European Journal of Epidemiology **17**: 823–827, 2001.

Helicobacter pylori colonization and diarrhoeal illness: Results of a population-based cross-sectional study in adults

Günter Bode[1,2], Dietrich Rothenbacher[2] & Hermann Brenner[2]

[1]*Department of Epidemiology, University of Ulm, Ulm;* [2]*Department of Epidemiology, German Centre for Research on Ageing, University of Heidelberg, Heidelberg, Germany*

Accepted in revised form 12 February 2002

Abstract. It has been suggested that *Helicobacter pylori* colonization may protect against diarrhoeagenic gastrointestinal infections. The aim of this analysis was to investigate the association between *H. pylori* infection and the frequency of diarrhoeal episodes among adults. *Helicobacter pylori* infection status was determined by ^{13}C-urea breath test. Overall, 784 adults (mean age: 48.7 ± 17.7; range 18–85 years) who participated in two epidemiological studies were included in the analysis. Overall *H. pylori* prevalence was 25.5%. Episodes of diarrhoea within prior 3 months were less often reported for *H. pylori* infected subjects compared with *H. pylori* negative subjects (40.2 vs. 51.6%, $p = 0.016$). Compared to *H. pylori* negative subjects the odds ratio (OR) for the occurrence of diarrhoea within the prior 3 months was 0.63 (95% CI: 0.45–0.87) for *H. pylori* infected subjects. After adjustment for covariates the OR was 0.67 (95% CI: 0.47–0.95). These results support the hypothesis that colonization with *H. pylori* may protect from gastrointestinal infections that cause diarrhoea.

Key words: Adults, Diarrhoea, *Helicobacter pylori*

Introduction

Helicobacter pylori has been identified as a causative agent of gastroduodenal pathology such as gastritis, peptic ulcer, and gastric adenocarcinoma [1, 2]. Infection with *H. pylori* causes a mucosal inflammation and a vigorous immune response of the host, however, without resulting eradication. Recently, it has been proposed that *H. pylori* benefits from the tissue alteration caused by the immune response keeping a balance between pro- and anti-inflammatory immune responses [3].

In contrast to the well-known harmful effects of *H. pylori* infection, potential beneficial effects of this agent have only recently been addressed [4–6], and the factors and mechanisms are yet speculative. Nevertheless, one study reported that *H. pylori* infected subjects had a significantly stronger specific IgA-antibody response in the gastric antrum after oral cholera vaccination compared with non-infected subjects [3]. Furthermore, one recent study showed that *H. pylori* is able to synthesize peptides with antibacterial activity, against which *H. pylori* itself is resistant [7]. These observations support the concept that *H. pylori* developed mechanisms to persist within its host over a lifelong period thereby preventing other faster growing bacteria from colonizing the gastric mucosa and other parts of the gastrointestinal tract.

If this provocative hypothesis turns out to be true, then *H. pylori* infected subjects should suffer from less gastrointestinal infections and as a consequence from less diarrhoeal diseases than subjects without *H. pylori* infection. In fact, for the first time we could recently show a clear inverse relationship between gastric colonization of *H. pylori* and diarrhoeal illnesses in children [8].

In the present study, we compared the occurrence of self-reported diarrhoea episodes within prior 3 months in relation to *H. pylori* infection status in asymptomatic adults.

Participants and methods

Study design and study population

We conducted two population-based studies in Ulm, a city located in the South of Germany with about 120,000 inhabitants in the year 1996 to determine prevalence of and risk factors for *H. pylori* infection [9, 10].

The first study (study I) was a cross-sectional study among the employees of a health insurance company and their household members aged 5–69 years. The employees were recruited at the office of the insurance company during working hours (response rate

76.5%). The household members had the opportunity to participate at their home.

The second study (study II) was a cross-sectional study among participants aged 50–85 years of a general education programme at the University of Ulm (response rate 69.0%). The current analysis includes participants aged 18–85 from the two studies. To exclude the possibility of false negative *H. pylori* test results, subjects under current antibiotic medication were excluded.

