

CLINICAL—ALIMENTARY TRACT

Inverse Association of Esophageal Eosinophilia With *Helicobacter pylori* Based on Analysis of a US Pathology Database

EVAN S. DELLON,^{*,‡} ANNE F. PEERY,^{*,‡} NICHOLAS J. SHAHEEN,^{*,‡} DOUGLAS R. MORGAN,^{*,‡} JENNIFER M. HURRELL,^{§,||} RICHARD H. LASH,^{||} and ROBERT M. GENTA^{§,||}

^{*}Center for Esophageal Diseases and Swallowing and [‡]Center for Gastrointestinal Biology and Disease, Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina; [§]Dallas Veterans Affairs Medical Center, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas; and ^{||}Caris Research Institute, Caris Life Sciences, Irving, Texas

BACKGROUND & AIMS: Eosinophilic esophagitis (EoE) is of increasing prevalence and believed to result from allergic processes. *Helicobacter pylori* has been inversely associated with allergic diseases, but there is no known relationship between *H pylori*, EoE, and esophageal eosinophilia. We investigated the association between esophageal eosinophilia and *H pylori* infection. **METHODS:** We performed a cross-sectional study of data, collected from a US pathology database, on 165,017 patients in the United States who underwent esophageal and gastric biopsies from 2008 through 2010. Patients with and without *H pylori* on gastric biopsy were compared, and odds of esophageal eosinophilia were determined. **RESULTS:** From the data analyzed, 56,301 (34.1%) had normal esophageal biopsy specimens, 5767 (3.5%) had esophageal eosinophilia, and 11,170 (6.8%) had *H pylori* infection. Esophageal eosinophilia was inversely associated with *H pylori* (odds ratio [OR], 0.77; 95% confidence interval [CI], 0.69–0.87). Compared with patients with normal esophageal biopsy specimens, odds of *H pylori* were reduced among patients with ≥ 15 eosinophils per high-power field (eos/hpf) (OR, 0.79; 95% CI, 0.70–0.88), ≥ 45 eos/hpf (OR, 0.75; 95% CI, 0.61–0.93), ≥ 75 eos/hpf (OR, 0.72; 95% CI, 0.50–1.03), and ≥ 90 eos/hpf (OR, 0.52; 95% CI, 0.31–0.87) (*P* for trend $< .001$). A similar dose-response trend was observed for increasing clinical suspicion for EoE and decreasing prevalence of *H pylori*. Additionally, severity of histologic effects of *H pylori* was inversely associated with esophageal eosinophilia. All trends held in multivariate analysis. **CONCLUSIONS:** In a large cross-sectional analysis, *H pylori* infection was inversely associated with esophageal eosinophilia. This relationship could have implications for the pathogenesis and epidemiology of EoE.

Keywords: Epidemiology; Esophagus; Inflammation; Histologic Analysis.

Eosinophilic esophagitis (EoE) is a chronic disease of the esophagus characterized by dysphagia and dense esophageal eosinophilia in the absence of gastroesophageal reflux disease (GERD).¹ First described in 1978 and initially believed to be rare,^{2,3} the incidence and prevalence of EoE have rapidly increased over the past decade.^{4–8} Currently, between 5% and 15% of patients undergoing

endoscopic evaluation for dysphagia will have EoE,^{9–11} and more than 50% of patients presenting to an emergency department with food impaction are now diagnosed with EoE.^{12,13} The pathogenesis of EoE is believed to be an immune-mediated allergic process,¹⁴ but the etiology is unknown.

Given the dramatic epidemiologic shift regarding EoE, environmental exposures have been postulated to play a role.¹⁵ One early life exposure, *Helicobacter pylori*, has been inversely associated with conditions such as asthma, allergic rhinitis, and atopic dermatitis, and biologic plausibility for a protective role of *H pylori* in allergic disease is emerging.^{16–19} Although there is an ecologic association between the decreasing prevalence of *H pylori* and the increase in EoE, the association between *H pylori* infection, EoE, and esophageal eosinophilia is poorly understood.

