Review

The Controversies of the Relationship Between *Helicobacter Pylori* Infection and Inflammatory Bowel Disease: A Review

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Review

The Controversies of the Relationship Between *Helicobacter pylori* infection and Inflammatory Bowel Disease: A Review

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Abstract

Background: The relationship between *Helicobacter pylori* (*H. pylori*) infection and inflammatory bowel disease (IBD) remains controversial. While *H. pylori* is a well-established pathogen in gastroduodenal diseases, emerging evidence suggests it may exert immunomodulatory effects that influence the pathogenesis and clinical course of IBD. **Objective:** This review aims to explore the association between *H. pylori* infection and IBD, focusing on infection prevalence among IBD patients, the potential protective or harmful roles of *H. pylori*, and the impact of eradication therapy on IBD onset and activity. **Methods:** A comprehensive literature search was conducted using PubMed up to May 25, 2025, including clinical studies, meta-analyses, systematic reviews, and observational data. A total of 40 studies met the inclusion criteria and were critically reviewed. **Results:** The majority of studies indicate a significantly lower prevalence of *H. pylori* infection among patients with IBD compared to the general population. Several meta-analyses support a potential protective effect, particularly in Crohn's disease and among CagA-positive *H. pylori* strains. However, data on the impact of eradication therapy on IBD progression remain inconclusive. Some studies suggest a higher relapse risk post-eradication, while others report no change in disease activity. Variability in outcomes may be influenced by geographic, demographic, and methodological differences, as well as disease activity at the time of eradication. **Conclusion:** Although numerous studies support an inverse association between *H. pylori* infection and IBD, the nature and direction of this relationship remain unclear. Given the complex interplay between host immunity, gut microbiota, and antibiotic exposure, the decision to eradicate *H. pylori* in IBD patients should be individualized. Further prospective studies are needed to clarify the immunological and microbiological mechanisms underlying this association and to inform clinical guidelines.

Keywords: *Helicobacter pylori*; inflammatory bowel disease; challenges; eradication; treatment; Crohn's disease; ulcerative colitis

1. Introduction

Helicobacter pylori (*H. pylori*) has co-evolved with humans for over 60,000 years [1] and was first successfully isolated from a gastric biopsy in 1983 by Marshall and Warren [2]. This spiral-shaped, microaerophilic, Gram-negative bacterium infects more than 50% of the global population [3]. Its prevalence is positively correlated with advancing age and lower socioeconomic status, although substantial geographic and demographic variations exist due to environmental and population-specific factors [4]. Early-life conditions, particularly poor hygiene and overcrowded living environments during childhood, have been identified as key risk factors for acquisition of the infection [5,6].

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H. pylori is primarily transmitted via oral-oral and fecal-oral routes, with contaminated water sources also recognized as a potential vehicle for transmission [7]. Infection typically occurs during childhood and, in the absence of treatment, tends to persist throughout the host's lifetime [8].

Clinically, *H. pylori* is associated with a wide spectrum of gastrointestinal and extra-gastrointestinal diseases. These include peptic ulcer disease, autoimmune gastritis, and gastric malignancies including mucosa-associated lymphoid tissue (MALT) lymphoma and adenocarcinoma, as well as conditions such as iron deficiency anemia, vitamin B12 deficiency, and idiopathic thrombocytopenic purpura [9,10]. Also, increasing evidence has suggested a potential association between *H. pylori* infection and several autoimmune diseases. It has been reported a higher prevalence of *H. pylori* infection among patients with autoimmune conditions compared to the general population [11]. One of the most thoroughly investigated associations is with idiopathic thrombocytopenic purpura (ITP), where several clinical studies have shown that eradication of *H. pylori* can lead to a significant increase in platelet counts in a subset of patients. A similar trend has been observed in autoimmune thyroid diseases, including Hashimoto's thyroiditis and Graves' disease, where *H. pylori* infection appears more frequently in affected individuals than in healthy controls. Elevated rates of infection have also been reported in patients with systemic lupus erythematosus (SLE), rheumatoid arthritis, and primary Sjögren's syndrome [11].

