ORIGINAL PAPER

Available from: http://www.jgld.ro/wp/archive/y2018/n2/a2
DOI: http://dx.doi.org/10.15403/jgld.2014.1121.272.hpy

Helicobacter Pylori Eradication Therapy is Not Associated with the Onset of Inflammatory Bowel Diseases. A Case-Control Study

Rosa Rosania[1], Ulrike Von Arnim[1], Alexander Link[1], Mirjana Rajilic-Stojanovic[2], Caspar Franck[1], Ali Canbay[1], Peter Malfertheiner[1], Marino Venerito[1]

1) Department of Gastroenterology, Hepatology and Infectious Diseases, Otto-von-Guericke-University Magdeburg, Magdeburg, Germany
2) Department of Biochemical Engineering & Biotechnology, University of Belgrade, Belgrade, Serbia

Address for correspondence:
Marino Venerito
Otto-von-Guericke University Hospital,
Magdeburg,
Germany
m.venerito@med.ovgu.de

Received: 20.03.2018
Accepted: 29.05.2018

ABSTRACT

Background & Aims: A negative association between *H. pylori* and inflammatory bowel disease (IBD) has been previously reported. There were also case reports suggesting a new onset of IBD 6-12 months after *H. pylori* eradication therapy. In a case-control study we investigated whether previous *H. pylori* eradication therapy was associated with the risk of developing IBD.
Methods: IBD outpatients with both Crohn´s disease (CD) and ulcerative colitis (UC) were enrolled. Age- and sex-matched blood donors served as controls in a 1:2 fashion. Information on demographics, medical history, previous *H. pylori* infection and eradication therapy was recorded. Serum samples for *H. pylori* serology testing (anti-*H. pylori*-IgG and anti-CagA-IgG) were obtained. Controls that received *H. pylori* eradication therapy during the 12 months previous to enrollment were excluded.
Results: Overall, 127 IBD patients (CD N= 90; UC N= 37) and 254 controls were enrolled. The prevalence of *H. pylori* infection (positive *H. pylori* serology and/or previous eradication) in IBD patients and controls was 11% and 23%, respectively (OR 0.4, 95% CI 0.21-0.74, p<0.003). Four patients (3%) developed IBD (3 MC and 1 CU) after receiving successful *H. pylori* eradication (latency 6-12 months). The rate of previous *H. pylori* eradication therapy in patents who successively developed IBD was lower but not statistically different from that observed in the control group (OR 0.43, 95% CI 0.14-1.29, p=0.16).
Conclusions: In our study previous *H. pylori* eradication therapy was not associated with the onset of IBD. Whether in a subgroup of patients, *H. pylori* eradication therapy may trigger a latent IBD, cannot be excluded.

Key words: Crohn´s disease – ulcerative colitis – *Helicobacter pylori* – inflammatory bowel disease.

Abbreviations: CD: Crohn's disease; EHH: entero-hepatic Helicobacter; IBD: Inflammatory bowel disease; IBDU: unclassified IBD; MALT-lymphoma: mucosa-associated lymphoid tissue lymphoma; UC: ulcerative colitis.

INTRODUCTION

Inflammatory bowel disease (IBD) is a group of chronic, relapsing, inflammatory disorders of the gastrointestinal tract. Ulcerative colitis (UC) and Crohn's disease (CD) are the principal types of IBD [1]. According to the most widely accepted hypothesis, environmental factors may trigger IBD onset in individuals with genetic susceptibility by altering the intestinal mucosal barrier and the healthy balance of the gut microbiota, resulting in an aberrant immune response of the gut [2]. Recently, an association of IBD with changes in gut microbiota composition has been reported [3], but no mechanistic explanation for this association has been provided [4].

Helicobacter species are gram-negative curved or spiral bacteria. Depending on the site of the gastrointestinal tract colonized, Helicobacter species are divided into entero-hepatic Helicobacters (EHH) and gastric Helicobacters [5]. Different studies have investigated the association between IBD and Helicobacter species. In case-control studies, both UC [6] and CD [7] were associated with the presence of EHH species DNA in intestinal biopsies.