Both studies were approved by the Ethics board of the University of Ulm and informed consent was obtained from each participant.

Data collection

In both studies, current *H. pylori* infection status was determined by ^{13}C-urea breath test (^{13}C-UBT). An initial breath sample and, after administration of 75 mg non-radioactive labelled ^{13}C-urea (Mass Trace, Woburn, MA, USA) in 200 ml of apple juice (pH 2.2–2.4), a 30 min breath sample was collected. Breath samples were analysed with an isotope selective non-dispersive infrared spectrometer (NDIRS; Wagner Analytical Systems, Bremen, Germany). A change of the $^{13}CO_2/^{12}CO_2$ ratio over baseline of more than 5‰ was considered positive [11].

Information about family demographics, socioeconomic status, housing and living conditions and medical history including abdominal symptoms were obtained by a standardized questionnaire in both studies. Frequency of diarrhoea within the prior 3 months was ascertained on a four level ordinal scale (never, rarely, sometimes, often). To evaluate the potential for reporting bias, we also assessed reported history of flatulence, an abdominal symptom not believed to be related to *H. pylori* status, according to *H. pylori* infection. Frequency of flatulence within prior 3 months was ascertained in the same way as frequency of diarrhoea. Questionnaire data were checked for completeness and plausibility during the examination by trained research assistants.

Statistical analysis

We first described the study population of the pooled sample according to sociodemographic characteristics and then calculated a Mantel–Haenszel χ^2 statistic for the association of the infection status with the frequency of diarrhoea after adjustment for age. Then, multiple logistic regression was used to estimate crude and adjusted odds ratios (OR) with 95% confidence intervals (95% CI) for reported frequency of diarrhoea within the prior 3 months (rarely, sometimes or often vs. never) according to *H. pylori* infection status defined by ^{13}C-UBT (yes/no). The following covariates were adjusted for: age, sex, education ($\leq$9, >9 years) and history of antibiotic treatment within past 3 months (yes/no).

Results

Characteristics of the study population

In total, 784 adults (mean age: 48.7 ± 17.7; range 18–85 years) were included in this analysis (449 participants of study I; 335 participants of study II).

Table 1 shows basic characteristics of the study population. 59.4% of participants were females, and 65.8% were married. Overall, 25.5% of study participants were infected with *H. pylori*.

History of diarrhoea

Information on diarrhoea was missing in 11 subjects. Therefore, 773 subjects were included in the present analysis. Overall, 47.5% of the subjects reported diarrhoea at some point within the prior 3 months. In most of these subjects (29.9%) occurrence of diarrhoea was reported to be rare, whereas only 15.4 and 2.2% of subjects reported that they had suffered from diarrhoea sometimes or often, respectively.

Helicobacter pylori infection and history of diarrhoea

The association of *H. pylori* infection with the frequency of diarrhoea is shown in Table 2. *Helicobacter pylori*-positive subjects reported occurrence of diarrhoea less often than *H. pylori*-negative subjects ($p < 0.016$, after adjustment for age). This pattern

Table 1. Sociodemographic characteristics of study population

	N	(%)
Study I	449	55.2
Study II	335	44.8
Total	784	100
Sex		
Male	318	40.6
Female	466	59.4
Age (years)		
18–39	271	34.6
40–59	243	31
>60	270	34.4
School education		
⩽9 years/in training	221	28.2
10–11 years	325	41.5
⩾12 years	237	30.3
Unknown	1	
Family situation		
Single	174	22.2
Married	516	65.8
Divorced/widowed	93	11.9
Unknown	1	
H. pylori infection		
Yes	200	25.5