The primary objective of this study was to determine the association between esophageal eosinophilia and *H pylori* in a large set of gastric and esophageal biopsy specimens. We hypothesized that the presence of *H pylori* would be inversely associated with increasing esophageal eosinophilia. The secondary objectives were to determine the association between patients suspected of having EoE and *H pylori* and between esophageal eosinophilia and different *H pylori* disease manifestations in the stomach. We hypothesized that the presence of *H pylori* would be inversely associated with increasing clinical suspicion for EoE and that esophageal eosinophilia would be inversely associated with more severe manifestations of *H pylori*.

Patients and Methods

Study Design and Data Source

This is a cross-sectional study of all patients with esophageal biopsy specimens examined between January 1, 2008, and November 26, 2010, by pathologists at Caris Life Sciences. The

Abbreviations used in this paper: CI, confidence interval; EGD, esophagogastroduodenoscopy; EoE, eosinophilic esophagitis; eos/hpf, eosinophils per high-power field; GERD, gastroesophageal reflux disease; OR, odds ratio.

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Caris Institutional Review Board and the University of North Carolina Institutional Review Board approved the study.

Caris Life Sciences is a specialized pathology laboratory serving outpatient endoscopy centers throughout the United States. They review samples from 43 states, Washington DC, and Puerto Rico, with central specimen processing in 1 of 3 laboratories (Irving, TX; Phoenix, AZ; and Boston, MA). Each laboratory follows identical sectioning and staining procedures. An experienced group of subspecialty trained gastrointestinal pathologists originally reviewed the slides for clinical purposes. Biopsy interpretation is performed using a standardized protocol with uniform diagnostic criteria. All biopsy reports are deposited into a central database, which also includes information about patient age, sex, and indication for esophagogastroduodenoscopy (EGD). For the purposes of this study, a de-identified database of preexisting records from unique patients with esophageal biopsy specimens was generated.

Study Population

Cases comprised all patients with esophageal eosinophilia on esophageal biopsy. By definition, cases had histology showing a prominent epithelial infiltration of eosinophils, as described in standardized coding by pathologists (either as “active esophagitis with increased intraepithelial eosinophils” or as an “eosinophilic esophagitis pattern or injury”).²⁰ Cases were termed “any esophageal eosinophilia.”

Controls were all patients with normal esophageal biopsy specimens (unremarkable squamous mucosa). By definition, controls had no evidence of esophageal eosinophilia or other pathologic processes such as noneosinophilic inflammation of any type, epithelial erosion or ulceration, infection with viral or fungal pathogens, or cellular metaplasia, dysplasia, or neoplasia.

The main exposure was the presence of active *H pylori* infection on gastric biopsy. A diagnosis of *Helicobacter* gastritis was made when *H pylori* organisms were detected in a gastric biopsy specimen using an *H pylori*-specific immunohistochemical stain (anti-*H pylori* rabbit polyclonal antibody; Cell-Marque, Rocklin, CA) and there was concomitant chronic and/or active inflammation (with or without intestinal metaplasia) in the gastric mucosa, per the updated Sydney classification.^{21,22}

Other histologic characteristics of interest included a quantification of the severity of esophageal eosinophilic density in ranges of eosinophils per high-power (400 \times) field (eos/hpf; area per hpf = 0.237 mm²), the presence of eosinophilic microabscesses (defined as clusters of ≥ 4 contiguous eosinophils),²³ the presence of reflux esophagitis (defined as a mixed active/chronic inflammatory pattern with squamous papillomatosis and basal hyperplasia), the presence of intestinal metaplasia (Barrett's esophagus), and the presence of infectious esophagitis (defined as histopathologic evidence of either candida, herpes simplex virus, or cytomegalovirus on esophageal biopsy specimens).

