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TOPIC HIGHLIGHT

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Helicobacter pylori infection and inflammatory bowel disease: Is there a link?

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Abstract

Helicobacter pylori (*H. pylori*) infection is one of the most widely spread infectious diseases in humans. It can cause chronic gastritis, peptic ulcer disease and gastric malignancies and has been associated with extra-gastric disorders. *H. pylori* elicit a chronic systemic inflammatory response which, under certain conditions, may trigger autoimmune reactions and may be implicated in the pathogenesis of autoimmune diseases. Although the pathogenesis of inflammatory bowel disease (IBD) is unknown, it is thought to result from complex interactions between environmental factors and microbiota in the gut of individuals who are genetically susceptible. Several bacterial and viral agents have been implicated in the aetiology of IBD. In theory, *H. pylori* infection could be involved in the pathogenesis of IBD by inducing alterations in gastric and/or intestinal permeability or by causing immunological derangements resulting in absorption of antigenic material and autoimmunity via various immunological pathways. Similar mechanisms may also be responsible for the co-existence of IBD with other autoimmune diseases and/or extra-intestinal manifestations. However, the epidemiological data fail to support this association. In fact, various studies indicate that the prevalence of *H. pylori* infection is low in patients with IBD, suggesting a protective role for this infection in the development of IBD. In this report, we aim to shed light on proposed mechanisms and confounding factors underlying the potential link between *H. pylori* infection and IBD.

Key words: *Helicobacter pylori*; Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Colorectal cancer

Core tip: By gathering a large volume of published data, this review attempts to shed light on the mechanisms and confounding factors underlying the potential link between *Helicobacter pylori* (*H. pylori*) infection and Inflammatory Bowel Disease (IBD). However, whether the link between *H. pylori* and IBD is coincidental, epiphenomenal or mechanistic remains to be elucidated as there are contradictory data regarding both the causative and the protective role of *H. pylori* infection against IBD. This review provides a tool for researchers in this field to use as they perform further research to find the missing links.

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INTRODUCTION

Inflammatory bowel diseases (IBDs), which includes Crohn's disease (CD) and ulcerative colitis (UC), are chronic, relapsing-remitting diseases that constitute a growing worldwide health burden[1-3]. Over time, these

diseases may lead to intestinal damage, complications, surgical interventions, gut failure and/or disability[4-7]. IBD is thought to result from complex and unidentified interactions between environmental factors (such as infections, medicines, tobacco, food particles) and genetic factors of the host, resulting in abnormal and/or inappropriate immunological reactions to elements of the intestinal flora. For example, Gradel *et al*[8] demonstrated that infection with either *Campylobacter* or *Salmonella* species predisposed individuals to subsequent development of IBD.

Helicobacter species easily colonize the gastrointestinal surface due to microaerophilic metabolism, spiral shape, and peculiar motility[9]. Based on their location within the gastrointestinal system, they are divided into gastric *Helicobacters,* such as the *Helicobacter pylori* (*H. pylori*), and enterohepatic *Helicobacters* (EHH), which predominantly colonize the intestine and the hepato-biliary system and have been linked to chronic liver and intestinal diseases[9]. *H. pylori* usually resides in the surface epithelium of the stomach, but *H. pylori* DNA has also been identified in both the colon[10] and stool of infected patients[11-13].

H. pylori is a gram-negative, spiral-shaped pathogenic bacterium that causes chronic gastritis. Peptic ulcer disease and/or gastric malignancies may develop in a small number of individuals infected with the bacterium[9,14]. The inflammatory response of the gastric mucosa to *H. pylori* most likely reflects the combined effects of a cellular immune response that is driven by an on-going stimulation of the host's immune system by the bacterium. This results in high production of interleukin (IL)-12, leading to a T helper type 1 (Th1)-polarized response and elevated levels of Th1 cytokines[15-18]. Products of the local immune reactions may travel to extra-gastric sites, thus linking *H. pylori* infection to the pathophysiology of a variety of extra-gastric diseases, including autoimmune disorders[19-21]. Interestingly, however, *H. pylori* has been proposed to play a protective role against the development of certain autoimmune disorders[21] such as asthma[22] and type 1 diabetes mellitus[23]. The mechanisms underlying this protective role of *H. pylori* infection is thought to be differential expression of an acute and/or chronic local mucosal inflammatory response, which may elicit a systemic release of cytokines[24], which in turn may down-regulate systemic immune responses and suppress autoimmunity.