Table 2. Frequency of diarrhoea according to *H. pylori* infection

Age (years)	*H. pylori* infection	N	Diarrhoea Frequency during the last 3 months (%)				*p*-Value
			Never	Rarely	Sometimes	Often	
18–39	Negative	244	45.9	34.9	16.4	2.9	
	Positive	24	50	29.2	20.8	0	
40–59	Negative	157	47.1	35	15.3	2.6	
	Positive	80	60	30	8.8	1.3	
>60	Negative	175	53.1	26.3	17.7	2.9	
	Positive	93	62.4	22.6	14	1.1	
All	Negative	576	48.4	32.3	16.5	2.8	
	Positive	197	59.8	26.4	12.7	1	0.016[b]
	Overall	773[a]	52.5	29.9	15.4	2.3	

[a] Information on diarrhoea was missing in 11 subjects.
[b] *p*-Value (Mantel–Haenszel χ^2 test) for association of infection status with diarrhoea after adjustment for age.

was seen in all age groups, but the association of *H. pylori* infection with diarrhoea was most prominent in the age category 40–59 years.

The crude OR for the occurrence of diarrhoea within the prior 3 months (rarely, sometimes or often vs. never) was 0.63 (95% CI: 0.45–0.87) for *H. pylori*-positive subjects compared to *H. pylori*-negative subjects (Table 3). The OR for diarrhoea changed to 0.69 (95% CI: 0.49–0.97) after adjustment for age. After further adjustment for other covariates (sex, education, history of antibiotic treatment within past 3 months), the OR was 0.67 (95% CI: 0.47–0.95).

In study II, participants were also asked for history of severe diarrhoea in their childhood. We observed the same pattern (severe diarrhoea in *H. pylori* infected subjects reported less often than in uninfected subjects), although this association was not statistically significant given the limited power to address this question in this subsample (data not shown).

The analysis of the data concerning flatulence shows that the crude OR was 1.06 (95% CI: 0.75–1.49) for *H. pylori*-positive subjects (Table 4). The OR for flatulence remained essentially unchanged after adjustment for age and the other covariates (1.08, 95% CI: 0.75–1.55).

Table 3. Crude and adjusted OR with 95% CI for reported occurrence of diarrhoea within past 3 months (rarely, sometimes or often vs. never) according to *H. pylori* infection

H. pylori infection	Crude OR (95% CI)	Partly adjusted OR (95% CI)[a]	Fully adjusted OR (95% CI)[b]
No	1[reference]	1[reference]	1[reference]
Yes	0.63 (0.45–0.87)	0.69 (0.49–0.97)	0.67 (0.47–0.95)

[a] Adjusted for age.
[b] Adjusted for age, sex, education, history of antibiotic medication within prior 3 months.

Table 4. Crude and adjusted OR with 95% CI for reported occurrence of flatulence within past 3 months (rarely, sometimes or often vs. never) according to *H. pylori* infection

H. pylori infection	Crude OR (95% CI)	Partly adjusted OR (95% CI)[a]	Fully adjusted OR (95% CI)[b]
No	1[reference]	1[reference]	1[reference]
Yes	1.06 (0.75–1.49)	1.00 (0.70–1.43)	1.08 (0.75–1.55)

[a] Adjusted for age.
[b] Adjusted for age, sex, education, history of antibiotic medication within prior 3 months.

Discussion

The analysis of this population-based study showed an inverse association between *H. pylori* infection and reported occurrence of diarrhoea within prior 3 months in adults. These data support suggestions that attribute some beneficial effects to the host of colonization with *H. pylori* [4–6] and confirms data of a large population-based study performed in children [8, 12].

In general, diarrhoea in adults represents a non-specific response of the intestine to a number of different kinds of insults, including infections, adverse drug and dietary reactions, malabsorption, inflammatory bowel disease, and ischemia [13, 14]. However, the main reason for acute diarrhoea in adults is infections, primarily caused by viruses but also by bacteria and parasitic agents [15, 16]. Although clinical relevance of episodes of diarrhoea reported in this study among healthy adults in Germany may be limited, infections of the gastrointestinal tract represent an important cause of morbidity and mortality among both children and adults worldwide.