Helicobacter species dominate the microbiota community of the gastric mucosa and influence duodenal and oral communities [8]. *Helicobacter pylori* (*H. pylori)* is typically acquired during early childhood and causes a chronic active gastritis in the infected subject. A subset of subjects with *H.*

pylori gastritis may develop peptic ulcer disease, gastric cancer or MALT-lymphoma. Various studies have consistently shown a low *H. pylori* seroprevalence in patients with IBD, suggesting a protective role of this infection for the development of IBD [9]. Recently, IBD onset after successful *H. pylori* eradication therapy has been reported in three clinical cases [10-12]. Accordingly, the hypothesis that profound changes of the intestinal microbiota induced by eradication therapy (i.e. a combination of two antibiotics and a proton pump inhibitor) may trigger IBD appears attractive. On the other hand, the loss of *H. pylori* induced immune response may play a role in increasing the susceptibility to develop IBD as well. These aspects may lead to anxiety in patients and even induce the physician to refrain from prescribing appropriate *H. pylori* eradication therapy. The aim of the present study was to investigate whether previous *H. pylori* eradication therapy may be associated with an increased risk of developing IBD.

METHODS

Study design and study population

The primary aim of the present study was to evaluate whether previous *H. pylori* eradication therapy may represent a risk factor for developing IBD. For answering this question we chose a case-control study design. The prevalence of previous *H. pylori* eradication therapy - the putative risk factor - was studied in IBD patients (cases) and controls.

Patients with IBD were enrolled between December 2016 and May 2017 at the outpatient Department of Gastroenterology, Hepatology and Infectious Diseases at the Otto-von-Guericke University (Magdeburg, Germany). In our clinic, biological therapy for IBD patients is scheduled on Fridays (ca. 25 patients per day). To simplify the recruitment, only IBD patients receiving a biological therapy (i.e. Infliximab, Vedolizumab, Ustekinumab) were enrolled.

Sex- and age-matched (± 5 years) controls were selected from a cohort of 516 consecutive healthy blood donors that were enrolled between May and June 2016 in a prospective epidemiological study on the seroprevalence of *H. pylori* infection in Saxony-Anhalt [13].

Patients and controls were interviewed using the same structured questionnaire that comprised information on demographics, number of siblings, medical history and previous *H. pylori* eradication therapy. Study participants with previous *H. pylori* eradication therapy provided records of the eradication including the regimen used for eradication therapy and the test performed to confirm successful eradication.

In patients with IBD disease, onset was also recorded. IBD activity was clinically evaluated by the Mayo Clinic score and the Harvey-Bradshaw Severity Index for patients with UC and CD, respectively [14]. Enrolled patients received a physical examination and medical history was collected. After insertion of a peripheral venous line for biological therapy, blood samples for routine laboratory tests and *H. pylori* serology were obtained.

Inclusion criteria for IBD patients were the presence of a confirmed IBD and a written informed consent. Patients with missing written informed consent were excluded from the analysis.

Controls that received *H. pylori* eradication therapy less than 12 months before enrollment were excluded from matching, as cases of new-onset IBD reported in the literature were diagnosed 6-12 months after eradication therapy.

Study participants who were seropositive for *H. pylori* infection and/or self-reported previous *H. pylori* infection and successful eradication therapy were considered *H. pylori*-positive. We chose this definition to include the largest number of patients with current or past *H. pylori* infection.

The study was conducted according to the Declaration of Helsinki [15] and approved by the Ethics Committee of the Otto-von-Guericke University Hospital of Magdeburg (protocol number 80/11).

H. pylori serology

Serum samples of patients and controls were analyzed using an enzyme-linked immunosorbent assay for the presence of immunoglobulin G (IgG) both against *H. pylori* in general and specific for the CagA antigen of *H. pylori* as described previously [16]. Subjects with specific anti-*H. pylori* titer >30 EIU and/or anti-CagA titer >6.25 U/mL were classified as *H. pylori* positive.

