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Does *Helicobacter pylori* Protect against Eosinophilic Esophagitis in Children?

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**Keywords**

*Helicobacter pylori*, eosinophilic esophagitis, children.

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**Summary**

**Background:** *Helicobacter pylori* infection and eosinophilic esophagitis (EoE) in children seem to have a reversed association with socioeconomic status (hygienic condition) and allergy conditions. While Hp infection (Hp) is highly associated with poor hygiene and/or poor socioeconomic status, but not with allergic conditions (asthma, rhinitis, etc.), EoE has the opposite epidemiological relationship (high association with allergy but low with low hygienic conditions).

**Aim:** To investigate the association between Hp infection and EoE in children.

**Methods:** A retrospective chart review of all children who undergo the first upper endoscopy procedure in the gastroenterology clinic, between 2007 and 2012, was performed. Demographic, endoscopic and histological data were collected. The data was divided into 4 diagnostic groups: Hp infection, EoE, reflux esophagitis, and children who had normal histology. The relationship between Hp positive children and the other groups was performed.

**Results:** A total of 966 charts were available for review. Esophagitis, idiopathic gastritis, EoE, and Hp infection were detected in 268 (28%), 480 (49%), 62 (6%), and 31 (3%) children, respectively. The mean age of the EoE group was significantly lower compared to all reference groups \((p < .002)\), but no significant different was detected among the reference groups (gastritis, GERD, and Hp infection; \(p = 1.00)\). Simple logistic regression analysis using Hp infection as a predictor for EoE did not find a significant relationship between these two variables \((p-value = .471, OR = 0.478, 95\% CI 0.06–3.56)\). However, multivariable logistic regression analysis between EoE and the reference groups indicated a significant negative relationship between Hp infection and EoE \((p-value = .023, adjusted OR = 0.096, 95\% CI 0.013–0.72)\). Neither gastritis nor GER showed significant relationship with EoE \((p-values are 1.000 and .992, respectively)\).

**Conclusion:** A reversed association between Hp and EoE was found in a cohort of West Virginia children. The possible explanations for these findings are discussed.

*Helicobacter pylori* infection in children has been well characterized, and treatment guidelines have been established [1]. *Helicobacter pylori* infection is associated with poor hygiene, low socioeconomic conditions, and family crowding [2]. Indeed, the rate of *H. pylori* infection in children from developing countries is higher compared with children living in developed countries [3]. On the contrary, an inverse association between the prevalence of *H. pylori* infection and allergic diseases was reported. For example, the prevalence of asthma, rhinitis, eczema, or other allergies was lower in *H. pylori*-infected compared with non-*H. pylori*-infected children [4–8].

Eosinophilic esophagitis (EoE) is a newly established chronic esophageal disease in adults and children with clinical and pathological characterizations [9]. Previous
studies have documented that the prevalence of EoE in children is increasing, especially in those who live in developed countries [9]. Clinical and laboratory experiments on animal models documented the close association between environmental allergies (asthma, rhinitis) and EoE. In fact, over three quarters of children diagnosed with EoE have associated food or environmental allergies, suggesting that those allergens are the trigger for the development of EoE in children [9]. Moreover, several clinical studies have documented that various protocols of food elimination diets resulted in clinical and histologic resolution of EoE [10–13].

The opposite role of environmental allergies in EoE and H. pylori infection has raised the possibility that both diseases may have an inverse burden in human disease, that is, one disease may “protect” the human from getting the other. Indeed, a recent report by Dellon et al. [14] showed an inverse association between esophageal eosinophilia and H. pylori infection in adult patients. In this report, the authors analyzed data collected from the US pathology database (>160, 000 patients) and reported a reduced rate of H. pylori infection in patients with EoE (defined as eos >15 eos/HPF) (OR 0.79; 95% CI: 0.70–0.88). In another study, Furuta et al. compared the rate of H. pylori infection in adult patients with EoE and eosinophilic gastroenteritis (EGE) and normal control. The authors reported that the odds ratio of H. pylori infection in the tested groups compared with control was 0.22 and 0.31 in EoE and EGE, respectively [15]. Although the diagnosis of H. pylori infection was established by serology and not histology, it suggested a reversed relationship between H. pylori infection and the eosinophilic gastrointestinal disorders (EGIDs). To our knowledge, a similar study in children has not been published. In the present study, we evaluated the association between H. pylori infection and EoE disease in the children diagnosed and treated for EoE in our pediatric gastroenterology clinic, at Marshall University School of Medicine.