At first glance, it is not evident how gastric colonization with *H. pylori* should influence the infection

of the lower intestinal tract, as acute infectious diarrhoea is acquired predominantly through oral ingestion of pathogenic microorganisms like viruses, *Vibrio cholerae*, *Campylobacter jejuni*, toxigenic *Escherichia coli*, *Salmonella*, *Yersinia*, and *Shigella*. The observation that *H. pylori* is able to influence the immunologic responsiveness to transient intestinal pathogens by increasing specific mucosal IgA-antibody secretion may be one explanation [3]. A further mechanism is suggested by a recent study demonstrating that *H. pylori* possesses anti-bacterial activity to which it is itself resistant [7]. This study could show that *H. pylori* synthesizes a cecropin-like peptide exerting anti-bacterial activity against Gram-negative and Gram-positive bacteria. Although the precise role of these peptides remain to be defined they represent a particularly efficient mode of control over faster growing microorganisms which may compete for colonization with *H. pylori* [17, 18]. Furthermore, these small peptides can diffuse and may be liberated during passage of *H. pylori* organisms from the stomach to the colon [19, 20]. Thus, long distance effects of *H. pylori* infection even in the lower part of the gastrointestinal tract mediated by anti-bacterial peptides appear biologically plausible.

Infective organisms have to overcome gastric passage, which is lethal to many organisms because of the hostile gastric pH [21]. However, an impaired host with hypochlorhydria, for example children with recent *H. pylori* infection or older subjects with chronic atrophic gastritis, may be more susceptible to certain microorganisms that may cause acute infectious diarrhoea [22, 23]. On the other hand, *H. pylori* is able to increase gastric acid secretion in subjects with chronic *H. pylori* infection, resulting in improved barrier function to ingested pathogens [24]. However, this could depend on the type of *H. pylori* colonizing the stomach. The differentiation of the infecting strains was unfortunately not possible in the present study.

It could be shown in a recent cross-sectional study of the 1991 Peruvian cholera epidemic, that serologic evidence of *Vibrio cholerae* 01 infection was associated with *H. pylori* infection, particularly in young children [25]. These data seem to contradict our results at first view. However, despite an increased seroprevalence of cholera, infection with *H. pylori* was associated with reduced frequency of diarrhoea (adjusted OR 0.6 [95% CI: 0.4–1.1]). This pattern would be consistent with the observation, that *H. pylori* infection may stimulate the local mucosal immune system [3] and furthermore, that *H. pylori* organisms may interfere with *Vibrio cholerae* organisms with a consequent reduction in reported diarrhoeal symptoms [25]. Clemens et al. reported an overall risk of cholera to be not significantly increased among *H. pylori* infected subjects, however, the risk of cholera of life-threatening severity was significantly elevated [26]. This association was only seen among persons lacking natural vibriocidal immunity and may therefore not be related with an increased risk of *Vibrio cholerae* 01 diarrhoea due to *H. pylori* infection.

Furthermore, there are some smaller studies conducted in developing countries in children suffering from malnutrition and severe gastrointestinal infections to assess the role of *H. pylori* infection in weakening the gastric acid barrier against infectious organisms [27–31]. However, most of these studies [28–31], with the exception of the study by Sullivan et al. [27], showed that *H. pylori* infection is not associated with an increased risk of diarrhoeal disease. We suppose that, in these studies, effects of malnutrition and transient hypochlorhydria following acute *H. pylori* infection and the anti-diarrhoeal effect of *H. pylori* as seen in our studies may have cancelled out.

