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# H.pylori Infection inhibits Inflammatory Bowel Disease(IBD) by affecting the intestinal flora: A systematic Review

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**Abstract**
**Background:** Inflammatory bowel diseases (IBD) are chronic, relapsing-remitting diseases of the gastrointestinal tract, including Crohn's disease (CD), Ulcerative Colitis (UC), and Unclassified IBD (IBDU). Their pathogenesis involves genes and the environment as cofactors in inducing autoimmunity; mainly, the interactions between enteric pathogens and immunity are studied. For example, Helicobacter pylori (HP) is a common pathogen causing gastric inflammation. However, studies found that the number of people with HP was lower than those with IBD. Therefore, it suggests that HP might protect against IBD.
**Methods:** The search terms "helicobacter pylori," "inflammatory bowel disease," "Crohn's disease," and "ulcerative colitis" were entered into the PubMed database. Embase, Medline, Web of Science, Scopus, PubMed publisher, Cochrane, and Google Scholar were also searched. The HP prevalence rates in IBD patients, CD patients, UC patients, and IBDU patients were calculated. So its to prove that there is an inverse relationship between HP and IBD, each group was compared to a control group.
**Results:** Even when the comparison was made separately between each group of newly diagnosed patients and controls to rule out the possibility of pharmacologic bias, the data showed an inverse relationship between the IBD group and the controls.
**Conclusion:** The results of this review demonstrate a striking inverse association between HP infection and the prevalence of inflammatory bowel disease (IBD), regardless of the type of IBD considered across different geographic regions. Anyway, data should be interpreted with care because more research is needed on this topic that is broader, more prospective, and more consistent. This could lead to new ideas about how the environment could cause IBD.
**Keywords:** Inflammatory bowel disease; Helicobacter pylori; Crohn's disease; Ulcerative colitis; Colorectal cancer
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## 1. Introduction

The global health burden of inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn's disease (CD), is significant and increasing[1-3]. In the last few decades, the number of people with IBD has risen dramatically in many developing countries[4-6]. People think that easier access to a cleaner environment and the resulting drop in common childhood infections may have something to do with this rise by making people more likely to get autoimmune diseases like IBD. So, this theory says that getting sick with microbes as a child might protect against IBD. People who have Helicobacter pylori in their stomachs are more likely to develop gastric cancer, mucosa-associated lymphoid tissue (MALT) lymphoma, and chronic gastritis than people who do not have the bacteria[7,8].

The bacterium's effect on the host's immune system is the main reason why the gastric mucosa reacts with inflammation. This causes a response from T helper type 1 (Th1) cells and higher levels of cytokines from Th1 cells[9-11]. Because of this, products of the immune reactions in the stomach may move to other parts of the body. This may explain the link between H. pylori infection and a number of diseases outside of the stomach, such as autoimmune diseases. Epidemiological data, on the other hand, suggests that H. pylori infection protects against the development of some diseases with an autoimmune component, like asthma[12,13]. This is most likely because H. pylori can cause immune tolerance and limit inflammatory responses[14,15].

The protective effect of H. pylori infection is thought to be caused by the different ways in which local mucosal inflammatory responses are expressed. This may lead to a system-wide release of cytokines, which in turn may downregulate systemic immune responses and prevent autoimmune disease. Because of these things, many studies have looked into the link between H. pylori infection and IBD. But there are many different kinds of writing out there. So, many studies have found that the number of people with IBD who have H. pylori infections is lower than the number of people who don't have IBD. However, this has not been confirmed by other studies.

## Methods

We searched the PubMed, MEDLINE, and Embase databases from 1980 to 2021 using the following key words or Medical Subject Headings (MeSH) terms to identify all relevant English-language medical literature for human studies: (Inflammatory bowel disease OR ulcerative colitis OR Crohn's disease) AND Helicobacter pylori. Specifically, the following search terms were employed: OR ("helicobacter pylori" OR ("helicobacter pylori") OR ("h pylori")) AND ("inflammatory bowel diseases" OR ("inflammatory" AND "bowel" AND "diseases") OR ("colitis, ulcerative" (MeSH Terms) OR ("colitis" AND "ulcerative") OR "ulcerative colitis" OR ("ulcerative" AND "colitis") OR ("ulcerative" AND "colitis")In addition, we conducted a comprehensive manual search of all published review articles and editorials and retrieved original studies. The research was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. All 16 studies were included in this analysis if they fulfilled all of the following criteria: (1) a full article published; (2) data on the association between H. pylori infection and IBD retrievable; and (3) confirmation of H. pylori infection studies that did not meet the criteria as mentioned above were excluded, as were duplicate publications.