Material and Methods

A retrospective chart review of all children who underwent their first upper endoscopy procedure in the gastroenterology clinic, between 2007 and 2012, was performed. Demographic, endoscopic, and histologic data were collected. The data were then divided into four diagnostic groups: Children with H. pylori infection, children with EoE, children with reflux esophagitis, and children who had normal histology. The relationship between H. pylori-positive children and the other groups was performed.

Endoscopic Procedure

The endoscopic procedures were scheduled for various clinical indications. All endoscopic procedures were performed under general anesthesia given by an anesthesiologist or nurse anesthetist using propofol (iv), versed (iv), or inhalation of nitric oxide or sevoflurane gas. The mode of anesthesia was given per the discretion of the anesthesiologist. All endoscopic procedures were performed by one experienced physician (YE), and biopsies were taken from all procedures irrespective of the mucosal appearance at the time of the procedures. The following number of biopsies was included in each endoscopic procedure: esophagus (distal – 3; mid – 3 when EoE was suspected); stomach (antrum – 4 for histology, two for rapid urease test, body – 2); two from the duodenal bulb, and two from the duodenum (second part). All biopsies were reviewed by our board-certified pathologist team according to established diagnostic standards. Helicobacter pylori organism was evaluated by H&E and Giemsa staining. When high number of eosinophils was suspected in the esophagus, a specific eosinophil count was performed. Helicobacter pylori was diagnosed when the organism was positive by histology and by positive rapid urease test (CLO test). EoE was established according to histologic guidelines for EoE diagnosis, that is, when esophageal eosinophil count was >15/HFP (at magnification ×400) in the distal and mid esophagus with low eosinophil counts in the gastric or duodenal mucosa. All EoE patients had failed adequate PPI therapy according to previously published guidelines [9]. Esophageal reflux was defined when eosinophil count was <15/HFP. Helicobacter pylori-associated gastritis was defined when H. pylori organism was found by positive histology and positive rapid urease test and mucosal inflammation. Gastritis was defined according to established histologic findings but with negative H. pylori organism on both tests (H&E and CLO test). Normal histology was defined where no histologic pathology identified in the esophagus, stomach, or duodenum was determined by the pathologist who reviewed the patient’s biopsies.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics Software, version 21 (Armonk, NY, USA). Logistic regression analysis was used to determine the association between H. pylori infection as a predictor variable and EoE as a response variable. Multivariable logistic regression analysis included GER and idiopathic gastritis as covariates. Unadjusted and adjusted odds...
ratios (OR) between EoE and \textit{H. pylori} infection were computed.

**Results**

A total of 966 charts were available for review. The mean age and M : F ratio were 11.3 years and 1 : 1.18, respectively. Histologic diagnoses of esophagitis (GERD), idiopathic gastritis, EoE, and \textit{H. pylori}-associated gastritis (\textit{H. pylori} infection) were detected in 268 (28%) EGDs, 480 (49%) EGDs, 62 (6%) EGDs, and 31 (3%) EGDs, respectively [Table 1]. The male/female ratio for the different groups was 1.3 : 1.0, 0.9 : 1.0, 2.0 : 1.0, and 0.5 : 1.0 for GERD, Gastritis, EoE, and \textit{H. pylori} infection, respectively [Table 1]. The mean age of the EoE group was significantly lower compared with all reference groups (\(p < .002\), Mann–Whitney test), but no significant difference was detected among the reference groups (gastritis, GERD, and \textit{H. pylori} infection; \(p = 1.00\)) [Table 1]. The proportion of EoE-infected patients among \textit{H. pylori}-infected patients was 0.032 (or 3%), while the proportion of EoE-infected patients among patients without \textit{H. pylori} infection was 0.065 (or 6.5%). Simple logistic regression analysis using \textit{H. pylori} infection as a predictor for EoE did not find a significant relationship between these two variables (\(p\)-value = .471, OR = 0.478, 95% CI 0.06–3.56). However, multivariable logistic regression analysis with \textit{H. pylori} infection, gastritis, and GER as covariates indicated a negative significant relationship between \textit{H. pylori} infection and EoE (\(p\)-value = .023, adjusted OR = 0.096, 95% CI 0.013–0.72). Neither gastritis nor GER showed significant relationship with EoE (\(p\)-values are 1.000 and .992, respectively).