In IBD, dysregulation of the immune response of the host to commensal bacteria has been proposed as an important underlying pathogenetic mechanism. Increased attachment of gut bacteria to the intestinal epithelium has been documented in IBD. A Th1 immune reaction and secretion of pro-inflammatory cytokines is implicated in the pathogenesis of IBD, especially CD[5]. Up-regulation of cell signalling molecules, such as the macrophage inflammatory protein 3a (MIP-3a), has also been documented in IBD[25]. Some IBD patients suffer from concomitant autoimmune diseases and autoimmune-type extra-intestinal manifestations. The similarities between the immunobiology of IBD and that of *H. pylori* infection provides background for the hypothesis that *H. pylori* infection may be implicated in the pathogenesis of IBD.

Nevertheless, there is epidemiological evidence that contradicts the association between *H. pylori* and IBD. *H. pylori* infection is an infection that occurs in underprivileged societies and its prevalence declines when environmental hygienic conditions improve. In contrast the prevalence of IBD increases in societies adapting a Western life style[26]. Thus, it appears that there is an inverse relation between the prevalence of IBD and *H. pylori* infection. IBD is highly prevalent in the United States[27], an area with low rates of *H. pylori* infection whereas, a steady rise in the incidence of IBD has been observed in *H. pylori* endemic regions following widespread use of therapeutic regimens to treat *H. pylori*[28]. Although environmental changes may be the confounding factor underlying this inverse relationship, many (but not all) epidemiological studies have shown a low incidence of *H. pylori* infection in patients with IBD[29-60]. This has led to the hypothesis that *H. pylori* infection may exert a protective role against IBD. However one can argue that it is the medication used to treat IBD that eradicates *H. pylori* and /or the IBD associated mucosal alterations that may prevent colonization of the stomach by *H. pylori*. The latter may be true, especially in IBD patients with focally enhanced gastritis (FEG) who have a particularly low incidence of *H. pylori* infection, even if they live in *H. pylori* endemic areas[33,34,61-64].

Possible mechanisms of the potential protective role of *H. pyloric* infection against the development of IBD may be alteration of the host immunologic response away from the pro-inflammatory Th1/Th17 response towards an increased T-regulatory cell immune response[65,66]. Moreover, *H. pylori* may induce the production of antibacterial peptides that counteract potentially harmful bacteria implicated in the pathogenesis of IBD[67] or compete with bacteria for the same ecologic niche in the upper gastrointestinal tract[68].

CAUSAL ASSOCIATION OF *HELICOBACTER* SPECIES AND *H. PYLORI* WITH IBD

In animal models, EHH such as *Helicobacter hepaticus* (*H. hepaticus*) and *Helicobacter bilis* (*H. bilis*) have been shown to induce a persistent inflammation in the colon and cecum in immuno-deficient rodents[69,70]. *Helicobacter hepaticus* triggers colitis in a specific pathogen-free IL-10-deficient mice through an IL-12 and interferon-gamma (IFN-γ) dependent mechanism[69]. *Helicobacter muridarum* increases disease activity and inflammation in an acute colitis model[71] and provokes a CD-like inflammation in severe combined immunodeficiency mice upon receipt of T cells[72]. Accumulating evidence from gene knockout rodents also indicate that the presence of EHH worsens the severity or hastens the development of colitis[73,74].