Statistical analysis

Sample size calculation with a power of 80% and a desired significance level of 5% was performed with an online calculator (http://osse.bii.a-star.edu.sg/calculation1.php). Given that the eradication rate in the cohort of 516 blood donors was of 5.4% and the number of cases eradicated before IBD onset unknown, the sample size needed for cases and controls in a 1:2 fashion was 105 and 210, respectively.

Distribution of the demographic characteristics and related factors were compared by the Mann–Whitney U test for continuous data and by Fisher´s exact test for categorical variables, which were performed using an online calculator (https://www.graphpad.com/quickcalcs/ttest1.cfm). A statistical p value of 0.05 (two sided) was considered significant for all comparisons. For the analysis of the association between *H. pylori* infection and IBD onset, estimated odds ratios (OR) with corresponding 95% confidence intervals (CIs) were calculated (https://www.easycalculation.com/statistics/odds-ratio.php).

RESULTS

Epidemiological data

Overall, 127 consecutive patients with IBD (71 M: 56 F, median age 42, mean age 40.12±12.01 years, range 18-72 years) were prospectively enrolled between December 2016 and May 2017. A detailed description of demographics, medical therapy and clinical score of IBD patients at enrollment is reported in Table I. Ninety of them had CD (34 M: 56 F, mean age 41.5±12.02 years, range 18-72 years), 37 had UC (22M: 15 F, mean age 42±11.98 years, range 18-67 years) and none had unclassified IBD (IBDU). Fifteen IBD patients (10 CD and 5 UC) had a mild disease, defined by a Mayo Clinic score of 2 to 5 points and a Harvey-Bradshaw Severity Index of 6 or 7 points. All other IBD patients were in clinical remission (Mayo Clinic score of less than 2 points and a Harvey-Bradshaw Severity Index lower than 5).

Table I. Demographics, medical therapy and clinical scores in patients with inflammatory bowel diseases (IBD) at study enrollment.

	CD (%)	UC (%)
Patients (N)	90	37
Male/female	34/56	22/15
Mean age, SD (years), (range)	41.5±12 (18-72)	40±11.9 (18-67)
Mayo Clinic score[1]: mild colitis/ remission	-	5/32
HBSI[2]: mild colitis/remission	10/80	-
Biological therapy ±5-ASA		
Infliximab ± 5-ASA	36 (40)	15 (41)
Vedolizumab ± 5-ASA	10 (11)	8 (22)
Ustekinumab ± 5-ASA	5 (6)	1 (3)
Thiopurine[3] + biological therapy ± 5-ASA		
Thiopurine +Infliximab ± 5-ASA	23 (6)	8 (22)
Thiopurine +Vedolizumab ± 5-ASA	13 (14)	4 (11)
Thiopurine +Ustekinumab ± 5-ASA	3 (3)	1 (3)

CD: Crohn's disease, UC: ulcerative colitis; [1] Mayo Clinic score: remission defined as a score < 2 points, mild disease defined as a score of 2 to 5 points; [2]HBSI: Harvey-Bradshaw Severity Index, remission defined as score ≤ 5, mild disease defined as a score of 6 to 7 points; [3] Thiopurine: Azathioprine or 6-mercaptopurine

Sex- and age matched blood donors (N=254 median age 41, mean age 41 ± 12.4 years, range 18-74 years) served as controls. The descriptive characteristics of cases and controls are shown in Table II. All patients and controls were German, living in Magdeburg or its neighborhood, in the constituent state of Saxony-Anhalt. No differences were observed in the number of siblings between IBD patients and controls. In the subgroup analysis comparing UC and CD there were no differences with respect to sex, age and number of siblings (Table III).

We further performed a subgroup analysis comparing both CD and UC patients with sex- and age-matched controls. In either sub-analyses of CD or UC patients no differences were found with respect to the number of siblings compared to controls (Table IV and V, respectively).

Previous *H. pylori* eradication

The rate of previous *H. pylori* eradication therapy in patients who thereafter developed an IBD was lower but not statistically different from that observed in the control group (3% and 7%, respectively, OR 0.43, 95% CI 0.14-1.29, p=0.16).

