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Pediatrics 2004;113;54

Influence of *Helicobacter pylori* Eradication on Gastroesophageal Reflux Symptoms and Epigastric Pain in Children and Adolescents

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ABSTRACT. *Objective.* **Conflicting reports have noted a possible association linking eradication of *Helicobacter pylori* with aggravation of gastroesophageal reflux (GER) disease. We prospectively evaluated the effect of eradication of *H pylori* on GER symptoms and epigastric pain and the association among these 3 parameters in a pediatric cohort.**

Methods. **Patients who were referred for gastroscopy were evaluated for frequency, severity, and nocturnal presence of symptoms related to GER as well as epigastric pain. Patients who were positive for *H pylori* received triple antibiotic therapy. The patients were followed for at least 6 months after therapy. Patients with successful eradication had symptoms compared with their pre-eradication state and were compared with a cohort of patients without *H pylori* or those with persistent *H pylori*.**

Results. **Of 119 children and adolescents who were recruited, 95 patients completed the study, with a mean follow-up of 11.2 months. The distribution of outcomes for each GER symptom (better, worse, unchanged) was similar before and after eradication and did not depend on prior *H pylori* status. Among patients with GER and epigastric pain, improvement in epigastric pain was significantly correlated with the improvement in GER symptoms but not with eradication of *H pylori*.**

Conclusions. **Eradication of *H pylori* is not associated with increased symptoms of GER in children and adolescents. Improvement in epigastric pain in children is significantly correlated with the improvement in GER symptoms but not with eradication of *H pylori*. *Pediatrics* 2004;113:54–58; *gastroesophageal reflux,* Helicobacter pylori*, child, esophagitis, abdominal pain, dyspepsia.***

ABBREVIATIONS. GER, gastroesophageal reflux.

Helicobacter pylori infection has been implicated in the development of gastritis and duodenal and gastric ulcers. In patients with clinical symptoms and endoscopic findings supporting *H pylori*–related disease, the indication for eradication of the organism by a combination of antibiotics along with a proton pump inhibitor is clear cut.[1] However, a large cohort of patients will be found to have *H pylori* infection, although it is not the cause of their symptoms. These patients are also at increased risk for developing long-term *H pylori*–related morbidity such as peptic disease or neoplasia.[2,3] The theoretical benefits involved in decreasing the lifetime risk have to be weighed against drawbacks of trying to eradicate the organism. Aside from increasing resistance to antibiotic therapy, the major concern related to eradication has been the possible emergence of gastroesophageal reflux (GER) and its sequelae.

The hypothesis that eradication of *H pylori* may be deleterious is based on theoretical grounds as well as epidemiologic and clinical studies. *H pylori* has been found to be inversely correlated with the prevalence of reflux esophagitis, and certain studies have shown aggravation of esophagitis with eradication.[4–9] Suggested mechanisms include presence of atrophic or significant body gastritis leading to a posteradication increase in acid secretion; decreased buffering as a result of elimination of *H pylori*, which produces ammonia via bacterial urease; masking of reflux by acid neutralizing medications given for *H pylori*–related disease; and increased appetite with weight gain–mediated reflux. These observations are controversial, because several studies have not found a correlation between eradication of *H pylori* and reflux disease.[10–14] The interaction between *H pylori* and reflux symptoms has not been studied prospectively in children and adolescents.

Abdominal pain in children is often poorly localized or periumbilical and has not been found to be related to *H pylori.* Studies evaluating the relationship between *H pylori* or GER and abdominal pain[14,15] in children have not focused specifically on epigastric pain, a true peptic symptom. The relationship between epigastric pain and GER has not been evaluated prospectively in children. To answer these questions, we evaluated the effect of *H pylori* eradication on GER symptoms and epigastric pain in this age group.