Clinical characteristics of interest included upper gastrointestinal symptoms or conditions as derived from the indication for endoscopy (ie, suspected EoE, dysphagia symptoms, reflux symptoms or GERD [defined as a report of heartburn, regurgitation, or reflux], screening or follow-up of a known diagnosis of Barrett's esophagus, abdominal pain or dyspepsia, chest pain, nausea or vomiting, and weight loss or failure to thrive).

Statistical Analysis

Means and SDs were reported for continuous variables. Proportions were reported for categorical data. Bivariate analyses were performed using Student *t* test for continuous charac-

teristics or Pearson's χ^2 for categorical characteristics. Unadjusted odds ratios (ORs) were calculated to assess the association between case-control status and the presence of *H pylori*. To adjust for potential confounders noted on bivariate analysis, multivariate analyses were performed using logistic regression. A backward elimination strategy was used to reduce the model, retaining those covariates for which removal would have caused a change in estimate of $> 10\%$ in the estimate of the effect of the association between *H pylori* and esophageal eosinophilia. The initial model contained age, sex, dysphagia, abdominal pain, and reflux symptoms as defined previously. Age was retained in the final model. Analyses were performed with Stata (version 11.0; StataCorp LP, College Station, TX).

Sensitivity Analyses

We planned for several a priori sensitivity analyses. First, a dose-response analysis was performed for the association between *H pylori* and increasing levels of esophageal eosinophilia on biopsy (nested categories of ≥ 15 , ≥ 45 , ≥ 75 , and ≥ 90 eos/hpf), and a *P* value for trend was calculated. These categories were chosen empirically based on the available data distributions. In addition, there were some reports in which the level of esophageal eosinophilia was included in the text of the pathology report but there was not an associated standardized pathology code. These cases were included in the “ ≥ 15 eos/hpf” category but were not previously included in the “any esophageal eosinophilia” case definition as described previously.

A second analysis was performed to approximate an increasing clinical likelihood of EoE. We began with patients who were unlikely to have EoE who had pathology consistent with reflux esophagitis. We then applied progressively restrictive limits on the presence of esophageal eosinophilia. First, we defined a group termed “histologic eosinophilic esophagitis,” composed of only patients with the standardized pathology interpretation code of “eosinophilic esophagitis pattern of injury” on esophageal biopsy (as outlined previously). We then restricted this group to those who also had an EGD indication of dysphagia or clinical suspicion for EoE and had no histologic evidence of reflux esophagitis or Barrett's esophagus. This definition was then further limited to patients who also had eosinophilic microabscesses in the esophageal epithelium. The last group definition included only patients with ≥ 90 eos/hpf on esophageal biopsy. We also performed a subanalysis of the association between *H pylori* and esophageal eosinophilia based on whether the esophageal biopsy was taken from the proximal or distal esophagus.

The final sensitivity analysis examined the association of “histologic eosinophilic esophagitis” with different manifestations of *H pylori* disease in the stomach, including chronic active gastritis without *H pylori* present, chronic active gastritis with *H pylori* present, and intestinal metaplasia present (with or without *H pylori*). The purpose was to investigate esophageal eosinophilia from the perspective of increasing severity of infection with *H pylori*.^{24,25}

Results

Patient and Biopsy Characteristics

Between January 1, 2008, and November 26, 2010, a total of 233,662 unique patients had esophageal biopsy specimens reviewed (Table 1). The mean age was 55.8 years, and 46.1% were male. The most common indica-

tions for endoscopy were GERD (48.6%), abdominal pain (32.9%), and dysphagia (22.6%). There were 26,982 patients (11.6%) who underwent endoscopy for suspected EoE on a clinical basis. We identified 165,017 patients with both esophageal and gastric biopsy specimens. Of

these patients, 56,301 (34.1%) had normal esophageal biopsy specimens, 5767 (3.5%) had "any esophageal eosinophilia," and 11,170 (6.8%) had *H pylori* on gastric biopsy (Table 1). Although there were many statistical differences given the large sample size between those who had both esophageal and gastric biopsy specimens and those with esophageal biopsy specimens only (Table 1), for the large majority of variables the absolute difference between groups was 1% or less, differences that were not clinically significant.