Interestingly, some studies have demonstrated an inverse association between *H. pylori* colonization and the incidence of certain autoimmune diseases, particularly inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis. In these cases, *H. pylori* infection was significantly less common in affected individuals compared to control populations, leading to hypotheses regarding a possible protective role [12].

While the exact nature of the relationship remains unclear, current literature supports a statistically significant association between *H. pylori* infection and various autoimmune conditions. These findings highlight the need for further research to clarify potential causality and to evaluate the clinical relevance of screening or treating *H. pylori* infection in patients with autoimmune diseases.

Inflammatory bowel disease (IBD) is a chronic, relapsing-remitting inflammatory disorder of the gastrointestinal tract, encompassing Crohn's disease (CD), ulcerative colitis (UC), and other related entities [13]. The hallmark feature of IBD is mucosal inflammation of the intestinal tract, manifesting clinically with abdominal pain, diarrhea, rectal bleeding (hematochezia), weight loss, and histologically with infiltration of neutrophils and macrophages. These immune cells release pro-inflammatory cytokines, proteolytic enzymes, and reactive oxygen species, contributing to tissue injury, ulceration, and progressive mucosal damage [13,14].

IBD typically presents early in life, affects both sexes, and persists throughout the patient's lifetime. Its pathogenesis is multifactorial, involving a complex interplay of genetic susceptibility, environmental influences, and immune system dysregulation. A positive family history is a strong risk factor, indicating a significant genetic contribution. Environmental triggers-such as Westernized diet, smoking, and antibiotic exposure—are believed to disturb the composition of the gut microbiota (dysbiosis), thereby promoting chronic inflammation. Immune dysregulation plays a central role, wherein an aberrant immune response mistakenly targets the intestinal epithelium. The systemic nature of IBD is evidenced by its common extraintestinal manifestations, including arthritis, dermatologic conditions, and hepatobiliary disorders [15].

Since the mid-20th century, the global incidence and prevalence of IBD have increased substantially, making it one of the most common chronic gastrointestinal diseases in the 21st century. Although the incidence in Western countries has plateaued or slightly declined since the 1990s, newly industrialized regions in Asia, Africa, and South America are experiencing a rapid rise in IBD cases [16–18]. For instance, the highest prevalence rates have been documented in Europe, with ulcerative colitis reaching 505 per 100,000 individuals in southeastern Norway and Crohn's disease 322 per 100,000 in Hesse, Germany. Similarly, in North America, ulcerative colitis and Crohn's disease were reported at 286.3 and 318.5 per 100,000 individuals, respectively, in Olmsted County (USA) and Nova Scotia (Canada) [18]. Despite a decline in the age-standardized incidence rate, the global burden of

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IBD among the elderly is projected to rise significantly by 2051, necessitating strategic planning for healthcare systems worldwide [19].

Crohn's disease most frequently involves the terminal ileum, cecum, perianal region, and colon, but it may affect any segment of the gastrointestinal tract in a discontinuous (skip lesion) pattern [15,20,21]. In contrast, ulcerative colitis is characterized by continuous mucosal inflammation beginning in the rectum and extending proximally to varying lengths of the colon [15,20,21]. Histopathological features further distinguish the two conditions: CD demonstrates transmural inflammation, submucosal thickening, fissuring ulcers, and granuloma formation, while UC is confined to the mucosa and submucosa, typically presenting with cryptitis, crypt abscesses, and architectural distortion [15,21,22].

As chronic, immune-mediated disorders, IBDs necessitate lifelong management strategies aimed at achieving and maintaining clinical remission, minimizing flares, and preventing complications. Immunosuppressive and biologic therapies are the cornerstone of treatment, targeting the inflammatory cascade to modulate disease activity.

