, and it is in these children that any significant decrease in symptomatology, even if less than complete or permanent, is greatly appreciated by patients and caregivers. A further refined and standardization of the use of antireflux surgery, not change the results of the study.

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