## Results

Lord et al. gathered information on H. pylori infection with and without the cagA variant from 212 patients with Crohn's disease (CD), 235 with ulcerative colitis (UC), and 258 healthy individuals. All patients were recruited between January 1996 and November 2009 from the IBD clinic at the Royal Brisbane and Women's Hospital in Brisbane, Australia. The prevalence of H. pylori was 11.49 percent, whereas CagA positivity was found in 4.77 percent of the population. We found that CagA protects against CD (OR 0.13, 95% CI (0.03 to 0.57), p0.001). This effect appears to be unique to CD, as CagA positivity was not found to be protective in UC (OR 0.78, 95% CI (0.44 to 1.44); p=0.41). In addition, the prevalence of CagA was higher in UC than in CD, albeit at a trend level (OR 0.57, 95% CI (0.30 to 1.10), p=0.09). It is well known that the prevalence of H. pylori increases with age. However, the prevalence of cagA-positive strains increased with age for unaffected individuals and UC (0.095% per year) but not for CD patients (figure 1). We observed a trend level effect of H. pylori on CD (OR 0.57, 95% CI (0.31 to 1.10), p = 0.09), but this effect was not present in CagA-negative participants (OR 0.80, 95% CI (0.40 to 1.55), p = 0.55)[17].

P. O. Vaure et al. looked at 296 unselected patients with inflammatory bowel disease (IBD), including 185 with ulcerative colitis (UC), 94 with Crohn's disease (CD), and [17] with indeterminate colitis (IC). Seventy healthy subjects of the same age and gender served as controls. H. pylori antibodies were analyzed in serum samples. The patient's medical records and a face-to-face interview were used to compile a complete medical history. The prevalence of H. pylori infection was lower in IBD patients (24%) than in controls (37%; P = 0.029), and lower in CD (13%; P = 0.002) than in UC (30%; P = 0.002). There was no correlation between sulphasalazine treatment and seropositivity. The average age of onset of IBD in seropositive patients was 40 years, compared to 30 years in seronegative patients (P 0.001). With a peak between 30 and 40 years, the age of onset of IBD was unimodal in H. pylori-seronegative patients, whereas there was evidence of bimodality in CD. In contrast, seropositive patients for H. pylori exhibited a bimodal distribution with peaks at 20–40 and 50–60 years of age. Our findings confirm the low prevalence of H. pylori infection in IBD and, more specifically, in CD. The significantly older age of onset and bimodal pattern of age-specific incidence in seropositive IBD patients suggest that infection with H. pylori significantly modifies the development of IBD and may have a protective effec[18].

Another study was conducted on 100 consecutive Crohn's disease patients, 100 consecutive ulcerative colitis patients, and 100 age- and gender-matched controls. Using an enzyme immunoassay, the IgG and IgA antibody titres against H. pylori in serum were measured. The seroprevalence of H pylori was 15% in people with inflammatory bowel disease (13% in people with Crohn's disease and 18% in people with ulcerative colitis), but it was 43% in people who did not have inflammatory bowel disease. The seroprevalence of Hpylori was much

lower in IBD patients than in controls in all age groups that were tested. In all tested age groups, the seroprevalence of H pylori was significantly lower in IBD patients compared to controls. The treatment with sulphasalazine or any other medical therapy administered to H. pylori-positive and negative patients did not differ significantly. At the time of blood sampling, neither the level of education nor the employment status of the patients differed from those of the controls. Patients with IBD were less likely to have H. pylori infection than age-and gender-matched controls. Neither medical care nor socioeconomic factors could account for the disparity[19].

Sonnenberg and Genta examined a total of 65,515 patients, 1061 of whom had IBD and 64,451 of whom did not. There was a correlation between the histological presence of H. pylori and the demographic and histological presence of oesophageal disease, Crohn's disease (CD), and ulcerative colitis in patients (UC). When H. pylori was present, the adjusted odds ratios for IBD were 0.48 (0.27–0.79) for CD, 0.59 (0.39–0.84) for UC, and 0.43 (0.15–0.95) for IND. H. pylori-negative gastritis was associated with IBD, with adjusted odds ratios of 11.06 (7.98–15.02) for CD, 2.25 (1.31–3.30) for UC, and 6.91 (3.50–12.30) for IND. Our study confirms an inverse relationship between H. pylori and IBD, as well as a positive relationship between H. pylori-negative gastritis and IBD. These findings may shed light on the pathogenesis of IBD[20].