METHODS

This was a prospective study conducted from 1999 to 2002 in symptomatic children and adolescents who were aged 8 to 19 and referred for gastroscopy because of upper abdominal pain, reflux symptoms, vomiting, hematemesis, and abdominal pain with weight loss. It was performed at 2 hospitals in central Israel. These hospitals serve a mostly lower socioeconomic region of central Israel, with a high prevalence of *H pylori* infection. Patients were interviewed by participating physicians and filled out a questionnaire that was compiled from a simplified modification of the questionnaire evaluated by Locke et al[16] in adults that addresses

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Received for publication Feb 18, 2003; accepted May 15, 2003.

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both presence and severity of GER disease. We chose this method in the absence of a validated pediatric severity scale for older children. Physicians evaluated the presence of 2 key symptoms, heartburn and regurgitation, reported to be the most specific symptoms and used for assessment in multiple studies,[11] as well as 3 different measures of disease activity: severity of heartburn, frequency, and nocturnal presence of the symptom. Nocturnal presence was defined as a symptom that awakened a patient from sleep. We also evaluated epigastric pain (as opposed to abdominal pain), usually considered a dyspeptic symptom, using the same method, to assess the association among epigastric pain, *H pylori*, and GER.

After consent was obtained, patients and parents received clarification by a participating physician about grading and symptoms, including examples. The same physician reviewed the form with the patients. There were 4 possible answers for frequency of symptoms: less than once a week, once a week, several times a week, or daily. Severity was analyzed by an analog scale from 1 to 10, where 1 is the mildest and 10 is the severest. The severity scale was explained in simple terms with examples. Symptoms off therapy were reevaluated at each visit.

Patients who were positive for *H pylori* infection by histology from an antral biopsy and a rapid urease test (CUTest; Temmler Pharma, Marburg, Germany) were treated with a combination of omeprazole and 2 antibiotics (clarithromycin and amoxicillin, or metronidazole if penicillin allergy was reported) for 7 days. Patients with gastritis, duodenitis, or an ulcer received omeprazole for an additional month, whereas patients with esophagitis received omeprazole for 2 months. Patients with evidence of *H pylori* were invited back for a ^{13}C urea breath test to evaluate eradication at least 6 weeks after completion of therapy. The same symptom assessment was performed at 6 months and at continued follow-up visits until termination of the study. Patients who were still positive for *H pylori* after the initial treatment were offered a second course of the alternative treatment regimen. Patients who refused or did not take the therapy were not excluded and served as a noneradicated control group.

Patients were considered to have possible GER when they had erosive esophagitis (LA grading system), the presence of heartburn, or regurgitation and vomiting at least once a week for >1 month at entry. GER was considered to be worse at follow-up when the frequency of a symptom was both greater than once a week and had increased or when the severity had increased by at least 3 points or new nocturnal symptoms were present. A decrease in the same criteria (disappearance of symptom, decreased frequency, decreased severity, or disappearance of nocturnal symptoms) were used to define improvement.

Patients were excluded at entry when they could not understand or fill out the form; had an eating disorder, gastrostomy tube, or gastric outlet obstruction; had a history of gastric surgery or fundoplication; or *H pylori* status was not ascertained at gastroscopy from 2 antral biopsies and a rapid urease test. Biopsies were also taken from abnormal-appearing tissue. Patients were excluded when they did not perform a follow-up breath test, did not have at least 6 months of follow-up, or had received antibiotics or antireflux medication for 7 days before the breath test or gastroscopy.

For judging the effect of eradication on reflux symptoms and epigastric pain, patients with eradicated *H pylori* had symptoms compared with baseline and were also compared with a group without *H pylori* and with patients with *H pylori* that was not eradicated. Patients who were negative for *H pylori* were classified as group 1, those with *H pylori* and successful eradication by breath test were defined as group 2, and patients with unaltered status (continued *H pylori* infection) were defined as group 3. This study was authorized by an institutional review board.