The coexistence of *H. pylori* infection and IBD raises important clinical questions. Epidemiological studies consistently report a lower prevalence of *H. pylori* infection among IBD patients compared to the general population [23]. This observation has been attributed to factors such as frequent antibiotic use in IBD management, immune dysregulation that may impair bacterial colonization, and the altered gut microbiota environment in IBD patients. However, the implications of *H. pylori* eradication therapy in this population remain unclear, with conflicting evidence regarding its impact on IBD disease activity, symptomatology, and long-term outcomes.

The impact of *Helicobacter pylori* eradication on inflammatory bowel disease (IBD) activity remains controversial. While some evidence suggests a potential increase in disease relapse following antibiotic therapy, findings are inconsistent. A recent meta-analysis reported a 1.41-fold increased risk of IBD relapse after *H. pylori* eradication [23]. In contrast, a study by Rosania et al. found no significant recurrence among over 100 IBD patients [24]. Similarly, a large retrospective cohort study in Japan involving more than 400 IBD patients revealed no significant exacerbation of disease activity at two and six months post-eradication therapy compared to controls [25]. Additionally, studies such as that by Lahat et al., which excluded patients with active IBD at baseline, reported no statistically significant changes in clinical indices or inflammatory markers up to eight weeks post-therapy [26]. However, the small sample size in that study limits the generalizability of its conclusions. Collectively, current evidence remains inconclusive, underscoring the need for larger, prospective studies to clarify the relationship between *H. pylori* eradication and IBD activity.

Despite ongoing research, the implications of *Helicobacter pylori* eradication for inflammatory bowel disease remain uncertain, especially in the context of disease activity and potential exacerbations. Moreover, eradication of *Helicobacter pylori* has been considered a potential environmental factor in the development of inflammatory bowel disease, particularly among individuals with underlying genetic susceptibility. This possibility warrants a cautious approach when contemplating eradication therapy in IBD patients and emphasizes the importance of further prospective, controlled investigations into its long-term impact.

This article explores the complexities associated with diagnosing and treating *H. pylori* infection in IBD patients, with a focus on potential complications, therapeutic strategies, and areas for future research.

2. Materials and Methods

2.1. Information Source and Search Strategies

The aim of this review was to determine: 1) the association between *H. pylori* infection and inflammatory bowel diseases; 2) the prevalence of *H. pylori* infection in patients with inflammatory bowel diseases (ulcerative colitis and Crohn's disease), and 3) the impact of *H. pylori* eradication on the new occurrence of IBD or exacerbation of pre-existing inflammatory bowel disease; 4) and the

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general cause-and-effect relationship between these two chronic infections of the gastrointestinal tract.

A comprehensive literature search was conducted in PubMed electonic database from inception to 25th May 2025. The MeSH terms used in the search were "*Helicobacter pylori*", "inflammatory bowel disease", "eradication", "association". Using the simultaneous combination of these MeSH terms with "AND" as a boolean operator did not get the required research results, so we used a combination of terms "*Helicobacter pylori*" *AND* "inflammatory bowel disease" AND "eradication", and combination of these MeSH terms "*Helicobacter pylori*" AND "inflammatory bowel disease", AND "association".

Only publications in the English language were included. Inclusion criteria encompassed diverse study designs, including Clinical Study, Clinical Trial, Controlled Clinical Trial, Meta-Analysis, Multicenter Study, Observational Study, Randomized Controlled Trial, Review, Systematic Review, to ensure thorough evidence coverage.

The reference lists of the relevant articles were manually searched for additional studies.Only publications in the English language were included and free-full texts manuscripts. There was no restriction on the year of publication for the documents. All included publications were critically reviewed.The summary tables of articles used in this paper are available in the section Results.

2.2. Eligibilty Criteria

Specific inclusion criteria involved human studies with adult and pediatric study populations and animal studies, too. Clinical study, clinical trial, controlled clinical trial, meta-analysis, multicenter study, observational study, randomized controlled trial, review and systematic review written in English with free full text availability are included in our review.

Exclusion criteria for this review were delineated as follows: (1) studies with primary endpoints not aligned with the scope of this review, (2) books and documents, letter, commentaries, preprint, case reports, and case series, (3) in vitro studies, (4) studies published in languages other than English, (5) articles without full-text availability.