Roka et al. conducted a retrospective study on children who underwent their first esophago-gastroduodenal endoscopy from 2002 to 2011. Patients with Crohn's disease (CD), ulcerative colitis (UC), IBD not otherwise specified (IBDU), and non-IBD individuals were studied (non-IBD). A positive culture or positive histology and CLO test determined infection with Helicobacter pylori. Children with a negative or unavailable culture and a single positive test (histology or CLO) were evaluated further with a urea breath test, and positive results were also included in the infected group. We examined 159 IBD patients (66 CD, 34 UC, and 59 IBDU) and 1209 patients without IBD. Helicobacter pylori gastritis was significantly less prevalent in the IBD group (3.8% versus 13.2% in the control group, p.001), whereas IBD patients were substantially older than non-IBD children (p.001). Children with H. pylori-negative gastritis were three times as likely (p =.006) as those with H. pylori-positive gastritis to have IBD.H. pylori gastritis occurs less frequently in children with IBD compared to healthy controls. This study confirmed that H. pylori are inversely associated with IBD. More research was needed for children with IBD to determine if H. pylori protected them or if it was just because they had taken antibiotics before[21].

In Babol teaching hospitals, a case-control study was conducted; IgA and IgG ELISA tests were used to investigate H. pylori exposure in 60 newly diagnosed IBD cases without Helicobacter eradicating treatment and 120 control patients without evidence of inflammatory bowel disease in the biopsy. The case group's average age was 42.2713.64 years, while the control group was 45.5213.83 years. In the IgG study of the following subgroups, there was a significant difference between the case and control groups: age under 30, females, males, urban, higher education level, and BMI between 18.5 and 24.9 (p-value was respectively; 0.004, 0.014, 0.047, 0.002, 0.013, 0.003). Based on logistic regression, IBD was less prevalent among females, patients with less education, and patients with a positive IgG test result (p-value were respectively 0.002, 0.013, and 0.010). This study suggests that Helicobacter pylori exposure may protect against inflammatory bowel disease[22].

Sonenberg and Genta conducted a study in 2016 to determine the odds ratios and 95% confidence intervals between microscopic colitis and the presence of H. pylori-positive chronic active gastritis (CAG), H. pylori-negative CAG, intestinal metaplasia, or gastric atrophy. Multivariate logistic regression analyses were used to adjust these associations for sex, age, percentage of white, black, Hispanic, and Asian residents per ZIP code, percentage of residents with a college degree, average housing values, annual income, and population size of individual ZIP codes. Patients with microscopic colitis were less likely to have H. pylori-positive CAG (odds ratio = 0.61; 95% confidence interval = 0.52–0.70). Also, intestinal metaplasia occurred less frequently in patients with microscopic colitis than those without it (0.75, 0.65–0.86). Adjustments for ethnicity and socioeconomic standing did not affect these inverse relationships.

In contrast to H. pylori-positive CAG, H. pylori-negative CAG was more prevalent in patients with microscopic colitis than in those without (1.54, 1.17–1.97). Infection with H. pylori and microscopic colitis are inversely related. Similar inverse associations between H. pylori and inflammatory bowel disease support this observation. These associations may shed light on the still-unknown cause of microscopic colitis[23].

A study was conducted on the Korean population, which included 316 unselected patients with inflammatory bowel disease (IBD), including 169 ulcerative colitis (UC) patients and 147 with Crohn's disease (CD), and 316 age-and gender-matched healthy individuals who underwent a comprehensive medical examination for a routine

checkup. Using the urea breath test, the infection rates of H. pylori were compared between IBD patients and the controls group. Statistically significant differences in the rate of occurrence were found to be statistically significant for H. pylori infection between IBD patients (25.3%) and controls (52.5%; p 0.001), as well as between UC (32.0%) and CD patients (17.5%; p=0.04). Among IBD patients, those over the age of 60 and those who had previously taken metronidazole (13.0%; p = 0.038) or ciprofloxacin (6.7%; p=0.001) had a significantly lower infection rate than controls (CD 22.0% vs. UC 33.8% vs. Control 52.0%, p0.001). Except for age, there were no significant associations between phenotypic characteristics and the H. pylori infection rate in CD patients. The rate of H. pylori infection among Korean patients with IBD, particularly CD, was significantly lower than that of the control group. This association was more pronounced in individuals 60 years of age or older, suggesting that H. pylori infection may be deemed to reduce the risk of IBD in younger adults[24].