**Discussion**

In the present study, we showed a significant reversed association between \textit{H. pylori} and EoE under multivariable logistic regression analysis. The association between EoE and \textit{H. pylori} infection has not been adequately investigated in the literature. Utilizing a large database, collected from biopsy results, Dellon et al. [14] reported a reversed association between \textit{H. pylori} infection and esophageal eosinophilia. The relationship was stronger with higher number of eosinophils. In comparison with Dellon’s study [14], our study cohort was smaller but included real patients who were diagnosed with EoE according to the clinical and histologic expert’s guidelines [9]. Moreover, unlike in the cited study, all of our EoE patients failed anti-acid medication trials before the diagnosis of EoE was established.

The possible association between EoE and \textit{H. pylori} infection is intriguing and deserves further discussion. With the explosion of novel clinical information involving the human microbiome project, the “hygiene theory” becomes more plausible and acceptable by the medical scientific community. Epidemiological studies have supported the “hygiene theory” as an important factor in the etiology of several human diseases, such as IBD, autoimmune diseases, and \textit{H. pylori} infection [1, 16–18]. The higher prevalence of \textit{H. pylori} infection in the developing countries was attributed to the lower socioeconomic and hygienic conditions that exist in those countries [2]. Indeed, in the last several decades, the improvement of the socioeconomic conditions in the developed areas has directly impacted the rate of \textit{H. pylori} infection [19–21]. Similarly, the “hygienic theory” was also applied to allergic conditions. Countries with low hygienic conditions and low socioeconomic conditions (overcrowding, low income, etc.) have higher infection rates and lower allergy-related diseases, such as asthma, eczema, allergic rhinitis, and others [4,5].

The association of EoE with allergies (environmental and/or food) is well documented, but its association with poor hygienic conditions has not been well established. It is interesting to note that most of the global

<table>
<thead>
<tr>
<th>Disease</th>
<th>Hp infection</th>
<th>GERD</th>
<th>Gastritis</th>
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<tbody>
<tr>
<td>EoE</td>
<td>Hp +</td>
<td>Hp −</td>
<td>GERD +</td>
</tr>
<tr>
<td>EoE +</td>
<td>1</td>
<td>61</td>
<td>62</td>
</tr>
<tr>
<td>EoE −</td>
<td>30</td>
<td>874</td>
<td>206</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>935</td>
<td>268</td>
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| M/F ratio | 0.5 : 1 | 1.3 : 1 | 0.9 : 1 |
| Age (years) ± SD | 12.0 ± 3.3 | 11.4 ± 4.7 | 11.4 ± 4.3 |
| EoE group | 9.4 ± 5.0 | 9.4 ± 5.0 | 9.4 ± 5.0 |

\(p\) (Mann–Whitney) .022 .006 .004
reports on EoE originated from the developed countries [9,22], but as the disease is more recognized by the health providers, reports on EoE disease in the developing countries are emerging [23,24]. On the other hand, in the US, the rate of EoE in rural areas was reported lower compared with the rate in the urban areas [25]. This datum suggests that air pollution (environmental allergens) may explain those differences rather than hygienic conditions [26]. In support of this hypothesis are the data published from WV. The state of WV is considered a rural state, known for its low-income and low socioeconomic population, and a state with low environmental pollution (www.cdc.gov). Considering this background, it is not surprising that the rate of H. pylori infection in the pediatric population was reported high, while the prevalence of EoE among those children was low [27]. In recent years, due to improved socioeconomic conditions, we observed a significant drop in H. pylori prevalence among our children [28]. This drop is reflected by our low number of H. pylori infections seen in this study.

We acknowledge some limitations of our study, including the retrospective nature of the report that prevented us from controlling for possible confounding factors, that is, demographic and socioeconomic conditions, as well as the small number of patients diagnosed with H. pylori infection and/or EoE disease. The strength of the report is demonstrated by the fact that this is the first time that the relationship between EoE and H. pylori infection was evaluated in the pediatric population using data from existing patients that have been followed by the authors and do not consist of gathering data from the national pathological database [14]. With limited data available in children, it is clear that prospective studies are needed to shed further information on this topic.

In conclusion, this is the first study to investigate the association between H. pylori infection and EoE disease in children. We showed that there is a significant reverse association between EoE disease and H. pylori infection. Additional, prospective studies in children are needed to further investigate this association.

**Acknowledgements and Disclosures**

**Competing interests:** The authors have no competing interests.

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