3. Results

Using MeSH terms "*Helicobacter pylori*" *AND* "inflammatory bowel disease" AND "eradication" the article search identified twenty-six relevant full-text articles from the PubMed electronic database, of witch sixteen articles met the full inclusion criteria [12,23,27–41]. By searching electonic database PubMed using MeSH terms "*Helicobacter pylori*" AND "inflammatory bowel disease" AND "association" we have identified seventy six full text articles. After elimination of duplicate articles with the first search and identification of additional manuscripts, twenty-four studies that met the full inclusion criteria for this article were retrieved and fully reviewed [11,42–65].

Summarizing all forty selected articles for this article, 18 review articles, 9 meta-analyses, 4 systematic reviews, 1 umbrella review of meta-analyses, 2 bibliometric analysis, 3 multicenter studies, and 3 observational studies were included in this review.

See the results in the Table 1.

Table 1. List of studies/research on the topic of the association/eradication between *H. pylori* infection and inflammatory bowel diseases.

Authors/Year of Publication (Reference)	**Type of study**	**Study population Number/N/ of IBD subjects or publications**	**Results**	**Conclusions possible beneficial effects of *H. pylori in IBD* *YES/NO/UN***

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Gravina, A.G. et al./ 2024. (27)	**review**	**Adults Case reports, N=5 N=4 clinical studies, N=563 subjects**	**The onset of IBD after the eradication treatment of *H. pylori* infection. No significant association between *H. pylori* eradication and recurrence or exacerbation of IBD**	**no specific recommendations for this particular situation in the leading international IBD and *H. pylori* guidelines UN**
Dilaghi, E. et al./2024. (28)	**prospective multicenter study**	**Pediatric population N=76subjects**	**The occurrence of Hp-infection did not differ between IBD and no-IBD patients. No differences in CAI or ESS were observed at the diagnosis, and after ET no worsening of CAI or ESS was noted at one-year FU, between Hp-positive and -negative IBD patients.**	**No asociation between *H. pylori* eradication and exacerbation of IBD. NO**
Kotilea, K. et al/2024. (29)	**retrospective multicenter study**	**Pediatric population N=1292 subjects**	**H.pylori was identified in** 8.5% IBD patients. The prevalence differed significantly between Europe (Eastern 5.2%, Southern 3.8% , Western 5.6%) and the Middle East 26.6%. Eradication treatment was prescribed in 35.8% IBD.	**Identifying *H. pylori* incidentally during UGE performed for the most common gastrointestinal diseases varies significantly among regions but not among diseases. NO**

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Bretto, E. et al./2024. (30)	**systematic review**	**Pediatric and adults population N= more than 6000 subjects**	**Reduced incidence of *H. pylori* infection in patients with IBDs. Potential protective role of H.pylori against the development of immune-mediated diseases, particularly when considering the CagA-positive strain, regardless of age, ethnicity, previous treatment with corticosteroids, antibiotics and mesalazine. Conflicting findings highlight potential risks, particularly in CD.**	**The relationship between *H. pylori* infection and IBDs remains a topic of debate, with conflicting evidence from different studies. UN**
Wang, Z. et al./2024. (40)	bibliometric analysis	Adults N= 246 publications	the number of papers on *H. pylori* and IBD has increased significantly over the past two decades.China, the United States, and Australia are at the forefront of this field.	Despite notable progress in the last decade, challenges remain. The exact relationship between *H. pylori* and IBD is still uncertain. Many studies suggest that *H. pylori* infection may reduce the risk and severity of IBD, but others present different perspectives. UN
Li, Y. et al./2024. (41)	bibliometric analysis	Adults N=1196 publications	Most studies focus on the immune mechanism of *H. pylori* negatively correlated with IBD, and there are still a lot of gaps for researchers to fill.The question of whether *H. pylori* definitively offers protective effects against IBD remains	Therefore, further investigation could explore the underlying mechanisms of their relationship or initiate long-term prospective cohort studies to gather more compelling evidence. UN