However, observations from human studies are conflicting. Several EHH species have been identified in the

large intestine of patients with enteritis and / or proctitis[75]. *Helicobacter macacae* has been linked with chronic idiopathic colitis in young rhesus monkeys[76]. Similarly, Laharie *et al*[77] found that *Helicobacter pullorum* (*H. pullorum*) or *Helicobacter canadensis* infection was significantly associated with CD in adults. *Helicobacter* species were found either in faecal specimens[78] or in colonic biopsy samples[79] of children with CD, and the prevalence of the *Helicobacteraceae* was significantly higher in children with CD (32/77, 41.5%) compared to controls (23/102, 22.5%)[80]. A German group found *Helicobacter fennelliae* and *H. pullorum* in colonic samples of 12% of CD patients[81]. *Helicobacter* genus PCR positivity was also significantly higher in UC than in controls (32/77 *vs* 11/59, $P = 0.004$)[82]. *H. pylori* was isolated and detected by PCR in the intestinal mucosa of patients with UC-like CD and UC[53,54,83]. Moreover, in another study *H. pylori* was found in faecal specimens in the majority of children with CD[78]. In contrast, *Helicobacter* species were not detected in colonic biopsies of IBD patients in various studies[84-88]. Additionally, no significant difference was observed in the rate of detection of *Helicobacter* species in intestinal biopsy specimens from 160 Chinese IBD patients (10%) and 80 controls (6.3%)[57]. Furthermore, in an earlier study assessing gastrointestinal mucosal lesions in children with IBD, infection with *H. pylori* was found in only 2 of 41 children with CD (4.8%) and in 5 of 47 with UC (10.6%)[89].

H. PYLORI AND THE NATURAL HISTORY OF IBD

It is conceivable that *H. pylori* infection may influence the clinical course of CD by triggering both specific and nonspecific immune responses in the human intestine. Phenotype modification of CD was identified in a study in which seropositive non-smoking CD patients had significantly fewer relapses and a lower risk of bowel resection compared to seronegative non-smoking patients[90]. Moreover, serum anti-*H. pylori* IgG levels were significantly lower in subgroups of patients with fibro-stenotic and fistulising CD[54].

There are several hypotheses regarding how *H. pylori* may influence the host immune response and thus alter the clinical course of CD. *H. pylori* infection may exert a direct damaging effect via urease and cytotoxins on the ileal or colonic mucosa[91]. Moreover, *H. pylori* may induce an autoimmune-like reaction in the stomach with the production of anti-Lewis X and/or Y antibodies that have systemic auto reactive properties, thereby influencing the course of the disease[92]. Another mechanism could be the induction of platelet activation and aggregation as shown in murine gastric venules which can cause the formation of microthrombi in gastric and intestinal epithelium and lead to infarction and development of ulcers[93]. Another possibility is that *H. pylori* influences the host immune response via activation of the mucosa-associated lymphoid tissue (MALT), which may lead to a more generalized immune response to *H. pylori* infection in IBD, contributing to the initiation or perpetuation of inflammation. In fact, Duchmann *et al*[94] showed that bacteria-specific T cell clones are increased in inflamed intestinal mucosa of patients with IBD.

It appears that in *H. pylori* infected patients, CD is more often confined to the terminal ileum, a location that is frequently affected by complications, yet may be associated with a lower clinical disease activity[95]. *H. pylori* infection usually occurs early in life, before the onset of CD, so it is possible that this early infection may influence disease location in these patients[96]. As a result, *H. pylori* infection may not influence the course of the disease primarily, but may influences the location of the disease and thus secondarily alters its course.

PROTECTIVE ROLE OF *H. PYLORI* AGAINST IBD

Many studies have reported that the prevalence of *H. pylori* infection is lower in patients with IBD compared to controls, demonstrating an inverse relationship between IBD and *H. pylori* infection that suggests a protective role of *H. pylori* infection against the development of IBD (Table 1)[32-34,38,39,41-46,48,49,52,55,57-59]. However this has not been confirmed by other studies (Table 1)[30,35-37,53,56,60]. Väre *et al*[41] found that seropositive CD patients presented at a significantly later age (40 years) compared to seronegative patients (30 years, $P < 0.001$), suggesting that the higher age of disease onset in seropositive IBD patients is the result of a protective modifier effect that *H. pylori* infection exerts on the development of IBD[41], although this has not been confirmed by other studies[34,42]. Furthermore, a meta-analysis of 23 studies suggested a protective role of *H. pylori* infection in CD pathogenesis, but the heterogeneity among enrolled studies and the possibility of publication bias limited the reliability of these results[97]. The published literature on the prevalence of *H. pylori* infection in UC and CD is diverse. Various studies have found a lower prevalence of this infection in CD compared to UC[29,31,34,41-43], whereas others have found exactly the opposite[34,35,55]; still others have reported no difference in the occurrence of *H. pylori* between the two diseases[30,32,33,36,37,39,48,56,57].