Only 4 out of 127 patients developed an IBD (3 CD and 1 UC) after *H. pylori* eradication therapy. Detailed records of these four patients are reported in Table VI. Indications for *H. pylori* testing and eradication therapy previously to IBD onset were epigastric pain (N=2), bloating (N=1) and heartburn (N=1). In three out of four patients *H. pylori* gastritis was diagnosed by esophagogastroduodenoscopy with biopsies. In one patient the general practitioner made the diagnosis of *H. pylori* infection by serology only (not in line with guidelines). In all four patients, eradication therapy was prescribed by their general practitioner. The latency between *H. pylori* eradication therapy and IBD onset was of 6 to 12 months.

IBD patients and controls with previous *H. pylori* infection were eradicated according to the current German [17] and European [18, 19] guidelines and to the local clarithromycin resistance rate (less than 15%) [20]. In particular, all controls and all but two IBD patients were eradicated before 2016 and received a clarithromycin-based triple therapy for 7 days, whereas two IBD patients received eradication in 2016 and 2017 with a 14-day clarithromycin-based triple therapy and a 10-day quadruple therapy with Pylera® and omeprazole, respectively.

Successful eradication was documented by ^{13}C-urea breath test or *H. pylori* stool antigen test in all study participants.

T**able II**. Comparison of demographics data, *H. pylori* serology and history of *H. pylori* eradication therapy in patients with inflammatory bowel diseases (IBD) and controls.

	IBD (127)	Controls (254)	p[1]	OR (CI 95%)[2]
Male/Female	71/56	132/122	0.5	
Mean age, SD (years)	42 ±12.0	41±12.4	0.5	
Siblings (%)				
No Siblings	24(19)	50 (20)	0.89	0.95 (0.55-1.63)
< 3	82(65)	166 (65)	0.9	0.96 (0.61-1.5)
≥ 3	21(17)	38 (15)	0.88	1.06 (0.58- 1.91)
H. pylori positive (%)[a]	10(8)	63 (25)	0.0001[x]	0.25 (0.12-0.52)
H. pylori CagA positive[b]	6 (5)	31 (12)	0.02[x]	0.35 (0.14-0.87)
H. pylori positive IgG and CagA	2 (2)	23 (9)	0.003[x]	0.16 (0.03-0.69)
H. pylori positive IgG and/or CagA	14 (11)	60 (24)	0.003[x]	0.4 (0.21-0.74)
H. pylori positive IgG and/or CagA and/or previous *H. pylori* eradication (%)[c]	21 (17)	73 (29)	0.01*	0.4 (0.28-0.84)
Previous H. pylori eradication before IBD onset (%)	4 (3)	18 (7)	0.16	0.43 (0.14-1.29)

[a] anti- *H. pylori* IgG titer >30 EIU; [b]: anti-CagA titer >6.25 U/mL; [c] defined as positive anti- *H. pylori* IgG or positive anti-CagA or positive medical history for *H.pylori* eradication; * p< 0.05, [1] Mann–Whitney U test for continuous data and Fisher´s exact test for categorical variables; [2] odds ratios (OR) with corresponding 95% confidence intervals.

Table III. Comparison of demographics data, *H. pylori* serology and history of *H. pylori* eradication therapy in patients with Crohn´s disease (CD) and ulcerative colitis (UC).

	CD (90)	UC (37)	p[1]	OR (CI 95%)[2]
Male/female	34/56	22/15	0.3	
Mean age, SD (years)	41.5±12	40±11.9	0.4	
Siblings (%)				
No siblings	16 (18)	8 (22)	0.62	0.78 (0.30-2.02)
< 3	62 (9)	25 (68)	1	1.06 (0.46-2.41)
≥ 3	12 (13)	4 (1)	0.77	1.62 (0.38- 4.22)
H. pylori positive (%)[a]	8 (9)	2 (5)	0.72	1.70 (0.34-8.45)
H. pylori CagA positive[b]	3 (3)	3 (8)	0.35	0.39 (0.07-2.03)
H. pylori positive IgG and CagA	1 (1)	1 (3)	0.49	0.40 (0.02-6.64)
H. pylori positive IgG and/or CagA	11 (12)	4 (11)	1	1.14 (0.34-3.86)
H. pylori positive IgG and/or CagA and/or previous eradication therapy	17 (19)	5 (4)	0.6	1.4 (0.5-.4.3)
H. pylori eradication before IBD onset (%)	3 (3)	1 (3)	1	1.24 (0.12-12.33)