Of those with both esophageal and gastric biopsy specimens, patients with esophageal eosinophilia were significantly younger (44 vs 53 years; $P < .001$) and more likely to be male (62% vs 35%; $P < .001$) compared with patients with normal esophageal biopsy specimens (Table 2). They were also more likely to have an endoscopy indication for suspected EoE or dysphagia and less likely to have an indication for GERD, abdominal pain, or chest pain. Compared with patients without *H pylori*, patients with *H pylori* were more likely to have an upper endoscopy indication for abdominal pain and less likely to have an indication for suspected EoE, dysphagia, or Barrett's esophagus (Table 3).

Table 1. Patient Characteristics

Clinical characteristics	Esophageal biopsies (n = 233,662)	Esophageal and gastric biopsies (n = 165,017)	P value ^a
Mean age \pm SD (y)	55.8 \pm 16.2	55.1 \pm 16.5	<.001
Children (age younger than 18 y), n (%)	3674 (1.6)	3469 (2.1)	<.001
Male, n (%)	107,759 (46.1)	71,488 (43.4)	<.001
EGD indication, n (%) ^b			
Suspected EoE	26,982 (11.6)	17,089 (10.4)	<.001
Dysphagia	52,787 (22.6)	32,055 (19.4)	<.001
GERD/heartburn	113,465 (48.6)	81,843 (49.6)	<.001
Barrett's esophagus (screening or follow-up)	32,257 (13.8)	15,816 (9.6)	<.001
Abdominal pain/dyspepsia	76,935 (32.9)	64,720 (39.2)	<.001
Chest pain	9566 (4.1)	6776 (4.1)	.64
Nausea	15,218 (6.5)	12,426 (7.5)	<.001
Vomiting	8850 (3.8)	7108 (4.3)	<.001
Weight loss	6853 (2.9)	5311 (3.2)	<.001
Failure to thrive	96 (0)	92 (0.1)	<.001
Histologic characteristics, n (%)			
Normal esophageal biopsy specimens	71,948 (30.8)	56,301 (34.1)	<.001
Any esophageal eosinophilia ^c	9995 (4.3)	5767 (3.5)	<.001
Histologic EoE ^d	7156 (3.1)	3959 (2.4)	<.001
Level of esophageal eosinophilia (<i>eos/hpf</i>) ^e			
≥ 15	9981 (4.3)	5791 (3.5)	<.001
≥ 45	3104 (1.3)	1738 (1.1)	<.001
≥ 75	1078 (0.5)	607 (0.4)	<.001
≥ 90	703 (0.3)	388 (0.2)	<.001
Eosinophilic microabscesses	2448 (1.0)	1330 (0.8)	<.001
Barrett's esophagus on histology	30,139 (12.9)	13,933 (8.4)	<.001
Reflux esophagitis changes on histology	79,536 (34.0)	55,884 (33.9)	.006
Candidal esophagitis	4124 (1.8)	2648 (1.6)	<.001
Cytomegalovirus esophagitis	16 (0)	9 (0)	.21
Herpes simplex virus esophagitis	52 (0)	29 (0)	.02
<i>H pylori</i> on gastric biopsy	11,170 (4.8)	11,170 (6.8)	<.001

^aP values are for the comparison between patients with both esophageal and gastric biopsy specimens (n = 165,017) and those with esophageal biopsy specimens without gastric biopsy specimens (n = 68,645) and are based on t test for continuous variables and Pearson's χ^2 for categorical variables.

^bPatients could have more than one indication for EGD.

^cAny esophageal eosinophilia indicates that the examining pathologist noted prominent esophageal eosinophilia but does not require that the findings were histologically consistent with EoE in the correct clinical context. This is the main case definition for this study.