Moreover, the increased occurrence of *H. pylori*-negative FEG among IBD patients also confirmed the inverse association between the prevalence of *H. pylori* infection and IBD (Table 2). For example, *H. pylori*-negative chronic active gastritis was found in only 2% of patients without IBD compared to 20% of patients with IBD (CD 26%, UC 13%)[98]. Furthermore, permanent colonization of the stomach by *H. pylori* is unusual in children with IBD[40].

Heterogeneity among studies regarding the method of IBD and *H. pylori* diagnosis differences in study population, ethnicity and age across studies, and the possibility of publication bias may limit the certainty of the above findings. As environmental hygiene and intestinal

Table 1 Prevalence of *Helicobacter pylori* infection in patients with inflammatory bowel disease in different populations

CD	UC	C	Control group	Method	Positive (%)	Country	Ref.
42	51	40	Patients with irritable bowel syndrome	UBT, *H. pylori* IgG (+)	IBD: 17.2, C: 25 CD: 11.9, UC: 21.6	United Kingdom	[29]
110	213	337	Non-IBD patients with elective surgery[1]	*H. pylori* IgG (+)	IBD: 34.2, C: 36.2 CD: 33.3, UC: 34.7	United Kingdom	[30]
139	137	139	patients with functional GI disorders[1]	*H. pylori* IgG (+)	IBD: 9.4, C: 16 CD: 5, UC: 14	United Kingdom	[31][2]
47	63	100	Blood donors[1]	*H. pylori* IgG (+), UBT, histology	IBD: 21.8, C: 52 CD: 14.9, UC: 27,	United Kingdom	[32][2]
67	41	43	Non-IBD patients	Biopsies	IBD: 28.7, C: 39.5 CD: 28.4, UC: 29.3,	Italy	[33][2]
123	93	216	Blood donors[1]	*H. pylori* IgG (+), histology	IBD: 48.1, C: 58.8 CD: 40.7, UC: 55.9	Italy	[34][2]
32	40	72	Healthy subjects[1]	UBT	IBD: 47.2, C: 61.1 CD: 53.1, UC: 42.5	Italy	[35]
12	8	29	Patients with idiopathic constipation	UBT	IBD: 60, C: 41 CD: NR, UC: NR	Italy	[36]
45	66	77	Patients with non-organic dyspepsia[1]	histology	IBD: 66.7, C: 63.6 CD: 62.2, UC: 69.7	Turkey	[37]
0	90	120	Healthy subjects	Histology, RUT	IBD: 30, C: 52.5 CD: NA, UC: 30	Greece	[38][2]
39	77	127	Healthy subjects[1]	*H. pylori* IgG (+)	IBD: 31.7, C: 55.1 CD: 28.6, UC: 33.1	Greece	[39][2]
19	21	NA	NA	*H. pylori* IgG, IgA (+), histology	IBD: 0, C: NA CD: NA, UC: NA	Finland	[40][3]
94	185	70	Healthy subjects[1]	*H. pylori* IgG, IgA (+)	IBD: 24.4, C: 37.1 CD: 12.9, UC: 29.7	Finland	[41][2]
100	100	100	Patients with acute bacterial diarrhoea[1]	*H. pylori* IgG, IgA (+)	IBD: 15, C: 43 CD: 13, UC: 18	Finland	[42][2]
147	169	316	Non-IBD patients[1]	UBT	IBD: 25.3, C: 52.5 CD: 17.7, UC: 32	Korea	[43][2]
386	0	277	Blood donors[1]	*H. pylori* IgG, IgA (+)	IBD: 17.4, C: 35.4 CD: 17.4, UC: NA	Nederland	[44][2]
90	0	525	Non-IBD patients	Histology	IBD: 16.7, C: 40.2 CD: 16.7, UC: NA	Japan	[45][2]
38	0	12	Healthy subjects[1]	UBT	IBD:8, C: 42 CD: 8, UC: NA	Japan	[46][2]
80	39	98	Non-IBD patients[1]	*H. pylori* IgG (+)	IBD: 27.5, C: 41.7 CD: 13.5, UC: 30.8	Israel	[47][2]
51	82	200	Non-IBD patients[1]	UBT	IBD: 12.8, C: 39 CD: 13.7, UC: 12.2	Hungary	[48][2]
36	0	36	Healthy subjects[1]	Histology	IBD: 8.3, C: 36.1 CD: 8.3, UC: NA	Germany	[49][2]
75	0	200	Non-CD patients	Histology	IBD: 30.5, C: 35.2 CD: 33, UC: NA	Germany	[50]
56	0	382	Non-CD patients	Histology	IBD: 32.1, C: 46.1 CD: 32.1, UC: NA	USA	[51][3]
371	560	64451	Non-IBD patients	Histology	IBD: 4.5, C: 9 CD: 4, UC: 5	USA	[52][2]
0	42	74	Non-IBD patients	*H. pylori* IgG (+), UBT	IBD: 52.4, C: 51.4 CD: NA, UC: 52.4	Brazil	[53]
43	0	74	Non-IBD patients	UBT	IBD: 51.2, C: 70.3 CD: 51.2, UC: NA	Brazil	[54]
50	44	194	Non-IBD patients	Histology, RUT	IBD: 9.6, C: 38.5 CD: 14, UC: 4.5	Poland	[55][2,3]
21	23	76	Non-IBD patients	*H. pylori* IgG (+)	IBD: 54.5, C: 68 CD: 52.2, UC: 57.1	Mexico	[56]
104	104	416	Healthy subjects[1]	UBT	IBD: 19.7, C: 48.8 CD: 18.3, UC: 21.2	Chinese	[57][2]
229	0	248	Non-CD patients	UBT, culture, histology	IBD: 27.1, C: 47.9 CD: 27.1, UC: NA	Chinese	[58][2]
0	153	121	Non-UC patients	UBT, culture, histology	IBD: 30.5, C: 57 CD: NA, UC: 30.5	Chinese	[59]
30	30	20	Non-IBD patients[1]	UBT	IBD: 43, C: 40 CD: 50, UC: 37	Spain	[60]