Colonoscopy and a tissue sample were used to diagnose UC. The detection of H. pylori was based on the 14C urea breath test (UBT) and biopsy sample culture. The demographic, anthropometric, and serologic data of patients were chosen. A comparison was made between the rate of H. pylori infection in the UC and control groups, followed by a subgroup analysis of the association between H. pylori infection and the extent and severity of UC. In total, 153 and 121 patients were assigned to the UC and control groups. No significant age, gender, BMI, hypertension, or diabetes differences existed. However, in the UC group, smoking history was significantly lower, whereas WBC and CRP levels were significantly higher. The rate of H. pylori infection was significantly lower in the UC group (30.5%) than in the control group (57.0%). The H. pylori infection rate in the UC of the left colon and the entire colon was 33.9% and 24.2%, respectively (p 0.05), significantly lower than the infection rate in the control group. A considerably lower H. pylori infection rate in ulcerative colitis (UC) patients with varying degrees of extent and severity provide evidence for bacterial involvement in UC pathogenesis and reminds clinicians to exercise caution when considering H. pylori eradication in UC patients[25].

In the study by Caner et al., forty-nine individuals diagnosed with UC who had undergone upper gastrointestinal endoscopy for various reasons were included in the survey by Caner et al. The presence of H. pylori in the stomach was determined using histopathology. The 57.1 percent of UC patients had a positive H. pylori test. Intriguingly, the prevalence of H. pylori positivity was lower in pancolitis patients than in those with more limited illnesses. There was no correlation between the severity of the underlying disease, the number of medications taken, and the incidence of H. pylori infection. The spread of UC significantly affects the prevalence of H. pylori-positive patients. It was unclear whether the low number of positive tests for H. pylori in people with long-term UC was due to immunosuppressant drugs or the UC itself[26].

## Discussion

H. pylori may help the host fight IBD and other chronic inflammatory diseases by trying to help itself live. Several proposed mechanisms explain the inverse relationship between H. pylori and IBD. In CD, Th1 immune responses are predominant, whereas, in UC, Th2 or Th1/Th2 immune responses may predominate[27,28,29]. These altered immune responses to lumen antigens may affect the host's response to H. pylori infection. In contrast, a persistent bacterial infection in the stomach may protectively alter the host's immune responses or make the most susceptible to IBD. Multiple cytokines, including IFN-, TNF, IL-1, IL-6, IL-7, IL-8, IL-10, and IL-18, are elevated in the gastric epithelial cells of H. pylori-infected humans as compared to uninfected humans[30-32]. After H. pylori activate Toll-like receptors, dendritic cells (DC) may activate T cells in different ways, causing either a Th1 or Th2/regulatory T cell (Treg) response through the production of IL-12 or IL-10, respectively[33,34]. D'Elios et al. [35] The studies found that most H. pylori-specific T cell clones from uncomplicated chronic gastritis had a Th2-like phenotype, making interleukin IL-4 or IL-5 and INF-a, while only one-third of the gastric T cells that were specific to H. pylori were geared toward Th1 effectors. Thus, the ability of H. pylori to downregulate pro-inflammatory immune responses may be responsible for its protective effect against IBD. Since the adoptive transfer of Treg can prevent and treat colitis in multiple animal models, it is reasonable to assume that these cells produced in response to H. pylori infection may play a role in preventing IBD[36-40]. H. pylori can induce a Treg response and downregulate the pro-inflammatory Th1/Th17 pathway[41-46]. The development of spontaneous colitis in mice lacking IL-10, a key regulatory cytokine for Treg function, demonstrates the importance of Tregs in the pathogenesis of inflammatory bowel disease (IBD)[47]. Also, systemic levels of typeIIFN were lower in IBD patients colonized with H. pylori than in controls who were not colonized[48].