In this study, we have to consider several limitations. First, we have to rely on the reporting of symptoms by the participants of the study. However, diarrhoea and flatulence should be reliably remembered within the short 3-month time frame. Differential reporting is likewise unlikely, given that subjects were unaware of their *H. pylori* status at the time they filled out the questionnaire. The absence of an association of *H. pylori* infection with flatulence, a symptom thought to be unrelated to *H. pylori* infection, also suggests a reporting bias to be unlikely. Second, using a cross-sectional design in this study, it is difficult to relate the time of acquisition of *H. pylori* to the manifestation of diarrhoea. However, most *H. pylori* infections are acquired in early childhood, probably by the age of 2–3 years [32, 33]. Therefore it seems likely that most subjects of this population sample had been long colonized at the time of our study. Furthermore, using the ^{13}C-UBT to determine *H. pylori* infection status, we had the possibility to detect current *H. pylori* infection in our study.

In conclusion, our data support the hypothesis that infection with *H. pylori* may have a protective effect against infectious diarrhoea in adults. Although we have found similar associations in adults and in children, this hypothesis needs further confirmation, both in experimental studies and in clinical settings.

Acknowledgements

We thank the participating health insurance company (Allgemeine Ortskrankenkasse Ulm) and the Center for General Science-Oriented Continuing Education at the University of Ulm for their excellent cooperation.

References

1. NIH Consensus Development Panel on *Helicobacter pylori* in Peptic Ulcer Disease. *Helicobacter pylori* in peptic ulcer disease. J Am Med Assoc 1994; 272: 65–69.