^dHistologic EoE indicates that the examining pathologist thought that the findings were histologically consistent with EoE in the correct clinical context.

^eCategories are nested.

Table 2. Comparison of Patients With Esophageal Eosinophilia and Normal Esophageal Biopsy Specimens

	Any esophageal eosinophilia (n = 5767)	Normal esophageal biopsy specimens (n = 56,301)	P value ^a
Mean age \pm SD (y)	43.9 \pm 16.9	53.2 \pm 17.4	<.001
Children (age younger than 18 y), n (%)	345 (6.0)	2165 (3.9)	<.001
Male, n (%)	3592 (62.3)	19,744 (35.1)	<.001
EGD indication, n (%) ^b			
Suspected EoE	2110 (36.6)	8640 (15.4)	<.001
Dysphagia	2608 (45.2)	11,525 (20.5)	<.001
GERD/heartburn	2535 (44.0)	28,100 (49.9)	<.001
Barrett's esophagus (screening or follow-up)	252 (4.4)	3372 (6.0)	<.001
Abdominal pain/dyspepsia	1788 (31.0)	24,014 (42.7)	<.001
Chest pain	191 (3.3)	3183 (5.7)	<.001
Nausea	355 (6.2)	4578 (8.1)	<.001
Vomiting	266 (4.6)	2519 (4.5)	.629
Weight loss	99 (1.7)	1716 (3.1)	<.001
Failure to thrive	8 (0.1)	55 (0.1)	.351

^aBased on t test for continuous variables and Pearson's χ^2 for categorical variables for the group of patients with both esophageal and gastric biopsy specimens.

^bPatients could have more than one indication for EGD.

Table 3. Comparison of *H pylori*-Positive and -Negative Patients

	<i>H pylori</i> positive (n = 11,170)	<i>H pylori</i> negative (n = 153,847)	<i>P</i> value ^a
Mean age ± SD (y)	56.0 ± 15.4	55.0 ± 16.6	<.001
Children (age younger than 18 y), n (%)	82 (0.73)	3387 (2.2)	<.001
Male, n (%)	5105 (45.7)	66,383 (43.2)	<.001
EGD indication, n (%) ^b			
Suspected EoE	1070 (9.6)	16,019 (10.4)	.005
Dysphagia	1988 (17.8)	30,067 (19.5)	<.001
GERD/heartburn	5347 (47.9)	76,496 (49.7)	<.001
Barrett's esophagus (screening or follow-up)	409 (3.7)	15,407 (10.0)	<.001
Abdominal pain/ dyspepsia	5017 (44.9)	59,703 (38.8)	<.001
Chest pain	347 (3.1)	6429 (4.2)	<.001
Nausea	786 (7.0)	11,640 (7.6)	.041
Vomiting	455 (4.1)	6653 (4.3)	.207
Weight loss	531 (4.8)	4780 (3.1)	<.001
Failure to thrive	4 (0)	88 (0.1)	.355

^aBased on *t* test for continuous variables and Pearson's χ^2 for categorical variables.

^bPatients could have more than one indication for EGD.

Esophageal Eosinophilia and *H pylori*

The presence of “any esophageal eosinophilia” was inversely associated with *H pylori* (OR, 0.77; 95% confidence interval [CI], 0.69–0.87) (Table 4). Compared with patients with normal esophageal biopsy specimens, there were reduced odds of *H pylori* for patients with ≥ 15 intraepithelial eos/hpf (OR, 0.79; 95% CI, 0.70–0.88), ≥ 45 eos/hpf (OR, 0.75; 95% CI, 0.61–0.93), ≥ 75 eos/hpf (OR, 0.72; 95% CI, 0.50–1.03), and ≥ 90 eos/hpf (OR, 0.52; 95% CI, 0.31–0.87) (*P* for trend <.001). These associations held after adjusting for potential confounding factors on multivariate analysis (Table 4).