Another way the body might protect itself is by making antibodies against H. pylori. These antibodies might act as an immunization against other harmful Helicobacter or even different types of microbes linked to IBD[49]. Even though H. pylori-specific antibodies do not eradicate this bacterium, and they appear to confer immunity against

a subsequent Campylobacter infection, indicating antigenic cross-reactivity between these two bacterial species[50,51]. It's also possible that H. pylori's effect on acid production indirectly affects another type of infection that leads to IBD[52]. It has been demonstrated that H. bilis and H. pylori co-infection in mice attenuates H. pylori gastritis compared to mice infected with only H. pylori. H. pylori's protective effect may be caused by other confusing factors, such as genetic or environmental factors that make it easier for some people to get H. pylori and for others to get IBD. This hypothesis would fit the fact that IBD is linked to better hygiene, which could make H. pylori acquisition more difficult[53,54]. The low prevalence of H. pylori infection in inflammatory bowel disease (IBD) patients compared to non-IBD patients bolsters the importance of the "hygiene hypothesis" in developing autoimmunity and IBD. It suggests that inadequate microbial stimulation of gut-associated lymphoid tissue is a crucial factor in the maturation of mucosal immunity[55,56]. Improved access to a cleaner environment and the resulting decline in the incidence of common childhood infections, such as H. pylori, may contribute to autoimmunity by altering susceptibility to certain autoimmune diseases, such as IBD[57]. Regarding genetic factors, the CD variant of the autophagy gene ATG16L1 modifies susceptibility to H. pylori infection with an enteric microbe in human subjects at the population level, indicating a role for altered autophagy in regulating the host response to enteric microbes in CD pathogenesis. It is interesting to think that because people with the ATG16L risk allele are more likely to get sick, early exposure to and acquisition of H. pylori may lower their risk of developing IBD[58] later.

**Conclusion:**

The Gram-negative bacterium Helicobacter pylori are widely recognized for its close association with peptic ulcer disease and gastric cancer development. However, recent epidemiological and experimental evidence suggests that chronic infection with H. pylori may confer protection against gastroesophageal diseases, asthma, other allergic disease manifestations, and inflammatory bowel diseases (IBD) to the host. In this chapter, we summarize the epidemiological evidence currently available to support or disprove a possible negative correlation between H. pylori infection and diseases outside of the stomach. Furthermore, as demonstrated by additional experimental evidence generated primarily in mouse models of these diseases, the development of allergic diseases and inflammatory bowel disease (IBD) is inhibited in the presence of H. pylori. Researchers think that H. pylori's protective effects are caused by the production of regulatory T-cells (Trigs) that have much suppressive power.

**References**

1. Loftus EV. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and the role of the environment. In 2004, Gastroenterology 126: 1504–1517.
2. Thia KT, Loftus EV, Sandborn WJ, et al. An update on the epidemiology of inflammatory bowel disease in Asia American Journal of Gastroenterology 2008; 103: 3167–3182.
3. DC. Baumgart, CN Bernstein, Z Abbas, et al. The prevalence, diagnosis, and treatment of IBD worldwide: The meeting of the Inflammatory Bowel Disease Task Force on World Digestive Health Day 2010. Inflamm Bowel Disease, 17(6):639–644.Rokkas and colleagues '547
4. Molodecky NA, Soon IS, Rabi DM et al. Based on a systematic review, there is an increasing incidence and prevalence of inflammatory bowel diseases. Gastroenterology 142 (2012): 46–54.
5. Too clean, or not clean enough? The hygiene hypothesis and home hygiene. Clin Exp Allergy, 36, pp. 402–425, 2006.
6. Koloski NA, Bret L, and Radford-Smith G. The Hygiene Hypothesis in Inflammatory Bowel Disease: A Critical Review of the Literature. World Journal of Gastroenterology 2008; 14: 165–173.
7. Valle J, Kekki M, Sipponen P, et al. The long-term course and consequences of Helicobacter pylori gastritis Results of a 32-year follow-up study Scand J Gastroenterol 31: 546–550, 1996.
8. Sonnenberg A. Review article: Historic changes in Helicobacter pylori-associated diseases. 329–342 in Aliment Pharmacol Ther 2013.
9. Smythies LE, Waites KB, Lindsey JR, et al. Helicobacter pylori-induced mucosal inflammation is Th1 mediated and exacerbated in IL-4 but not IFNgamma gene-deficient mice. 1022–1029. J Immunol 2000; 165: 1022–1029.
10. Di Tommaso A, Xiang Z, Bagnoli M, et al. Helicobacter pylori-specific CD4 T-cell clones from peripheral blood and gastric biopsies. Infect Immun, 63, 1102–1106.