[1]Age and sex matched; [2]Statistically significant result (IBD *vs* control group); [3]Paediatric population. CD: Crohn's disease; UC: Ulcerative colitis; C: Controls; IBD: Inflammatory bowel disease; GI: Gastrointestinal; *H. pylori*: *Helicobacter pylori*; Ref: References; NA: Not applicable; NR: Not reported; FAT: Serology fecal antigen test; RUT: Rapid urease test; UBT: Urea breath test.

Table 2 Prevalence of both *Helicobacter pylori* negative and positive gastritis in patients with inflammatory bowel disease in different populations

CD	UC	C	Control group	Biopsies	*H. pylori* (+) gastritis (%)	*H. pylori* (-) gastritis (%)	Ref.
37	43	41	Non-IBD patients	Antrum, body	CD: 27, UC: 37.2 C: 53.7	CD: 29.6, UC: 22.2 C: 10.5	[61]
141	79	141	Non-IBD patients	Antrum, angulus, body	CD: 33, UC: 47 C: 60	CD: 43, UC: 12 C: 19	[34]
75	0	200	CD-free patients	Antrum, body	CD: 33.3, UC: NA C: 48	CD: 39, UC: NA C: 0.8	[50]
208	280	4943	Non-IBD patients	Antrum, body	CD: 4, UC: 6 C: 7	CD: 5, UC: 0 C: 0	[63]
67	41	43	Healthy subjects	Antrum, body	CD: 17.6, UC: 6.4 C: 20	CD: 45.4 , UC: 15.6 C: 30	[33]
62	0	0	NA	Antrum, corpus	CD: 9.7, UC: NA C: NA	CD: 32 , UC: NA C: NA	[64]

CD: Crohn's disease; UC: Ulcerative colitis; C: Controls; IBD: Inflammatory bowel disease; *H. pylori*: *Helicobacter pylori*; NA: Not applicable.