Statistics

Descriptive statistics for continuous data were determined and are reported as mean ± standard deviation. All data were visually scanned for normalcy of distribution. Means of normally distributed data were compared using the *t* test for independent samples entering patient group (eradicated for *H pylori* vs others) as the categorical variable. Frequency counts were conducted for nominal data and are reported as absolute value (%). These values were cross-tabbed and compared by patient group using the χ^2 test. In addition, in the group eradicated for *H pylori* only, frequency and severity of symptoms (epigastric pain, heartburn, vomiting) were compared before and after eradication using the Wilcoxon signed rank test. Nocturnal symptoms, a dichotomous variable, were compared before and after *H pylori* eradication using the McNemar test. The correlation between epigastric pain and heartburn at follow-up was performed with Spearman rho. The difference in outcome of epigastric pain by absence or presence of heartburn was calculated by Fisher exact test. Univariate general linear modeling was used to evaluate whether eradication of *H pylori* or improvement in heartburn or reflux symptoms best predict improvement in epigastric pain. All tests were considered significant at $P < .05$.

RESULTS

Patient Data

During the study, 119 patients were enrolled. Twenty-two patients (16 *H pylori* positive, 6 *H pylori* negative, 2 patients with nodular gastritis) were lost to follow-up, and 2 patients were excluded because of breath test exclusion criteria. The remaining 95 patients served as the study population. There were 58 girls and 37 boys (mean age: 14.2 ± 3.3 years). The mean follow-up for all patients was 11.2 months. Fifty-five patients were positive for *H pylori* at gastroscopy. Pathologic endoscopic findings at gastroscopy among patients who were included in the study were erosive esophagitis in 7 (5 *H pylori* positive), antral or body gastritis in 13 (11 *H pylori* positive), duodenitis in 4 (all *H pylori* positive), and duodenal ulcer in 3 (all *H pylori* positive). These patients had evidence of microscopic inflammation as well. Mild atrophic gastritis was found only in 1 patient with collagenous gastritis. Eradication was offered in all 55 patients. Four patients declined or did not take the therapy. Of the remaining 51 patients, 42 underwent successful *H pylori* eradication, an initial rate of 82.4%. Nine patients were retreated, and 2 of these patients' *H pylori* was eradicated by retreatment (overall eradication rate 86.3%). Altogether, we divided our patients into 3 groups. Patients without *H pylori* were designated group 1 ($N = 40$), patients with successful eradication were defined as group 2 ($N = 44$), and patients with persistent *H pylori* were designated group 3 ($N = 11$). Entry data for these groups (Table 1) indicate that they were similar in age, severity of epigastric pain, and GER symptoms at baseline.

Reflux Symptoms

One or more symptoms of GER were present in 35 of the 95 patients at baseline. Heartburn was present in 31 of the 95 patients, and 17 of these patients had daily heartburn. Regurgitation or frank vomiting occurred in 17 patients; only 6 patients had a daily occurrence of this symptom. Nocturnal symptoms of heartburn, nausea, choking, regurgitation, or vomiting were initially present in 27 patients. The presence of reflux symptoms was not correlated with *H pylori* status at entry.

Effect of Eradication on Reflux Symptoms

The effect on overall reflux, as manifested by worsening of any symptom (the endpoint), was not different between any of the groups. There was no significant deterioration or improvement for any

TABLE 1. Enrollment Data Baseline*

Parameter	Group 1 (N = 40; *H pylori* Negative)	Group 2 (N = 44; *H pylori* Positive, Eradicated)	Group 3 (N = 11; *H pylori* Positive, No Eradication)
Age (mean ± SD)	13.4 ± 3.0	14.9 ± 3.2	14.3 ± 2.8
Sex (M/F)	12/28	19/25	6/5
Reflux symptoms	16 (40%)	15 (34%)	4 (36.4%)
Heartburn	12 (30%)	14 (31.8%)	5 (45.4%)
Vomiting/regurgitations	7 (17.5%)	10 (22.7%)	1 (9.1%)
Nocturnal symptoms	10 (25%)	16 (36.4%)	2 (18.2%)
Epigastric pain	35 (87.5%)	40 (90.1%)	9 (82%)

SD indicates standard deviation.
None of these comparisons is statistically significant

specific reflux symptom or for overall reflux state between baseline or after treatment in patients whose *H pylori* was eradicated. This was true for both frequency and severity analysis. Data regarding effect of *H pylori* eradication on GER symptoms (any change) and comparison between groups are presented in Fig 1.