11. Meyer F, Wilson KT, and James SP. Modulation of innate cytokine responses by-products of Helicobacter pylori. Infect Immun 68: 6265–6272, 2000.

12. Van Amsterdam, A.H. van Vliet, J.G. Kusters, and colleagues, Diseases caused by Helicobacter pylori depend on microbes and people. 2006, FEMS Microbiol Rev 30: 131–156.

13. Ram, O. Barzilai, Y. Shapira, et al. Serology of Helicobacter pylori in autoimmune diseases: Fact or fiction? Clinical Chemistry and Laboratory Medicine, 51, 1075–1082, 2013.

14. Chen, Y., and MJ. Blaser. The opposite is true: Helicobacter pylori colonization is linked to asthma in kids. Journal of Infectious Diseases, 198: 553–560, 2008.

15. Reibman J, Marmor M, Filner J, et al. asthma is inversely associated with Helicobacter pylori status in an urban population. PLoS One 2 (2008): e4060.

16. Liberati, D. G. Altman, J. Tetzlaff, and colleagues elaborate on the PRISMA statement for reporting systematic reviews and meta-analyses of studies evaluating healthcare interventions. 62: e1–e34, 2009.

17. R. Lord, K. Hanigan, L.A. Simms, R.Sullivan, P.Hobson, and G.L. Radford-Smith. The cagA-positive strain of Helicobacter pylori is linked to the protective effects it has on IBD. 0:1–2. doi:10.1136/gutjnl-2017-313805.

18. J. A. Silvennoinen, R. Karttunen, S. E. Niemela, J. K. Lehtola, and T. J. Karttunen.Is Helicobacter pylori infection a Protective Factor in Inflammatory Bowel Disease? (12th)

19. M Leidenius, T U Kosunen. There is an inverse correlation between Helicobacter pylori infection and inflammatory bowel disease. J Clin Pathol, 49:65-67, 1996.

20. Sonnenberg, R. M. Genta. Helicobacter pylori infection is low among patients with inflammatory bowel disease patients. 469–476 in Aliment Pharmacol Ther, 2012.

21. Kleoniki Roka, Aikaterini Roubani, Kalliopi Stefanaki, Ioanna Panayotou, Eleftheria Roma, and Giorgos Chouliaras. Helicobacter pylori Gastritis in Newly Diagnosed Children with Inflammatory Bowel Diseases. 400–405

22. Rasoul Sayar, Javad Shokri Shirvani, Karimollah Hajian-Tilaki, Zeinab Vosough, and Mohammad Ranalli. The negative association between inflammatory bowel disease and Helicobacter pylori seropositivity Caspian Journal of Intern Medicine 2019; 10(2): 217-222.

23. Amnon Sonnenberg and Robert M. Genta. Helicobacter pylori Gastritis and Microscopic Colitis Have an Inverse Relationship. Inflamm Bowel Dis 2016, 22:182–186.

24. Min Jun Song, Dong II, Park, Sang Jun Hwang, Eun-Ran Kim, Young-Ho Kim, Byeong Ik Jang, Suck Ho Lee, Jeong Seon Ji, and Sung Jae Shin. The Prevalence of Helicobacter pylori Infection in Korean Patients with Inflammatory Bowel Disease: A Multicenter Study. Korean Journal of Gastroenterology 2009;53:341-347)

25. Xi Jin, Yi-peng Chen, Shao-Hua Chen, Zun Xiang. Association between Helicobacter Pylori Infection and Ulcerative Colitis-A Case-Control Study from China. International Journal of Medical Sciences, vol. 10, no. 11, pp. 1479–1484.

26. Sedat CANER, Akif ALTINBA, Yusuf YEL, Yavuz BEYAZIT, Barş YILMAZ, Osman YÜKSEL. The relationship between Helicobacter pylori and ulcerative colitis The Turkish Journal of Medical Sciences Turk J Med Sci 44: 820-823 (2014).

27. MacDonald TT, Murch SH. Etiology and pathogenesis of chronic inflammatory bowel disease. Baillieres Clin Gastroenterol, vol. 8, no. 1, pp. 1-34, 1994.

28. P. Parronchi, F. Annunziato, S. Sampognaro, A. Becchio, L. Giannarini, E. Maggi, C. Pupilli, F. Tonelli, and S. Romagnani.Type 1 T-helper cell predominance and interleukin-12 expression in the gut of patients with Crohn's disease Am J Pathol, 150: 823-832, 1997.