[a] anti- *H. pylori* IgG titer >30 EIU; [b] anti-CagA titer >6.25 U/mL; * p< 0.05; [1] Student *t*-test for continuous data and Fisher´s exact test for categorical variables; [2]odds ratios (OR) with corresponding 95% confidence intervals.

***H. pylori* status**

Overall, 11% (14 out of 127) patients with IBD had a positive serology for *H. pylori*. Increased titers of anti-*H. pylori*-IgG, anti-CagA-IgG or both were observed in 10, 6 and 2 patients, respectively (Table I). Twenty-one out of 127 IBD patients (7%) and 73/254 controls (29%) were *H. pylori*-positive (positive *H. pylori* serology and/or previous eradication therapy) (OR 0.4, 95% CI 0.28-0.84, p=0.01).

An inverse association between *H. pylori* infection and IBD (OR 0.4, 95% CI (0.21 to 0.74), p<0.003) was observed.

In the subgroups analysis of CD patients, a negative association with both *H. pylori* antibodies (OR 0.33, 95% CI 0.14-0.74, p=0.004) and with CagA IgG (OR 0.29, 95% CI 0.08-1.01, p<0.005) was found (Table IV). In addition, in the subgroup analysis of UC patients a negative association between IgG against *H. pylori* and UC (OR 0.4, 95% CI 0.19 to 0.82, p<0.01) was found. However, no association was observed between CagA seropositivity and UC (OR 0.72, 95% CI 0.18-2.92, p= 0.74, Table V).

DISCUSSION

In our study IBD onset was not associated with a previous *H. pylori* eradication therapy. However, four of our IBD patients received *H. pylori* eradication therapy prior to definitive IBD diagnosis. The hypothesis that profound changes of gut microbiota composition induced by *H. pylori* eradication therapy (two antibiotics plus a PPI) may contribute, in a subset of individuals and under certain circumstances, to the development of IBD is fascinating. Metagenomic studies demonstrated an uneven recovery of the human gut microbiome after treatment with antibiotics

Table IV. Comparison of demographic data, *H. pylori* serology and history of *H. pylori* eradication therapy in patients with Crohn´s disease (CD) and controls.

	CD (90)	Controls (180)	p[1]	OR (CI 95%)[2]
Male/female	34/56	79/101	0.3	
Mean age, SD (years)	41.5±12	38.3±11.9	0.4	
Siblings (%)				
No siblings	16 (18)	39 (22)	0.52	0.78 (0.40-1.49)
< 3	62 (9)	117 (65)	0.58	1.19 (0.69-2.04)
≥ 3	12 (13)	24 (13)	1	1 (0.47-2.10)
H. pylori positive (%)[a]	8 (9)	43 (24)	0.004*	0.33 (0.14-0.74)
H. pylori CagA positive[b]	3 (3)	19 (10)	0.084	0.29 (0.08-1.01)
*H. pylori*positive IgG and CagA	1 (1)	18 (1)	0.009*	0.10 (0.01- 0.81)
H. pylori positive IgG and/or CagA	11 (12)	46 (6)	0.01*	0.4 (0.19-0.82)
H. pylori positive IgG and/or CagA and/ or previous eradication therapy[c]	17 (19)	42 (23)	0.4	0.7 (0.3-1.3)

[a] anti- *H. pylori* IgG titer >30 EIU; [b] anti-CagA titer >6.25 U/mL; * p< 0.05; [1] Student *t*-test for continuous data and Fisher´s exact test for categorical variables; [2] odds ratios (OR) with corresponding 95% confidence intervals.

