

***Helicobacter pylori* infection is associated with a reduced risk of developing eosinophilic oesophagitis**

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SUMMARY

Background

Eosinophilic oesophagitis (EoE) represents a chronic immune-antigen-mediated allergic disease of the oesophagus of still unknown aetiology. Environmental exposure has been postulated to play a pathogenetic role. *Helicobacter pylori* (*H. pylori*) infection has been inversely associated with allergic diseases including atopic dermatitis, asthma and allergic rhinitis and *H. pylori* may play a protective role in these conditions. Little is known about the relationship between EoE and *H. pylori*.

Aim

To investigate in a case-control study whether *H. pylori* infection is associated with a reduced risk of developing EoE.

Methods

H. pylori infection was evaluated by serology in 58 [11(19%) female, 47 (81%) male, median age: 36.5 years, range 20–72 years] patients with a clinical and histologically proven diagnosis of EoE and 116 age and sex-matched controls (1 case: 2 controls). Antibodies against *H. pylori* were identified by enzyme-linked immunosorbent assay. Patients with *H. pylori*-specific IgG ≥ 30 enzyme immunounits were classified as *H. pylori*-positive.

Results

3/58 (5.2%) patients with EoE had serological evidence of *H. pylori* infection (EoE – *H. pylori* current infection) and 5/58 (8.6%) reported prior eradication therapy for *H. pylori* infection (EoE – *H. pylori* former infection). The control group demonstrated significantly higher seroprevalence of *H. pylori* (37.9%, $P < 0.0001$) when compared to patients with EoE. EoE was inversely associated with *H. pylori* infection [odds ratio (OR) 0.24, 95% confidence interval (CI) 0.11–0.50].

Conclusion

Helicobacter pylori infection is inversely associated with EoE. Our results may contribute to further understanding the pathogenesis and evolving aetiology of EoE.

INTRODUCTION

Eosinophilic oesophagitis (EoE) is a chronic immune/antigen-mediated oesophageal disease characterised clinically by symptoms related to oesophageal dysfunction and histologically by eosinophil-predominant inflammation.¹ Two decades ago, EoE was assumed to be an extremely rare disease, but epidemiologic studies have since confirmed an increasing incidence and prevalence in children, adults and in elderly (>65 years) mainly affecting populations from developed/industrialised countries.^{2–6} Depending on study population/design EoE is diagnosed with a prevalence of 0.99% (95% confidence interval, CI 0.7–1.3)⁷ to 12% (95% CI 8.5–16.4).⁸ A recently published study from a large database in Denmark calculated in an EoE case-finding model an estimated EoE prevalence of 13.8/100 000 persons in 2012 independently from increasing biopsy rates.⁹

Pathogenesis is hypothesised to involve both environmental and genetic factors, particularly food antigens and/or aeroallergens.^{10, 11} Younger adults with EoE commonly have a personal or family history of co-existing atopies (atopic dermatitis, allergic rhinitis, allergic asthma and atopic eczema),¹² interestingly elderly EoE patients present with a lower prevalence of atopic comorbidities.² It is well accepted that EoE is an immune-mediated allergic process¹³ and there is also an established potential link between allergy and childhood infection especially with *H. pylori*.^{14, 15} Furthermore, a protective role of *H. pylori* has been attributed in allergic conditions.¹⁶ As clinical and pathophysiological characteristics of EoE resemble allergic asthma, EoE is sometimes referred to as 'asthma of the oesophagus'. We hypothesised that *H. pylori* infection would be inversely associated with EoE.

PATIENTS AND METHODS

This is a case-control study analysing *H. pylori* prevalence in 58 patients with clinical and histological proven EoE and 116 age and sex-matched controls. The study was approved by the Ethics Committee of the Otto-von-Guericke University Hospital of Magdeburg (ethic number: 49/12) and was in accordance with the Helsinki Declaration of 1975, as revised in 1983. All study participants signed a written informed consent.

Study population

Patients. Eosinophilic oesophagitis patients were either recruited in our out-patient department ($n = 21$) or during an investigational study ($n = 37$).¹⁷

Eosinophilic oesophagitis patients were diagnosed according to the consensus recommendations.¹ Patients were interviewed using a structured questionnaire, providing information on demographics, medical history, and medication. All patients were specifically asked about symptoms of dysphagia, atopic diseases (e.g. allergic rhinoconjunctivitis, atopic dermatitis, allergic asthma, atopic eczema) and previous *H. pylori* infection and eradication therapy. All patients underwent upper oesophago-gastro-duodenoscopy and biopsies from the distal and proximal oesophagus, the stomach (at least two biopsies from both antrum and corpus) and the duodenum were taken.