29. Fuss IJ, Neurath M, Boirivant M, Klein JS, de la Motte C, Strong SA, Fiocchi C, Strober W. Disparate CD4+ lamina propria (LP) lymphokine secretion profiles in inflammatory bowel disease. Crohn's disease LP cells manifest increased secretion of IFN-gamma, whereas ulcerative colitis LP cells manifest increased secretion of IL-5. J Immunol, 157: 1261–1270, 1996.

30. Supajatura V, Ushio H, Wada A, Yahiro K, Okumura K, Ogawa H, Hirayama T, Ra C. Cutting edge: VacA, a vacuolating cytotoxin of Helicobacter pylori, directly activates mast cells for migration and production of pro-inflammatory cytokines. J Immunol 168: 2603-2607, 2002.

31. Asahi M, Azuma T, Ito S, Ito Y, Suto H, Nagai Y, Tsubokawa M, Tohyama Y, Maeda S, Omata M, Suzuki T, Sasakawa C. Helicobacter pylori CagA protein can be tyrosine phosphorylated in gastric epithelial cells. J Exp Med, 191:593-602, 2000.

32. Yaki K, Ro S, Okazaki R, Shiojima J, Tsuda K, Mimura H, Tomono H, Nakamura T. A water extract of Helicobacter pylori stimulates interleukin-8 secretion by a human gastric epithelial cell line (JR-St) through protein tyrosine phosphorylation. J Gastroenterol Hepatol, 15: 263-270, 2000.

33. Banchereau J, Briere F, Caux C, Davoust J, Lebecque S, Liu YJ, Pulendran B, Palucka K. Immunobiology of dendritic cells. 767-811 in Annual Review of Immunology, 2000.

34. Guiney DG, Hasegawa P, Cole SP. Helicobacter pylori preferentially induce interleukin 12 (IL-12) rather than IL-6 or IL-10 in human dendritic cells. Infect Immun 2003; 71: 4163-4166

35. D'Elios MM, Manghetti M, Almerigogna F, Amedei A, Costa F, Burroni D, Baldari CT, Romagnani S, Telford JL, Del Prete G. Different cytokine profile and antigen-specificity repertoire in Helicobacter pylori-specific T cell clones from the antrum of chronic gastritis patients with or without peptic ulcer. Eur J Immunol 27: 1751-1755, 1997.

36. CD4+CD25+ regulatory T cells are being used to treat colitis. J Immunol 170: 3939-3943, 2003.

37. Read S, Malmström V, Powrie F. Cytotoxic T lymphocyte-associated antigen 4 plays an essential role in CD25(+) and CD4(+) regulatory cells that control intestinal inflammation. J Exp Med 192: 295–302 in 2000.

38. De Winter H, Cheroutre H, Kronenberg M. Mucosal immunity and inflammation II. The yin and yang of T cells in intestinal inflammation: pathogenic and protective roles in a mouse colitis model. Am J Physiol 276: G1317-G1321, 1999.

39. Issue A, Coombes JL, Powrie F. Regulatory T cells suppress systemic and mucosal immune activation to control intestinal inflammation. Immunol Rev 212 (2006): 256-271.

40. Regulatory T cells in experimental colitis. [PMID: 15981481] Formalized paraphrase

41. 5. Lundgren A, Strömberg E, Sjöling A, Lindholm C, Enarsson K, Edebo A, Johnsson E, Suri-Payer E, Larsson P, Rudin A, Svennerholm AM, Lundin BS. In Helicobacter pylori-infected patients, mucosal FOXP3-expressing CD4+CD25high regulatory T cells were found. Infect Immun 2005;73(5):523-531.

42. Rad R, Brenner L, Bauer S, Schwendy S, Layland L, da Costa CP, Reindl W, Dossumbekova A, Friedrich M, Saur D, Wagner H, Schmid RM, Prinz C. CD25+/Foxp3+ Inflammatory cells regulate gastric inflammation and Helicobacter pylori colonization in vivo. Gastroenterology 131 (2006): 525–539.

43. Lundgren A, Suri-Payer E, Enarsson K, Svennerholm AM, Lundin BS. Helicobacter pylori-specific CD4+ CD25high regulatory T cells suppress memory T-cell responses to H. pylori in infected individuals. Infect Immun 71: 1755-1762, 2003.