Increasing clinical suspicion for EoE was also associated with decreasing odds of *H pylori*. Compared with patients with normal esophageal biopsy specimens, patients with no suspicion of EoE and reflux esophagitis on biopsy had a borderline inverse association with *H pylori* (OR, 0.95; 95% CI, 0.90–0.99). Patients with “histologic eosinophilic esophagitis” (as defined previously) had reduced odds of *H pylori* (OR, 0.72; 95% CI, 0.62–0.83). This inverse association was stronger when limited to those with dysphagia or a clinical suspicion of EoE, no reflux or Barrett's esophagus, and eosinophilic microabscesses (OR, 0.63; 95% CI, 0.45–0.87). Again, all associations held after adjusting for potential confounding factors on multivariate analysis (Table 4).

There were also differences when evaluating the presence of esophageal eosinophilia in patients with different manifestations of gastritis and *H pylori*. Compared with patients with normal gastric biopsy specimens, there were

reduced odds of “histologic EoE” among patients with chronic active gastritis but no identifiable *H pylori* (OR, 0.86; 95% CI, 0.64–1.17), patients with chronic active gastritis and *H pylori* present (OR, 0.69; 95% CI, 0.59–0.81), and patients with intestinal metaplasia with or without *H pylori* (OR, 0.34; 95% CI, 0.23–0.51; *P* for trend <.001). These associations also held on multivariate analysis (Table 5).

Assessment of biopsy location (proximal vs distal) as an effect modifier of the association between *H pylori* infection and esophageal eosinophilia showed no significant difference based on location of the esophageal biopsy (data and full models not shown).

Discussion

Over the past decade, EoE has become a major cause of dysphagia and morbidity and is commonly encountered in gastroenterology practice.^{1,4–6,8–13,26–28} With such a rapidly evolving epidemiology, it is plausible that environmental factors play a role. In some cases, specific food allergens or environmental triggers can be identified.^{29–32} However, the etiology of the dramatic increase in the incidence of EoE is unknown.

The present study used a nationwide pathology database to assess the association between esophageal eosinophilia and *H pylori*, and the results were striking. We found a strong inverse association between *H pylori* and esophageal eosinophilia, and as the level of esophageal eosinophilia increased, the odds of *H pylori* decreased. With increasingly stringent case definitions approximating EoE on a clinical basis, the odds of *H pylori* also decreased. In addition, the odds of esophageal eosinophilia were lower with progressively chronic manifestations of *H pylori* disease, as manifest by chronic active gastritis and intestinal metaplasia.

Despite the common nature of both conditions, the literature describing the relationship between *H pylori* infection and EoE is scant and conflicting. An inverse association of *H pylori* and esophageal eosinophilia has been suggested in one prior report.⁶ In this secondary analysis of a population-based study of the prevalence of Barrett's esophagus, distal esophageal biopsy specimens were re-reviewed for eosinophil counts. However, there were only 48 patients with esophageal eosinophilia and 8 with *H pylori*. The reported OR in this study was 0.41, similar to our results. In contrast, a study of eosinophilia throughout all segments of the gastrointestinal tract found that patients with *H pylori* gastritis had somewhat higher esophageal eosinophil counts than patients without *H pylori*. This study, too, was limited by small numbers, with only 8 patients with eosinophil counts ≥ 15 eos/hpf.³³ To our knowledge, there have been no prior investigations that also examined esophageal eosinophilia in relation to the manifestation of *H pylori* in the stomach.

There are several possible explanations for our findings. *H pylori* has been inversely associated with conditions such as asthma, allergic rhinitis, and atopic dermati-

Table 4. Unadjusted and Adjusted ORs for the Association Between *H pylori* and Histologic Esophageal Disease