Table V. Comparison of demographic data, *H. pylori* serology and history of *H. pylori* eradication therapy in patients with ulcerative colitis (UC) and controls

	UC (37)	Controls (74)	p[1]	OR (CI 95%)[2]
Male/female	22/15	44/30	1	
Mean age, SD (years)	40±11.9	42.8±12.0	0.6	
Siblings (%)				
No siblings	8 (22)	13 (18)	0.61	1.29 (0.48-3.46)
< 3	25 (68)	47 (4)	0.83	1.19 (0.51-2.75)
≥ 3	4 (1)	14 (19)	0.41	0.51 (0.15-1.7)
H. pylori positive (%)[a]	2 (5)	17 (23)	0.03*	0.19 (0.04- 0.87)
H. pylori CagA positive[b]	3 (8)	8 (11)	0.74	0.72 (0.18-2.92)
H. pylori positive IgG and CagA	1(3)	6 (8)	0.42	0.31 (0.03-2.71)
H*H. pylori* positive IgG and/or CagA	4 (11)	19 (26)	0.08	0.35 (0.1-1.12)
H. pylori positive IgG and/or CagA and/or previous eradication therapy[c]	5 (4)	20 (27)	0.1	0.4 (0.1-1.2)

[a] anti- H. pylori IgG titer >30 EIU; [b] anti-CagA titer >6.25 U/mL; * p< 0.05, [1] Mann–Whitney U test for continuous data and Fisher´s exact test for categorical variables; [2] odds ratios (OR) with corresponding 95% confidence intervals.

[21-23]. Furthermore, in a subset of subjects with lower initial microbiome diversity, recovery of gut microbiome 3 months after antibiotic therapy was characterized by enrichment in opportunistic pathogens [24].

In line with the 3 case reports available in the literature, the time frame for the development of IBD after eradication therapy was 6-12 months also in our four patients. This finding was also consistent with the results of a population-based case-control study that used the Rochester Epidemiology Project of Olmsted County (Minnesota) [25]. In this study the use of antibiotics was associated with an increased risk of developing both new-onset CD and UC and the risk was highest in the first year after antibiotic intake. One may speculate that "predisposed" subjects with lower initial microbiome diversity who receive antibiotic therapy may require at least 6-12 months for developing a clinically evident IBD. Thus, assessing prospectively microbiota prior and subsequent to *H. pylori* eradication therapy might be helpful for understanding the role of microbiota in relation to IBD onset.

The regimen used for *H. pylori* eradication therapy may also play a role for the hypothesized IBD risk. In particular, all the reported IBD cases developed following a clarithromycin-based triple therapy, whereas no cases of new-onset IBD have been described after quadruple bismuth-based eradication therapy. Indeed, at least for what metronidazole and the risk of IBD concerns, available data are inconsistent [26, 27].

The loss of *H. pylori* induced immune response may play a role in increasing the susceptibility to develop IBD as well. In an animal model of Mongolian gerbils [28], *H. pylori* infection induced a microbiota shift that became exclusively overt in the

Table VI. Characteristics of the 4 patients that developed inflammatory bowel disease (IBD) after *H. pylor*i eradication therapy

	Patient 1	Patient 2	Patient 3	Patient 4
Gender	female	male	female	male
Age at diagnosis of *H. pylori* infection (years)	43	34	41	33
Symptoms*	epigastric pain	epigastric pain	bloating	heartburn
H. pylori testing	EGD	EGD	EGD	Serology
Histological findings	chronic-active gastritis	chronic-active gastritis	chronic-active gastritis	-
H. pylori eradication therapy	7-day PAC	7-day PMC	7-day PAC	7-day PAC
Successfully eradication	yes	yes	yes	yes
IBD diagnosis	CD	UC	CD	CD
IBD localization	ileum	left colon	colon	ileum
Latency between *H. pylori* eradication and IBD Diagnosis	6 months	8 months	12 months	12 months
Biological therapy	Thiopurine[1] +Infliximab	Infliximab	Thiopurine[1] +Infliximab	Infliximab

* before the *H. pylori* diagnosis; EGD: esophagogastroduodenoscopy; PAC: Clarithromycin 500 mg bid, Amoxicillin 1g bid and Pantoprazole 40 mg bid; PMC: Clarithromycin 500 mg bid, Metronidazol 400 bid and Pantoprazole 40 mg bid; UC: ulcerative colitis; CD: Crohn´s disease; [1] Thiopurine: Azathioprine or 6-mercaptopurine.

large intestinal tract although no histopathological changes of the intestinal mucosa were detected. Hence, loss of *H. pylori* induced alteration of the stomach might trigger large intestinal microbiota changes predisposing to the development of IBD.