microbiota may be strong confounders, further mechanistic studies in *H. pylori* infection using mouse models are necessary to further define the mechanism of this negative association. Furthermore, when looking for explanations for the lower prevalence of *H. pylori* infection in IBD, some authors have suggested that treatment with sulfasalazine and other aminosalicylic compounds could be responsible for "spontaneous eradication" of *H. pylori* infection[32,34,35,38]; although their possible role has not been confirmed by other studies[29-31,37,39,41-45,55,57,60,99]. Various studies have suggested that sulfasalazine, but not 5-aminosalicylic acid (5-ASA), could account for the lower prevalence of *H. pylori* infection[32,34], whereas Piodi *et al*[35] found the opposite. Ishikawa *et al*[100] observed a lower prevalence of *H. pylori* infection in rheumatoid arthritis patients receiving sulfasalazine, whereas Taha *et al*[101] did not find any statistically significant difference. The mechanisms of how these agents prevent *H. pylori* infection is still unknown, but prevention may be the result of a direct action against germ adhesion to the gastric mucosa or due to immuno-modulatory actions of the drugs[30,102,103]. It has also been hypothesized that prolonged treatment with antibiotics used in IBD (especially metronidazole) could account for spontaneous eradication and lower prevalence of *H. pylori* infection. Indeed the prevalence of *H. pylori* infection was significantly lower in CD patients who had received antibiotics for $\geqslant$ 2 wk[45] while in another study, antibiotic therapy was negatively associated with *H. pylori* infection (20.5% *vs* 55%, $P = 0.0001$)[39]. Moreover, other studies have shown that prior treatment with ciprofloxacin and/or metronidazole had no influence on *H. pylori* status in IBD patients[48,104,105].

Finally, the data on the prevalence of virulent *H. pylori* strains in IBD patients are limited. Wagtmans *et al*[44] showed that the majority (66%) of *H. pylori* seropositive patients with CD were infected by *H. pylori* cagA (+) strains although a similar proportion of controls (69.4%) were also infected by these strains. These findings deserve further investigation as it is well known that the intense host responses, specifically to *H. pylori* cagA (+) strains may further alter Th1- and Th2-type immune responses with subsequent induction of immune-regulatory lymphocytes[106].

POTENTIAL PROTECTIVE MECHANISMS OF *H. PYLORI* AGAINST IBD

It is plausible to suggest that *H. pylori,* by attempting to promote its own survival, may benefit the host via a variety of mechanisms against other chronic inflammatory conditions such as IBD. Several mechanisms have been proposed to explain the inverse association between *H. pylori* and IBD. In CD, Th1 immune responses prevail, whereas in UC, Th2 or Th1/Th2 immune responses may be predominant[5,107,108]. These altered immune responses to lumen antigens in IBD may influence the way the host responds to *H. pylori* infection. Conversely, a perpetual bacterial infection in the stomach may either alter the host immune responses in a way that may be protective or render the host susceptible to IBD. The levels of numerous cytokines, including IFN-γ, TNF, IL-1β, IL-6, IL-7, IL-8, IL-10, and IL-18, are increased in the gastric epithelial cells of *H. pylori* infected humans compared to uninfected humans[109-111]. After activation of Toll-like receptors by *H. pylori,* dendritic cells (DC) may activate T cells in different ways, being capable of inducing either a Th1 or Th2/regulatory T cell (Treg) response by generation of IL-12 or IL-10, respectively[112,113]. This finding was reported by D'Elios *et al*[114] who observed that most (64%) of *H. pylori* specific T cell clones derived from uncomplicated chronic gastritis displayed a Th2-like phenotype, producing interleukin IL-4 or IL-5 together with INF-a, whereas only one third of *H. pylori*-specific gastric T cells were polarized with Th1 effectors.