Controls. According to local procedure, serum samples were taken from each patient presenting in the emergency department of the Otto-von-Guericke University Hospital of Magdeburg, as part of the routine medical workup from September 2009 to August 2010 and were stored at -30°C until analysis. *H. pylori* status was determined¹⁸ for 2318 patients and allocated in a database including data on age and sex for each of them. The paired controls used in this study were taken from this group. For best age and sex matching results we were able to set up two match groups (M1 and M2, see also statistical analysis).

Helicobacter pylori serology

Immunoglobulin G (IgG) antibodies against *H. pylori* were determined using an *H. pylori* IgG enzyme-linked immunosorbent assay (ELISA) (catalogue number 601040; Biohit, Rosbach, Germany) according to manufacturer's instructions. Patients with *H. pylori*-specific IgG ≥ 30 enzyme immunounits were classified as *H. pylori* positive.

Histology (patients)

Multiple histology sections (5 mm thick) were obtained from each paraffin embedded biopsy. Sections were stained with H&E, periodic acid-Schiff, and modified Giemsa for *H. pylori* and assessed analogue to the updated Sydney classification.¹⁹

Oesophageal biopsies two from distal (3–5 cm above oesophageal-gastric junction) and two from the proximal oesophagus were stained with haematoxylin-eosin and eosinophils were counted. Eosinophils ≥ 15 per high-power (400 $\times$) field (HPF) in one or more oesophageal biopsy sample was demanded to establish the diagnosis EoE.

Statistical analysis

Age is shown as means and standard deviations and was analysed by an unpaired Student's *t*-test. For each EoE patient, two age- and sex-matched normal controls were randomly selected. We created two control matching groups (M1 and M2) to ensure that controls and cases achieve the highest similarity concerning the variables age and sex.

Distribution of *H. pylori* status is presented as frequencies and comparisons were calculated using Chi-squared test and Fisher's exact test respectively.

For analysis of the association between EoE and *H. pylori* infection, estimated odds ratios (OR) with corresponding 95% confidence interval (CI) are given using an on-line calculator (<http://www.hutchon.net/ConfidOR.htm> and <http://www.hutchon.net/ConfidORnullhypo.htm>).

RESULTS

Mean age of EoE patients was 36.5 years (range 20–72 years), and 81% were male resulting in a male to female ratio of 4.3:1. The majority of patients were Caucasian, 1 patient was originally from India. Median age of EoE patients was 40.93 years, control groups M1 and M2 40.92 years, which represents an age deviation of only 3.7 days.

The majority of EoE patients reported concomitant atopic disorders ($n = 36$, 62%). The most common allergic diathesis was allergic rhinoconjunctivitis ($n = 30$, 52%) followed by atopic family history ($n = 19$, 35%), food allergy ($n = 14$, 24%), atopic dermatitis ($n = 8$, 14%) and allergic asthma ($n = 5$, 9%).

Current *H. pylori* infection: three EoE patients (5.17%) showed a positive *H. pylori* serology. Histological grading according to the Sydney classification revealed two *H. pylori* positive chronic active gastritis one patient remained seropositive for *H. pylori* infection, but histology confirmed successful eradication following therapy. EoE patients with a current *H. pylori* infection ($n = 3$) showed a significant lower prevalence than in the control groups M1 and M2 (Figure 1). Overall, cumulative seroprevalence of *H. pylori* infection (M total = M1 + M2) was 37.9% vs. 5.17% in EoE ($P < 0.0001$) (Figure 1).

Former *H. pylori* infection: five EoE (8.6%) patients reported prior eradication therapy for *H. pylori*. All five EoE patients presented a negative *H. pylori* serology and histology documented a status post-eradication therapy.

In total, differences in *H. pylori* prevalence varied significantly – even when the two EoE groups (current +

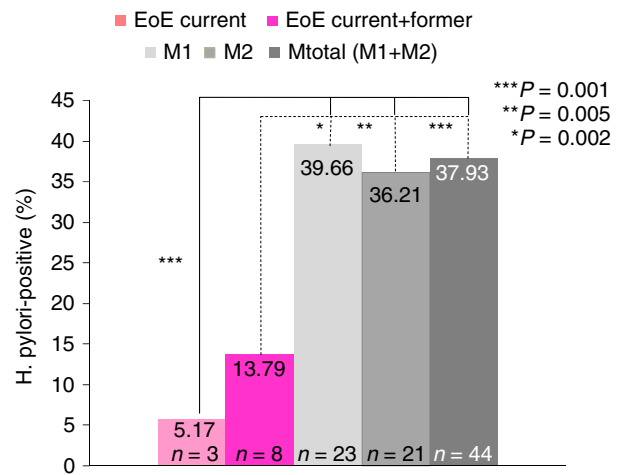


Figure 1 | Proportion of EoE cases (current *Helicobacter pylori* infection), EoE cases (current + former *H. pylori* infection) and control groups (M1, M2 and M total) with positive Anti-*H. pylori* – IgG serology using chi-squared test.

former infection, $n = 8$) are summarised – between cases and controls (EoE vs. M1 $P = 0.002$, EoE vs. M2 $P = 0.005$ and EoE vs. M total $P = 0.001$) (Figure 1).