The rate of patients receiving *H. pylori* eradication therapy before IBD onset in our study was very low and less than half of the rate observed in the control group. Thus, on a population scale, the benefit deriving from the cure of *H. pylori* infection overwhelms the hypothetical risk of developing an IBD.

In line with previous studies [9], we found a negative inverse association between *H. pylori* infection and IBD. Epidemiological studies in human populations have documented an inverse association between *H. pylori* infection and the risk of developing allergic diseases as well [29, 30]. The postulated protective effect of *H. pylori* infection against allergic diseases and possibly IBD may be mediated by regulatory T cells. Indeed, *H. pylori* is typically acquired during early childhood and the immunological tolerance towards *H. pylori* is driven by inducible regulatory T cells which are also required for the suppression of allergen-specific immune responses [31-33].

Recently, Lord et al. [34] reported that the inverse association of *H. pylori* with IBD was restricted to the CagA-positive strain and observed a protective effect of CagA only on CD. In our study, a negative inverse association between CagA status and IBD could not be confirmed, possibly as a consequence of the smaller number of IBD patients included.

All our IBD patients were under a biological therapy. It is unclear whether the negative association of *H. pylori* seroprevalence and IBD is confounded by other variables, such as immunosuppressive therapy or environmental factors. This aspect is currently under scrutiny at our site.

A strength of our study was the selection of controls from a well-characterized cohort of blood donors from the same region (Saxony-Anhalt, Germany) as the IBD group and tested both for the anti-*H. pylori* IgG in general and specific for the CagA antigen. In addition, in both IBD and control groups, information on previous *H. pylori* treatment was retrieved.

A limitation of the present study is the missing data on prior antibiotic use. However, this information is not reliable when collected on a patient´s history basis and we had no access to the prescription data of physicians who took care of our patients prior to IBD diagnosis. Whether previous antibiotic treatments may have increased the susceptibility of our patients to develop IBD after *H. pylori* eradication therapy cannot be excluded.

Based on previous case-reports and population-based studies we excluded controls who received eradication therapy less than 1 year before enrollment. As an increased risk of developing IBD may persist till up to 5 years after antibiotic treatment, the development of an IBD in our controls later on cannot be excluded [25, 26].

CONCLUSION

In our study population, previous *H. pylori* eradication therapy was not associated with an increased risk of developing IBD. Our data should reassure physicians when prescribing *H. pylori* eradication therapy. Further studies are warranted to address the question as to whether *H. pylori* eradication therapy (the loss of *H. pylori* induced immune response or the combination of two antibiotics and a proton pump inhibitor) may trigger IBD development in a specific subgroup of patients.

Conflicts of interest: M.V. has served as a speaker, a consultant or an advisory board member for Lilly, Bristol-Myers Squibb, Merck Serono, Bayer vital, Amgen, Nordic Pharma, Ipsen and Celgene. P.M. has served as a speaker for Abbott Laboratories, Allergan, Alfasigma, Bayer, Biocodex, AstraZeneca, Falk Pharma and Takeda. R.R. has served as a speaker for AbbVie. U.V.A. has served as a speaker, a consultant or an advisory board member for Falk Foundation, Merck Sharp Dohme, Abbvie, Takeda, Reckit Benckiser, Janssen, Vifor Pharma. A.L., A.C., F.C. and M.R.S. have nothing to declare.

Authors' contributions: M.V., R.R. and M.R.S. designed the research study. M.V., R.R., C.F. and A.L. collected and analyzed the data. R.R., A.C., P.M., A.L., M.R.S. and M.V. participated in drafting the article or revising it critically for important intellectual content. All authors approved the final version of the article, including the authorship list.

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