Thus, a protective role of *H. pylori* infection against IBD may be due to the ability of this microbe to down-regulate pro-inflammatory immune responses. Considering that adoptive transfer of Treg is able to prevent and/or treat colitis in various animal models, it is reasonable to suggest that these cells produced in response to *H.*

pylori infection may act in the prevention of IBD[115-119]. *H. pylori* can induce a Treg response and down-regulate the pro-inflammatory Th1/Th17 pathway[65,66,120-123]. The importance of Treg in the pathogenesis of IBD was illustrated by the development of spontaneous colitis in mice deficient of IL-10, a key regulatory cytokine for Treg function[124].

Moreover, the systemic levels of type I IFN were found to be lower in *H. pylori* infection-colonized IBD patients compared to non-colonized controls[125]. Luther *et al*[125] showed that prior oral administration of 20-50 μg *H. pylori* DNA ameliorated the severity of dextran sulphate sodium (DSS) induced acute or chronic colitis in mice in terms of both pathology and symptoms such as bleeding and weight loss. Thus, the protective properties of *H. pylori* DNA were attributed *in vitro* to inhibition of cytokine production by DC, which upon addition of the DNA failed to produce type I interferon and IL-12 in response to *E. coli* DNA[125]. A protective effect of *H. pylori* colonization in mice against experimental colitis was also demonstrated by Higgins *et al*[126]. Mice that were colonized with *H. pylori* SS1 6 wk prior to the induction of *Salmonella typhimurium* experimental colitis, experienced markedly less severity inflammation compared to mice that were not colonized with *H. pylori*. This result could be attributed to an up-regulation of IL-10 in the mesenteric lymph nodes and suppression of the Th-17 response in the cecum of the infected mice[126], illustrating an extra-gastric immune-modulatory effect of the bacterium, an immunological crosstalk between the upper and lower gastrointestinal tract and providing mechanistic support for the epidemiological observation of a negative association between *H. pylori* status and the risk of IBD.

Another protective mechanism may operate via the development of antibodies against *H. pylori,* which may confer an immunization-type protection against other pathogenic *Helicobacter* or even different types of microbes implicated in IBD. Although *H. pylori*-specific antibodies do not eradicate this bacterium, they seem to confer a degree of protective immunity from a subsequent *Campylobacter* infection, indicating an antigenic cross-reactivity between these two bacterial species[127-129]. It could also be that *H. pylori* induced reduction in acid secretion indirectly affects a different type of infection that ultimately results in IBD. Indeed, variable disease phenotype during dual infection by different *Helicobacter* species has been described by Lemke *et al*[130] who demonstrated that *H. bilis* and *H. pylori* co-infection in mice attenuates *H. pylori* gastritis compared to those infected only with *H. pylori*.

The protective effect of *H. pylori* may simply be due to other confounding variables such as the presence of inherent genetic or environmental factors that favour *H. pylori* acquisition in some and the development of IBD in others. This scenario would fit well with the observation that IBD is associated with better hygiene, which in itself may be detrimental to *H. pylori* acquisition[131,132]. The low prevalence of *H. pylori* infection in patients with IBD compared to non-IBD patients strengthens the importance of the "hygiene hypothesis" in the development of autoimmunity and IBD. It suggests that inadequate microbial stimulation of gut-associated lymphoid tissue is a critical point for maturation of mucosal immunity[133,134]. Improved access to a cleaner environment and the resulting decreased incidence of common childhood infections, including *H. pylori,* may be contributing to autoimmunity by altering susceptibility to certain diseases with an autoimmune component, such as IBD[26].

Finally, regarding genetic factors, the CD variant of the autophagy gene ATG16L1 alters susceptibility to *H. pylori* infection with an enteric microbe in human subjects at the population level, supporting a role for altered autophagy in regulating the host response to enteric microbes in CD pathogenesis. It is interesting to speculate that due to increased susceptibility to infection, early exposure and acquisition of *H. pylori* in individuals with the ATG16L risk allele may decrease their risk for the subsequent development of IBD[135].

ERADICATION OF *H. PYLORI* AND DEVELOPMENT OF IBD

There seems to be a rapid onset of CD after eradication of *H. pylori* infection, as illustrated by two cases[136]. A similar experience was recently described by Jovanovic *et al*[137], who described the onset of gastric CD only 6 mo after *H. pylori* infection eradication. Moreover, a steady rise in the incidence of UC was reported in *H. pylori* endemic regions after successful eradication of *H. pylori* infection[28].