	<i>H pylori</i> positive	<i>H pylori</i> negative	Unadjusted OR (95% CI)	Adjusted OR (95% CI) ^a
Main outcome				
Normal esophageal biopsy specimens	4048	52,253	1.00 (ref)	1.00 (ref)
Any esophageal eosinophilia	326	5441	0.77 (0.69–0.87)	0.82 (0.73–0.92)
By level of eosinophilia (<i>eos/hpf</i>)^b				
≥15	333 ^c	5458 ^c	0.79 (0.70–0.88)	0.83 (0.74–0.93)
≥45	96	1642	0.75 (0.61–0.93)	0.81 (0.66–1.00)
≥75	32	575	0.72 (0.50–1.03)	0.77 (0.54–1.10)
≥90	15	373	0.52 (0.31–0.87)	0.56 (0.33–0.97)
By EoE certainty^b				
Reflux esophagitis on biopsy	3798	52,086	0.94 (0.90–0.99)	0.94 (0.89–0.98)
Any esophageal eosinophilia	326	5441	0.77 (0.69–0.87)	0.82 (0.73–0.92)
Histologic EoE	208	3751	0.72 (0.62–0.83)	0.77 (0.66–0.89)
Histologic EoE with dysphagia or clinical suspicion for EoE and no reflux or Barrett's esophagus	121	2246	0.70 (0.58–0.84)	0.74 (0.61–0.89)
Histologic EoE with dysphagia or clinical suspicion for EoE and no reflux or Barrett's esophagus and esophageal eosinophilic microabscess	38	778	0.63 (0.45–0.87)	0.68 (0.49–0.94)
≥90 <i>eos/hpf</i>	15	373	0.52 (0.31–0.87)	0.56 (0.33–0.97)

^aAdjusted for age on multivariate analysis with logistic regression.

^bP for trend <.001.

^cThere are some reports in which the level of esophageal eosinophilia was included in the text of the pathology report but there was not an associated standardized pathology code. These cases were included in the “≥15 *eos/hpf*” category but could not be included in the “any esophageal eosinophilia” case definition.

tis.^{16–19} Given that EoE is believed to be an allergic condition, it makes sense that the same association exists. The hygiene hypothesis has been used to attribute the recent increase in all allergic diseases to improved sanitation and reductions in childhood infections, and *H pylori* is typically contracted during childhood.^{15,16,34} From a mechanistic perspective, a Th2-mediated allergic response is involved in the pathogenesis of EoE,^{14,35–37} whereas *H pylori* may drive a Th1 response¹⁶ with the regulatory T-cell population further modulating the Th1-Th2 balance. It is intriguing to hypothesize, as has been proposed with other allergic conditions,^{16,38} that early infection with *H pylori* might predispose toward a Th1 response and “protect” from an allergic Th2 response and in turn esophageal eosinophilia. The observations of the lower odds of *H pylori* with increasing esophageal eosinophilia, and also the low odds of esophageal eosinophilia in sub-

jects with intestinal metaplasia (arguably a manifestation of chronic infection and potentially a committed Th1 inflammatory response to *H pylori*²⁴), may lend some credence to this hypothesis. We observe that the exact mechanisms of immune modulation of allergy by chronic infections are largely unknown, with the model of Th1 versus Th2 responses most likely representing a simplification.³⁹ For example, recent studies have shown that *H pylori* may inhibit the Th17 response and alter the T regulatory cell balance,³⁹ and *H pylori*-derived DNA itself may directly inhibit a Th1 response.⁴⁰ It remains to be determined whether our findings are attributable to physiologic reflux of *H pylori* or its DNA, a field effect related to systemic immune alterations, or a different mechanism. In the present study, however, we did not see a clear trend by biopsy level in the esophagus for the inverse association between *H pylori* and esophageal eosinophilia,

Table 5. Unadjusted and Adjusted ORs for the Association Between Esophageal Eosinophilia and *H pylori* Gastritis

	Esophageal eosinophilia histologically consistent with EoE	No esophageal eosinophilia	Unadjusted OR (95% CI)	Adjusted OR (95% CI) ^a
Normal gastric biopsy specimens	841	30,481	1.00 (ref)	1.00 (ref)
Chronic active gastritis without <i>H pylori</i>	44	1851	0.86 (0.64–1.17)	1.01 (0.74–1.38)
Chronic active gastritis with <i>H pylori</i>	193	10,131	0.69 (0.59–0.81)	0.79 (0.68–0.93)
Intestinal metaplasia ^b	25	2641	0.34 (0.23–0.51) ^c	0.59 (0.40–0.89) ^c

^aAdjusted for age on multivariate analysis with logistic regression.