44. Kandulski A, Wex T, Kuester D, Peitz U, Gebert I, Roessner A, Malfertheiner P. Naturally occurring regulatory T cells (CD4+, CD25high, FOXP3+) in the antrum and cardia are associated with higher H. pylori colonization and increased gene expression of TGF-beta1. Helicobacter 13: 295-303, 2008.

45. Kao JY, Rathinavelu S, Eaton KA, Bai L, Zavros Y, Takami M, Pierzchala A, Merchant JL. Helicobacter pylori-secreted factors inhibit dendritic cell IL-12 secretion: a mechanism of ineffective host defense. Am J Physiol Gastrointest Liver Physiol 291: G73-G81, 2006.

46. Kao JY, Zhang M, Miller MJ, Mills JC, Wang B, Liu M, Eaton KA, Zou W, Berndt BE, Cole TS, Takeuchi T, Owyang SY, Luther J. Helicobacter pylori immune escape is mediated by dendritic cell-induced Treg skewing and Th17 suppression in mice. 1046–1054 (Gastroenterology, 2010).

47. Leach MW, Davidson NJ, Fort MM, Powrie F, Rennick DM. The role of IL-10 in inflammatory bowel disease: "of mice and men ."Toxicol Pathol. 1999;27:123-133.

48. Luther J, Owyang SY, Takeuchi T, Cole TS, Zhang M, Liu M, Erb-Downward J, Rubenstein JH, Chen CC, Pierzchala AV, Paul JA, Kao JY. Helicobacter pylori DNA decreases pro-inflammatory cytokine production by dendritic cells and attenuates dextran sodium sulfate-induced colitis. 60: 1479–1486, 2011.

49. Newell DG. Identification of the outer membrane proteins of Campylobacter pyloridis and antigenic cross-reactivity between C. pyloridis and C. jejuni. J Gen Microbiol 133: 163-170, 1987.

50. Tandberg Y, Bengtsson C, Bergström M, Granström M. The accuracy of serologic diagnosis of Helicobacter pylori infection in school-aged children of mixed ethnicity. Helicobacter 6: 24-30, 2001.

51. Epidemiologic and clinical features of Campylobacter jejuni infections. J Infect Dis, 176 Suppl 2: S103-S105, 1997.

52. Lemke LB, Ge Z, Whary MT, Feng Y, Rogers AB, Muthupalani S, Fox JG. Concurrent Helicobacter bilis infection in C57BL/6 mice attenuates pro-inflammatory H. pylori-induced gastric pathology. Infect Immun 2009; 77: 2147-2158

53. Elliott DE, Urban JF JR, Argo CK, Weinstock JV. Does the failure to acquire helminthic parasites predispose to Crohn's disease? FASEB J 2000; 14: 1848-1855

54. Mendall MA, Goggin PM, Molineaux N, Levy J, Topsy T, Strachan D, Northfield TC. Childhood living conditions and Helicobacter pylori seropositivity in adult life. The Lancet 339: 896-897, 1992.

55. Are DK, Lambretta P, Law L, Krupoves A, Chotard V, Costea F, Grimard G, Israel D, Mack D, Seidman EG. Investigating the hygiene hypothesis as a risk factor in pediatric-onset Crohn's disease: a case-control study. American Journal of Gastroenterology, 2006; 101: 1005-1011.

56. Kelly D, Conway S, Aminov R. Commensal gut bacteria: mechanisms of immune modulation. Trends Immunol. 2005;26:326-333.

57. Koloski NA, Bret L, Radford-Smith G. The hygiene hypothesis in inflammatory bowel disease: a critical review of the literature. World Journal of Gastroenterology 2008; 14: 165-173.

58. Raju D, Hussey S, Ang M, Terebiznik MR, Sibony M, Galindo-Mata E, Gupta V, Blanke SR, Delgado A, Romero-Gallo J, Ramjeet MS, Mascarenhas H, Peek RM, Correa P, Streutker C, Hold G, Kunstmann E, Yoshimori T, Silverberg MS, Girardin SE, Philpott DJ, El Omar E, Jones NL. Vacuolating cytotoxin and variants in Atg16L1 that disrupt autophagy promote Helicobacter pylori infection in humans. Gastroenterology 142: 1160–1171 (2012)

**Data availability statement:**

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

**Potential conflict of interest:**

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.