It is unknown why these patients developed CD after eradication of *H. pylori* infection, but this may be due to the induction of immune responses that in turn contributed to the development of the disease. Long-term *H. pylori* infection may cause an unstable equilibrium between the Th1 and Th2 phenotype pattern; eradication of *H. pylori* infection may diminish Th2 cytokine, with sudden consequent Th1 pattern prevalence and rapid increase of pro-inflammatory cytokines[106]. In genetically predisposed subjects, this Th1 predominant pattern may suddenly favour the onset of a typical Th1-related disease such as CD. Further studies investigating the effect of eradication of *H. pylori* on the development and natural history of IBD are warranted.

CAUSAL ASSOCIATION OF *H. PYLORI* WITH COLORECTAL CANCER?

A meta-analysis of 13 studies suggested an increased risk of colorectal cancer due to *H. pylori* infection[138]. Kapetanakis *et al*[139] demonstrated the presence of *H. pylori* in malignant colonic tissue in 34 of 41 (82.9%) patients with colorectal cancer. *H. pylori* colonizing colonic tumour tissue seems to be associated with increased cell proliferation and impaired apoptotic process in malignant tissue

compared with adjacent normal colonic mucosa, thereby further contributing to colon cancer progression[140]. Furthermore, *H. pylori* induced gastrin release can act as promoter of cell proliferation and differentiation (mainly by inducing COX-2 overexpression and PI3-kinase-mediated tyrosine phosphorylation of E-cadherin and b-catenin) in different gastrointestinal tract sites, including the colon[141]. *H. pylori* infection is also accompanied by bone-marrow–derived stem cell (CD34+) recruitment that ultimately facilitates colon cancer progression[142]. Finally, compared to normal gastric mucosa, *H. pylori* gastritis occurred more frequently among patients with hyperplastic polyps (OR = 1.24, 95%CI: 1.18-1.30), adenomatous polyps (OR = 1.52, 95%CI: 1.46-1.57), advanced adenomas (OR = 1.80, 95%CI: 1.69-1.92), villous adenomas or adenomas with high-grade dysplasia (OR = 1.97, 95%CI: 1.82-2.14), and adenocarcinomas (OR = 2.35, 95%CI: 1.98-2.80)[143]. It has therefore been proposed that *H. pylori* eradication might inhibit IBD-related or non-colon neoplasia[144].

CONCLUSION

Since the discovery of *H. pylori*, several epidemiological studies, therapeutic trials, case reports and/or *in vitro* studies have been published concerning a hypothetical damaging or protective role of *H. pylori* in the development of IBD. Whether the link between *H. pylori* and IBD is coincidental, epiphenomenal or mechanistic remains uncertain. There are contradictory data regarding both the causative and the protective role of *H. pylori* infection against IBD.

The discordance between studies may be explained by a number of confounding factors, such as variability in the power of the studies and the time periods in which these studies were conducted, geographical factors and the differences in the methods used to detect *H. pylori* infection[145]. To be more specific, the urease breath test is more sensitive in detecting *H. pylori* than histology. Histology involves the examination of tissue samples that may be insufficient for a correct diagnosis and is more timely than serology, which also detects previous infections. Furthermore, one limitation of the studies using serology for the presence of *H. pylori* is the fact that after successful eradication of *H. pylori* infection, positive titres of antibodies normalize very slowly within several months, or even years, leading to the possibility that negative findings from *H. pylori* serology do not reflect eradication of *H. pylori* infection[146]. Finally, from a clinical point of view, we must always bear in mind that any type of protection that exerts its influence on a general population level may not necessarily materialize in the individual patient.

In conclusion, the association between *H. pylori* infection and IBD is still controversial; however, it is worthy of further investigation, as the potential association of *H. pylori* with extra-gastric manifestations and disorders is always a very interesting and challenging research area[147]. It is unclear whether the apparent protective effect of *H. pylori* is simply confounding due to other variables, but the effect of the presence of the live bacterium remains to be elucidated. More studies investigating the effect of *H. pylori* infection eradication on the risk of development of IBD and the natural history of IBD are needed.

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