CI's of *H. pylori* positive EoE and controls strongly suggest these results to be true, with maximum values of the EoE groups range markedly below minimal value of M total and M1 (Figure 2).

Eosinophilic oesophagitis (current and former, $n = 8$) was strongly inversely associated with seroprevalence of *H. pylori* (OR, 0.24, 95% CI: 0.11–0.50).

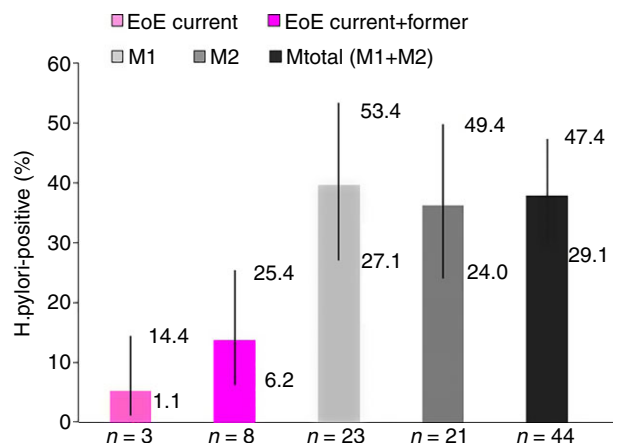


Figure 2 | Confidence intervals of *Helicobacter pylori* positive EoE cases (current *H. pylori* infection), EoE cases (current and former *H. pylori* infection) and control groups (M1, M2, M total).

DISCUSSION

In the present study we made use of a large local *H. pylori* serology database to assess the association between EoE and *H. pylori* infection compared to a well matched control population. We showed a remarkable inversed relationship between *H. pylori* infection and EoE, and the reported OR 0.24 allocates a protective role of *H. pylori* in developing EoE.

We found a low serological and histological prevalence of *H. pylori* in EoE patients compared to our matched controls, which was not due to younger age of EoE cases, because interference of age could be eliminated by almost 1:1 matching conditions (3.7 days age difference).

The control group revealed an overall *H. pylori* seroprevalence of 37.9% which is very close to the estimated current prevalence of anti *H. pylori* IgG (44.4%) in our region (Saxony Anhalt) in Germany and other European countries.^{20, 21} Assessment of previous antibiotic therapies (e.g. former eradication of *H. pylori*) in our control groups was not possible. *H. pylori* serology is accurate in determining prevalence of *H. pylori* infection, but often slow to respond to changing status (e.g. after treatment with antimicrobials). *H. pylori* antibodies disappear in up to 6 months after successful eradication of the infection.²² Because of this, the seroprevalence of *H. pylori* in our control groups might be underestimated, leading to an even more robust significance level regarding inverse association of EoE and *H. pylori* infection.

To date in literature two studies examined the association of *H. pylori* and oesophageal eosinophilia in adults.^{23, 24} Ronkainen *et al.* presented a population based secondary analysis to determine the presence of eosinophils in specimen from the distal oesophagus (Z-line and 2 cm above). They found 48 patients with oesophageal eosinophilia, eight of whom were *H. pylori* positive and in the four patients who were classified as having 'definite' eosinophilic oesophagitis, correlation with *H. pylori* lead to a reported OR of 0.41; suggesting an inverse association of *H. pylori* and oesophageal eosinophilia. However, the diagnosis of EoE requires symptoms of dysphagia, oesophageal eosinophilia which is limited to oesophagus and other causes of oesophageal eosinophilia should be excluded, specifically gastro-oesophageal reflux disease and proton pump inhibitor-responsive oesophageal eosinophilia.¹ Clinical data and oesophageal symptoms were not obtained in this study, instead patients were asked to fill out an abdominal symptom questionnaire. Under these circumstances 'definite' EoE in this study setting was not diagnosed according to the updated consensus recommendation.¹

Furthermore oesophageal eosinophilia might be under-represented, because only two biopsies from the distal oesophagus were considered in this analysis. The study from Dellon *et al.*²⁴ reported an inverse correlation of oesophageal eosinophilia and *H. pylori* infection (OR 0.77) in oesophageal biopsy specimens collected from a US pathology database. This retrospective analysis found that odds of *H. pylori* infection reduced as oesophageal eosinophilia increased (OR 0.52 for >90 Eos/HPF). As clinical data were not available in this study protocol, a distinct statement concerning the association of *H. pylori* and EoE is lacking, but with increasing clinical suspicion for EoE, a trend towards a decreasing *H. pylori* prevalence was found.