The overall outcome of GER symptoms during follow-up and after *H pylori* eradication was not uniform. Reflux worsened in 12% of group 1, 18% of group 2, and 36% of group 3 patients during follow-up, whereas it improved in 30%, 34%, and 36%, respectively. In fact, more patients showed improvement rather than deterioration in these symptoms during follow-up. This was true when comparing groups and in comparison with baseline within groups. The difference in overall outcome and in the percentage of patients with more reflux was independent of the presence of previous reflux symptoms at baseline. Of the 5 patients with *H pylori*–positive erosive esophagitis at entry, 3 improved, 1 became worse, and 1 had no change in symptoms. Results for specific symptoms and measures of severity over time are presented in Fig 2.

Effect of *H pylori* Eradication on Epigastric Pain

Improvement of pain was not correlated with *H pylori* eradication. The 3 groups did not differ with regard to frequency or severity of epigastric pain at onset or at follow-up. All 3 groups demonstrated a significant improvement in both frequency and severity of epigastric pain at the final follow-up in comparison with baseline. The mean decrease in severity score was 2.25 ± 0.58 points in group 1, 2.4 ± 0 .62 points in group 2, and 2.45 ± 0.52 points in group 3; this did not differ between groups.

Reflux Symptoms and Epigastric pain

Epigastric pain was present in 29 of 35 patients with frequent heartburn (at least twice a week for >1 month) at baseline. Univariate general linear modeling demonstrated that improvement in epigastric pain during follow-up was significantly correlated with improvement in reflux symptoms ($P < .01$) but not with *H pylori* eradication. Presence of epigastric pain at follow-up was found to be significantly correlated with the presence of heartburn (correlation coefficient: 0.837).

DISCUSSION

In our study, the change in GER symptoms after *H pylori* eradication was not worse than the initial baseline symptoms or the rate found in an age- and reflux-matched control group that did not have a change in *H pylori* status. Indeed, worsening of symptoms may not be the proper outcome to measure, as patients can also improve. In fact, a larger group (34%) of patients whose *H pylori* was eradicated showed improvement in reflux symptoms, although this was not statistically significant. The final outcome, as measured by the distribution of any outcome (reflux symptoms worse, same, or better) in

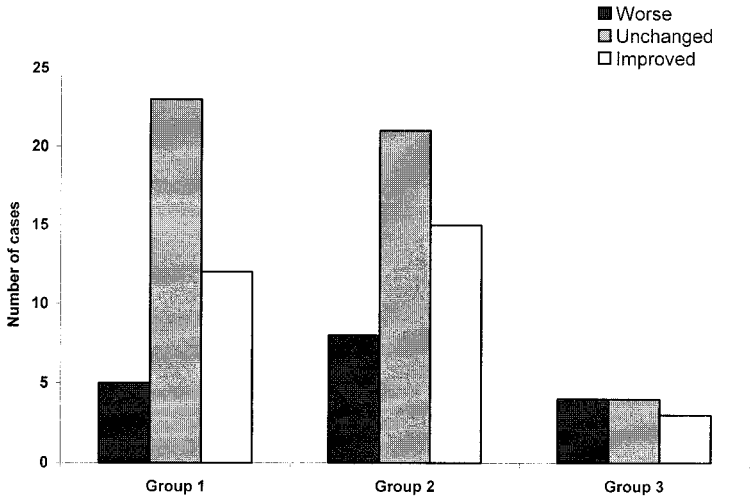

Fig 1. Overall change in reflux symptoms by *H pylori* status at follow-up (mean follow-up: 11.2 months). Group 1, *H pylori* negative; group 2, *H pylori* positive after eradication; group 3, *H pylori* positive, eradication failure.