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			unresolved.	
Kong, G. et al./2023. (42)	meta-analysis	Pediatric population N=2236 subjects	No significant difference in *H. pylori* prevalence (9.8% vs 12.7%) by comparing the children IBD group to controls. In children suffering UC and CD, the *H. pylori* infection rates were higher than in those with IBD-unclassified.	No correlation was found between *H. pylori* infection and the occurrence of IBD in children. NO
Ravikumara M. /2023. (31)	**review**	**Pediatric population N=UNsubjects**	*H. pylori* is a potent modulator of the immune system and prevents IBD.	possible beneficial effects *H. pylori* may confer against IBD especially in childhood. YES
Feilstrecker Balani, G. et al. /2023. (43)	**review**	**Adults N=UNsubjects**	*H. pylori* neutrophil-activating protein (HP-NAP) is a virulence factor that plays an important role in immunomodulation.	In this review we emphasize the role of *H. pylori* CagA+ and HP-NAP on favorable prognosis of IBD. YES
He, J. et al. /2022. (44)	review	**Adults N=UNsubjects**	Association between CagA seropositivity and lower odds of IBD.	*Helicobacter pylori* infection might play a protective role in inflammatory bowel disease (IBD). YES
Abd El-Wahab, E.W. et al./2022. (45)	Prospective observational study	Adults N=182 subjects	49.5% patients with IBD had evidence of *H. pylori* infection.The majority of patients who were *H. pylori* positive with IBD admitted undergoing *H. pylori* eradication	The number of patients who recovered from IBD among patients who were *H. pylori* negative was similar to that of patients who were *H. pylori* positive. The association between IBD

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			therapy during the previous 12 months, which raises questions about the efficacy of eradication therapy or revels reinfection among this group of patients.	and *H. pylori* infection is unresolved and should be further investigated. UN
Wang, L. et al. /2022. (11)	review	Adults N=UN subjects	The epidemiological literature generally supports a negative correlation between *H. pylori* and IBD.	Most studies support a negative association between *H. pylori* and IBD, but some scholars suggest that only CagA seropositive *H. pylori* exposure may be relevant to IBD. YES
Axelrad, J.E. et al./2021. (46)	systematic review	N=97 studies	Compared with CagA-negative *H. pylori* exposure or *H. pylori* non-exposure overall, exposure to CagA-positive *H. pylori* was associated with a significantly lower odds of IBD.	It is important to emphasize that not all *Helicobacter* species are inversely associated with IBD. YES
Murad, H.et al./2021. (32)	**observational cross-sectional study:**	**Adults** **N=203 subjects**	**Sequential eradication therapy did not affect serum OPG levels in patients with *H. pylori* infection and co-existing IBD. Thus, serum OPG elevation may be used as a marker of the development of IBD in patients of active or prior *H. pylori* infection.**	Further research is recommend. UN
Zhong, Y. et al. /2021. (23)	systematic review	**Adults** **N=209 studies**	**IBD, UC and CD were negatively correlated to *H. pylori* prevalence (all P<0.001).**IBD patients were 1.41 times	H. pylori prevalence was negatively correlated to IBD and *H. pylori* had a Protective effect against IBD. Eradication of *H.*

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			(OR=1.41, 95% CI=1.25–1.58) more likely to relapse after eradication of *H. pylori*. Finally, *H. pylori* infection was not related to IBD medication and classification.	*pylori* can lead to recurrence of IBD. YES
Reshetnyak, V.I. et al./2021. (33)	review	**Adults N=UNsubjects**	*H. pylori* persistence may be supposed to be a potentially beneficial factor against the development of IBD.	Perform more individualized eradication therapy in the context of assessment of additional risk factors. YES
Aguilera Matos, I. et al./2020. (34)	**review**	**Pediatric population N=UNsubjects**	**Meta-analysis suggests strong inverse association with CD in children.**	I. pylori may have immunoregulatory properties in IBD, and the inverse association seems stronger in paediatric patients and those with CD. YES
Gravina, A.G. et al. /2020. (47)	**review**	**Adults N=UN subjects**	The severity of IBD, UC in particular, increased after *H. pylori* eradication.	to define whether *H. pylori* products, such as Hp(2–20) peptide, might be considered as potential therapeutic agents in specific clinical settings, such as IBDs. YES
Santos, M.L.C. et al./2020. (48)	**review**	**Adults N=UN subjects**	The composition of gut microbiota, which seems to play a crucial role in IBD development	it is plausible to think that the changes in the intestinal microbiome may be decisive in the IBD onset after *H. pylori* treatment. YES
Axelrad, J.E. et al./2020. (49)	systematic review	**Adults N=63 studies**	Helicobacter pylori infections were associated with a generally consistent reduced risk of IBD.	H. pylori has inverse associations with incident IBD. YES