A study from Japan investigated the influence of *H. pylori* in patients with eosinophilic gastrointestinal disorders including EoE and eosinophilic gastroenteritis. In this case-control study, 18 EoE patients, each with three age and sex-matched controls were compared using *H. pylori* serology. The reported OR was 0.22 which is comparable to our results.²⁵

A retrospective review of histological biopsy samples in children, using multivariate logistic regression analysis to compare EoE and reference groups (reflux oesophagitis and idiopathic gastritis) found a significant negative relationship between *H. pylori* infection and EoE (adjusted OR = 0.096, 95% CI 0.013–0.72).²⁶ The study cohort was smaller (62 EoE cases, 61 *H. pylori* negative, 1 *H. pylori* positive) in comparison with Dellon's study, but these were 'real' EoE patients diagnosed according to the new clinical and histological expert's recommendations.¹

Interestingly, a study performed in infants found, that *H. pylori* positive children had higher eosinophils per high-power field than *H. pylori* negative ones both in oesophagus and in antrum.²⁷ This study has to be interpreted with caution, because histological features of eosinophilic oesophagitis with >15 Eos/HPF were found only in seven specimens of the oesophagus, the median age of infants was 9 months, and *H. pylori* is nowadays present in fewer than 10% of children under 10 years of age.²⁸

The possible association between EoE and *H. pylori* infection has not adequately been studied in literature and therefore deserves closer attention and further discussion. Prevalence of *H. pylori* infection rapidly decreased during the 20th century in many industrialised countries in comparison to developing countries which is explained by poor hygiene, low socioeconomic conditions and family crowding.²⁹ This observation, plus

the 'hygiene hypothesis' which suggests that the exposure to infectious agents and living in an insanitary environment might have an impact on the formation of our immune system and therefore protect against the development of allergic diseases,³⁰ illustrates the link between *H. pylori* and EoE. The association of EoE with allergies is highly visible¹² and EoE is reported more often in developed countries^{3, 6} with an increasing incidence since the last three decades. Further *H. pylori* infection was found to be inversely related with atopic diseases (asthma, atopic dermatitis, allergic rhinoconjunctivitis)^{16, 31, 32} and therefore it seems reasonable that a similar association with EoE, which is thought to be an allergic condition (asthma of the oesophagus), exists. In addition, there exist data about inverse associations of *H. pylori* and other non-allergic oesophageal diseases (e.g. gastro-oesophageal reflux disease, Barrett's oesophagus and oesophageal adenocarcinoma)³³ rising the question if *H. pylori* provides an 'ecological' or 'microbial ecology' – effect in the microbiom of the stomach.³⁴

Furthermore, it is hypothesised that allergic conditions are on the rise³⁵ because of an impaired balance between Th1 and Th2 type immune response mostly due to high standard of hygiene.³⁰ *H. pylori* infection induces a Th1 response³¹ and Th1 cytokines inhibit Th2-mediated allergic response, which represents the main pathogenetic pathway of EoE.^{13, 36} An imbalance or a skewed Th1/Th2 system because of reduced odds of bacterial infection is resulting in a higher chance of Th2 driven allergic conditions.³⁷ Our statement of lower odds of *H. pylori* in patients with EoE contribute to the above mentioned hypothesis and possible pathophysiological mechanisms involved in EoE. In addition to the well-known Th1/Th2 balance, regulatory immune

cells comprising of various natural or induced subtypes have entered the field of gastro-intestinal inflammation.³⁸ While their role is established for inflammatory bowel disease³⁹ and *H. pylori*- related diseases,⁴⁰ little is known for EoE. In a murine model⁴¹ and adults⁴² as well as children with EoE⁴³, an imbalance or increase in regulatory T cells were described, but pathophysiological relevance and therapeutic consequences of these findings need to be studied further.

AUTHORSHIP

Guarantor of the article: Ulrike von Arnim.

Author contributions: Ulrike von Arnim: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. Thomas Wex: analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. Marlen Messerschmidt: acquisition of data, laboratory analysis of data, data collection and analysis, this manuscript is the basis to her medical thesis. Alexander Link: laboratory analysis of data, data collection and analysis. Stephan Miehke and Marino Venerito: interpretation of data, critical revision of the manuscript for important intellectual content. Peter Malfertheiner: critical revision of the manuscript for important intellectual content, study supervision.

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