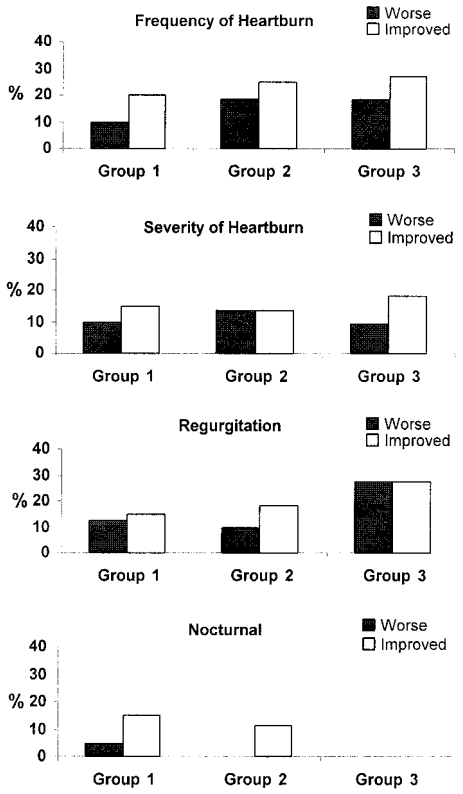

Fig 2. Change in specific reflux symptoms over time by group. Group 1, *H pylori* negative; group 2, *H pylori* positive after eradication; group 3, *H pylori* positive, eradication failure.

both groups, was not significant between groups or within groups. This was also true for the individual symptoms, when evaluated for both frequency and severity, and in patients with esophagitis at entry. Although the cohort was not large, these data indicate that *H pylori* eradication does not seem to aggravate GER. The similar distribution of symptom outcomes in groups 1 and 2 argues against a protective or a harmful role of *H pylori* in reflux symptoms in this age group, at least in the short term. Because we did not evaluate the presence of esophagitis after therapy, we cannot directly compare our results with the previously mentioned adult studies.[4,8]

Most studies aimed at evaluating the effect of *H pylori* eradication on reflux in adults have used selected populations such as with duodenal ulcer or patients with GER before eradication.[4,10–12] The spectrum of risk factors found in adults, such as atrophic gastritis, duodenal ulcer, or significant esophagitis, may influence the outcome of the study. These factors are less common in children and do not reflect the patient population that has to be addressed in making the decision to eradicate *H pylori* when found.

Dent[17] proposed that the outcome of *H pylori* eradication on gastroesophageal reflux is most likely determined by the population studied. Acid secretion in predominant antral gastritis with preserved body mucosa is hyperresponsive, thus enabling increased duodenal or esophageal injury. In these patients, eradication should improve or not affect reflux. This hypothesis is consistent with the results of other studies[1–12,18] that showed improvement in reflux symptoms in patients with duodenal ulcer. However, in patients with atrophic gastritis or severe body gastritis, *H pylori* eradication may result in increased acid secretion. Children and adolescents are more likely to behave like the first group, with predominant antral gastritis. In our study, we did not attempt to evaluate any connection between *H pylori* and the pathophysiology of reflux.

Any study evaluating reflux as an outcome is hampered by the absence of a single uniform valid scale for outcome.[10,16,19] Many of the symptoms that are present in questionnaires for adults would be overrepresented in the pediatric age group, making comparisons difficult. Heartburn and acid regurgitation are considered the most specific symptoms of GER in adults.[20,21] These data are not available in older children. We attempted to evaluate clinically relevant key symptoms that are prevalent in childhood,[14,22] which included the most specific aforementioned symptoms.

In our study, nearly two thirds of patients who had GER and were referred for gastroscopy had epigastric pain. Among patients with heartburn and epigastric pain, *H pylori* eradication was not associated with improvement in pain. Improvement in reflux symptoms, however, was significantly correlated and a strong predictor of improvement in epigastric pain. These findings suggest that epigastric pain is associated with and parallels GER in children. Children who present with epigastric pain may not initially have reflux symptoms, and the diagnosis of GER will not be entertained. Physicians may tend to focus on the presence of *H pylori* instead of the presence of a reflux symptom as being the clue to the cause of epigastric pain.

CONCLUSION

We have found that eradication of *H pylori* is not associated with increased symptoms of GER in children and adolescents. However, improvement in epigastric pain in children is significantly correlated with improvement in GER symptoms but not with eradication of *H pylori*.

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New Scientist. August 16, 2003

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