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Imawana, R.A. et al. /2020. (58)	meta-analysis	**Adults** N=32 studies N=4607 IBD subjects	The protective effect of *H. pylori* on IBD varied by both subtype (more protection against CD vs. UC) and region (East Asia more protected than Mediterranean regions).	protective effect of *H. pylori* against IBD. YES
Pellicano, R. et al./2020.(59)	review	**Adults** **N=UN**	an inverse correlation between H pylori infection and IBD prevalence has been confirmed.	inverse correlation YES
Tepler, A. et al./2019. (50)	meta-analysis	**Adults** **N=3 studies** **N=960 subjects**	CagA seropositivity was associated with decreased odds of IBD, particularly CD.	We found evidence for a significant association between CagA seropositive *H. pylori* exposure and reduced odds of IBD, particularly CD, but not for CagA seronegative H pylori exposure. YES
Wang, W.L. et al./2019. (51)	meta-analysis	Adults N=2055 subjects	There was a significant difference in Hp infection rate between CD patients and controls, showing a negative correlation.	I. *pylori* infection was negatively associated with the incidence of CD. YES
Piovani, D. et a. /2019. (63)	Umbrella Review of Meta-analyses	N=53 meta-analysis	H pylori infection reduce risk of IBD (CD, UC, and IBD).	*Protective rule of H.pylori.* YES
Yu, Y. et al./2018. (35)	**review**	**Adults** **N=UN subjects**	An inverse correlation between *H. pylori* infection and IBD onset.*H. pylori* infection induces tolerogenic dendritic cells and immunosuppressive Tregs who have a key role in systematic immunomodulation.	The immune tolerance property of *H. pylori* should be thoroughly considered when designing optimized and individualized treatments for *H. pylori*-infected patients. YES
Kayali, S. et al.	**review**	**Adults**	the difference in	Striking inverse

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/2018. (52)		**N=22 studies**	prevalence of HP infection between IBD affected patients and controls was significative in 16/22 studies.	association between HP infection and the prevalence of IBD, independently from the type of IBD considered (CD, UC and IBDU) across distinct geographic regions. YES
Castaño-Rodríguez, N. et al. /2017. (62)	**meta-analysis**	**Adults**	Analyses comprising patients with CD, UC and IBD), showed a consistent negative association between gastric *H. pylori* infection and IBD.	H. pylori infection is negatively associated with IBD regardless of ethnicity, age, *H. pylori* detection methods and previous use of aminosalicylates and corticosteroids. YES
Murad H.A./2016. (36)	**review**	**Adults N=UNsubjects**	The present review suggests that measuring fecal calprotectin, and patient counseling and follow-up, on eradicating *H. pylori* in CD patients and/or patients with a high risk for CD, may help monitor CD.	The current data that suggest a positive association between *H. pylori* eradication and development of CD are limited and provide a very little evidence. UN
Arnold, I.C. et al./2016. (37)	**review**	**Pediatric and adults population N=UNsubjects**	*H. pylori* infection is inversely associated with both CD and UC in European, Asian as well as American populations. Inverse association is especially strong in CD patients and in children and young adults. *H. pylori* reduce clinical and histopathological IBD symptoms	*H. pylori* is inversely associated with, and likely protective against, IBDs. YES
Robinson, K./2015. (38)	review	**Adults**	significantly reduced risk of IBD when	Reduced incidence of *H. pylori* infection in IBD