^bIncludes patients with *H pylori* (n = 7) and without *H pylori* (n = 18); there was no difference in the OR in these 2 subgroups.

^cP for trend <.001 for both the unadjusted and adjusted ORs.

arguing against direct exposure of *H pylori* or its DNA as a causal factor for the observed association.

Several potential limitations must be considered when interpreting these data. First, because this study was retrospective and cross-sectional in nature, we were unable to draw conclusions about causality or mechanisms, only about associations. Second, we had to restrict our primary outcome to the presence of esophageal eosinophilia, not to EoE itself. This is because current consensus guidelines hold that EoE is a clinicopathologic condition and require exclusion of competing causes of esophageal eosinophilia, including GERD, before the diagnosis of EoE can only be made on a clinical basis.¹ However, we recognized this possible limitation while designing the study and incorporated sensitivity analyses to specifically address this issue. The results of these analyses further support our conclusions. In particular, we observed a stronger inverse association as we assessed progressively more specific EoE case definitions with higher eosinophil counts, supportive histopathologic findings like eosinophilic microabscesses, and exclusion of reflux esophagitis and Barrett's esophagus.

Issues of possible confounding must also be considered. One possibility is that *H pylori* infection is not causally protective for esophageal eosinophilia but is instead a marker for general microbial or environmental exposures or other allergic conditions. If this were the case, however, it would be unlikely that the odds of esophageal eosinophilia would be lower with a chronic manifestation of *H pylori* such as intestinal metaplasia. It is also possible that GERD or proton pump inhibitor use could be confounding factors. *H pylori* is harder to detect in patients on concurrent proton pump inhibitor therapy⁴¹; thus, if patients had esophageal eosinophilia due to GERD and were treated with a proton pump inhibitor, it stands to reason that the prevalence of *H pylori* would be lower. In addition, *H pylori* can reduce gastric acid secretion, which may also have an impact on esophageal eosinophilia. However, when we controlled for reflux symptoms on multivariable analysis, there was no change in the observed association; in addition, when patients with reflux esophagitis or histologically confirmed Barrett's esophagus were excluded in our more stringent case definition, the OR for *H pylori* was farther from the null, the opposite of what would be expected if GERD were a confounder. The careful pathologic characterization of a large number of esophageal biopsy specimens using a standardized system of interpretation, in combination with the sensitivity analyses performed for this study, lend validity to our results. This is by far the largest number of subjects with esophageal eosinophilia analyzed in the medical literature.

In conclusion, we found that there was a strong inverse association between *H pylori* infection and esophageal eosinophilia in biopsy specimens from a large US national pathology database with a patient population reflective of general gastroenterology practice. The odds of *H pylori* decreased in a dose-response fashion with increasing lev-

els of esophageal eosinophilia and with increasingly restrictive pathologic definitions of EoE. In addition, the odds of esophageal eosinophilia decreased with chronic manifestations of *H pylori* gastritis and intestinal metaplasia. Although the results of this study cannot speak to causality or biologic mechanisms, this association may have important implications for future research into understanding the pathogenesis and evolving epidemiology of EoE.

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Reprint requests

Address requests for reprints to: Evan S. Dellon, MD, MPH, CB#7080, Bioinformatics Building, 130 Mason Farm Road, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-7080. e-mail: edellon@med.unc.edu; fax: (919) 843-2508.

Conflicts of interest

The authors disclose the following: Robert M. Genta and Richard H. Lash are employed by Caris Life Sciences (Irving, TX) and are shareholders in the company. The remaining authors disclose no conflicts.

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