2. Infection with *Helicobacter pylori*. IARC Monogr Eval Carcinog Risks Hum 1994; 60: 177–240.
3. Mattson A, Lönroth H, Quiding-Järbrink M, et al. Induction of B-cell responses in the stomach of *Helicobacter pylori*-infected subjects after oral cholera vaccination. J Clin Invest 1998; 102: 51–56.
4. Blaser MJ. Not all *Helicobacter pylori* strains are created equal: Should all be eliminated? Lancet 1997; 349: 1020–1022.
5. Blaser MJ. Helicobacters are indigenous to the human stomach: Duodenal ulceration is due to changes in gastric microecology in the modern era. Gut 1998; 43: 721–727.
6. Blaser MJ. Hypothesis: The changing relationships of *Helicobacter pylori* and humans: Implications for health and disease. J Infect Dis 1999; 179: 1523–1530.
7. Pütsep K, Brändén CI, Boman HG, et al. Antibacterial peptide from *Helicobacter pylori*. Nature 1999; 398: 671–672.
8. Rothenbacher D, Blaser MJ, Bode G, et al. Inverse relationship between gastric colonization of *Helicobacter pylori* and diarrheal illnesses in children: Results of a population-based cross-sectional study. J Infect Dis 2000; 182: 1446–1449.
9. Brenner H, Rothenbacher D, Bode G, et al. Active infection with *Helicobacter pylori* in healthy couples. Epidemiol Infect 1999; 122: 91–95.
10. Rothenbacher D, Bode G, Peschke F, et al. Active infection with *Helicobacter pylori* in an asymptomatic population of middle aged to elderly people. Epidemiol Infect 1998; 120: 297–303.
11. Ellenrieder V, Glasbrenner B, Stoffels C, et al. Qualitative and semi-quantitative value of a modified ^{13}C-urea breath test for identification of *Helicobacter pylori* infection. Eur J Gastroenterol Hepatol 1997; 9: 1085–1089.
12. Bode G, Rothenbacher D, Brenner H, et al. *Helicobacter pylori* and abdominal symptoms: A population based study among pre-school children in Southern Germany. Pediatrics 1998; 101: 634–637.
13. Guerrant RL, Hughes JM, Lima NL, et al. Diarrhea in developed and developing countries: Magnitude, special settings, and etiologies. Rev Infect Dis 1990; 12(Suppl 1): S41–S49.
14. Cheney CP, Wong RKH. Acute infectious diarrhea. Med Clin North Am 1993; 77: 1169–1196.
15. Dellert SF, Cohen MB. Diarrheal disease. Established pathogens, new pathogens, and progress in vaccine development. Gastroenterol Clin North Am 1994; 23: 637–649.
16. Levine MM, Levine OS. Changes in human ecology and behaviour in relation to the emergence of diarrheal diseases, including cholera. Proc Natl Acad Sci USA 1994; 91: 2390–2395.
17. Boman HG. Antibacterial peptides: Key components needed in immunity. Cell 1991; 65: 205–207.
18. Zasloff M. Antibiotic peptides as mediators of innate immunity. Curr Opin Immunol 1992; 4: 3–7.
19. Phadnis SH, Parlow MH, Levy M, et al. Surface localization of *Helicobacter pylori* urease and heat shock protein homolog requires bacterial autolysis. Infect Immun 1996; 64: 905–912.
20. Schraw W, McClain MS, Cover TL. Kinetics and mechanisms of extracellular protein release by *Helicobacter pylori*. Infect Immun 1999; 67: 5247–5252.
21. Gianella RH, Broitman SA, Zamcheck N. Influence of gastric acidity on bacterial and parasitic enteric infections. Ann Intern Med 1973; 78: 271–276.
22. El-Omar EM, Oien K, El-Nujumi A, et al. *Helicobacter pylori* infection and chronic gastric acid hyposecretion. Gastroenterology 1997; 113: 15–24.
23. Hackelsberger A, Günther T, Schultze V, et al. Role of aging in the expression of *Helicobacter pylori* gastritis in the antrum, corpus, and cardia. Scand J Gastroenterol 1999; 34: 138–143.
24. McColl KEL. *Helicobacter pylori* and acid secretion: Where are we now? Eur J Gastroenterol Hepatol 1997; 9: 333–335.
25. Shahinian ML, Passaro DJ, Swerdlow DL, et al. *Helicobacter pylori* and epidemic *Vibrio cholerae* 01 infection in Peru. Lancet 2000; 355: 377–378.
26. Clemens J, Albert MJ, Rao M, et al. Impact of infection by *Helicobacter pylori* on the risk and severity of endemic cholera. J Infect Dis 1995; 171: 1653–1656.
27. Sullivan PB, Thomas JE, Wight DGD, et al. *Helicobacter pylori* in Gambian children with chronic diarrhoea and malnutrition. Arch Dis Child 1990; 65: 189–191.
28. Kehrt R, Becker M, Brosicke H, et al. Prevalence of *Helicobacter pylori* infection in Nicaraguan children with persistent diarrhea, diagnosed by the ^{13}C-urea breath test. J Pediatr Gastroenterol Nutr 1997; 25: 84–88.
29. Rahman MM, Mahalanabis D, Sarker A, et al. *Helicobacter pylori* colonization in infants and young children is not necessarily associated with diarrhoea. J Trop Ped 1998; 44: 283–287.
30. Isenbarger DW, Bodhidatta L, Hoge CW, et al. Prospective study of the incidence of diarrheal disease and *Helicobacter pylori* infection among children in an orphanage in Thailand. Am J Trop Med Hyg 1998; 59: 796–800.
31. Castro-Rodriguez JA, Leon-Barua R, Penny M. *Helicobacter pylori* is not a determinant factor of persistent diarrhoea or malnutrition in Peruvian children. Trans R Soc Trop Med Hyg 1999; 93: 537–539.
32. Goodman KJ, Correa P. The transmission of *Helicobacter pylori*. A critical review of the evidence. Int J Epidemiol 1995; 24: 875–887.
33. Thomas JE, Dale A, Harding M, et al. *Helicobacter pylori* colonization in early life. Pediatr Res 1999; 45: 218–223.

Address for correspondence: Hermann Brenner, Department of Epidemiology, German Centre for Research on Ageing, University of Heidelberg, Bergheimer Str. 20, D-69115 Heidelberg, Germany
Phone: +49 6221 548140; Fax: +49 6221 548142
E-mail: brenner@dzfa.uni-heidelberg.de