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			infected with *H. pylori.*	patients. But warned of possible exacerbation following eradication therapy. YES
Yu, Q. et al. /2015. (53)	meta-analysis	**Pediatric population and adults** N=14 studies (11 adult studies and 3 pediatric studies) N=739 subjects	the patients with IBD tended to have a higher prevalence of enterohepatic Helicobacter species in the intestinal mucosa, although the prevalence of *H. pylori* was not significantly higher .	It appears that enterohepatic Helicobacter species was associated with IBD, while intestinal *H. pylori* infection was not significantly associated with IBD. NO
Wu, X.W. et al. /2015. (60)	meta-analysis	**Adults** **N=**1299 IBD subjects	The *H. pylori* infection rate in Asian IBD patients is significantly lower than in non-IBD patients	infection protects against the development of IBD. YES
Rokkas, T. et al. /2015. (61)	meta-analysis	**Adults** N=4400 IBD subjects	significant negative association between *H. pylori* infection and IBD	a possible protective benefit of *H. pylori* infection against the development of IBD. YES
Ierardi, E. et al. /2014. (39)	**review**	**Adults**	low incidence of *H. pylori* infection in patients with IBD compared with normal controls.	potential protective role of *H. pylori* on inflammatory bowel diseases needs to be better elucidated. YES
Papamichael, K. et al./2014 (54)	**review**	**Adults** **N=UNsubjects**	Potential protective role of *H. pylori* infection against the development of IBD. Rapid onset of CD after eradication of *H. pylori* infection.	the association between *H. pylori* infection and IBD is still controversial; however, it is worthy of further investigation. UN
Xiang, Z. et al./2013. (57)	**retrospective single-center study**	**Adults** **N=229 CD subjects**	The *H. pylori* infection rate in the CD group was 27.1%, significantly lower than that of 47.9% in the control group.	Lower *H. pylori* infection in CD patients suggests a correlation between bacterial infection and CD, suggesting caution when considering *H. pylori*

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				eradication in CD patients. YES
Owyang, S.Y. et al./2012. (55)	**review**	**Adults N=UN subjects**	immunoregulatory properties of the *H. pylori* genome and revealed the importance of TLR-9 mediated mechanism in the pathogenesis of IBD.	*H.pylori* genomic DNA contributes to the beneficial anti-inflammatory effect of *H. pylori* colonization in patients with chronic inflammatory conditions. YES
Luther, J. et al./2010. (12)	meta-analysis	**Adults N=** 5903 **subjects**	27.1% of IBD patients had evidence of infection with *H. pylori* compared to 40.9% of patients in the control group.	protective benefit of *H. pylori* infection against the development of IBD. YES
Song, M.J. et al./2009. (56)	multicenter study	**Adults N=316 subjects**	A statistically significant difference in *H. pylori* infection rate was noticed between the IBD patients (25.3%) and the controls (52.5%), and between UC (32.0%) and CD patients (17.7%).	Korean patients with IBD, particularly CD, were found to have a significantly lower *H. pylori* infection rate than the controls. YES

Legends: UN-unkown; *H. pylori-Helicobacter pylori*; Hp-infection-Helicobacter pylori-infection; IBDs-inflamatory bowel diseases; IBD- inflamatory bowel disease; CAI-clinical-activity-index; ESS- endoscopic-severity-score; ET-eradication therapy; FU-follow up; UGE-upper gastroscopy; OPG-osteoprotegerin; UC- **ulcerative colitis; CD-Crohn's disease.**

Research into the relationship between *Helicobacter pylori* infection and inflammatory bowel disease (IBD) began to take shape around 2009 and has gained momentum over the years. Since then, interest in this topic has grown steadily, with a marked increase in studies exploring possible protective, immunological, and microbial mechanisms. Importantly, many of these studies are based on high levels of evidence, including numerous systematic reviews and meta-analyses. These consistently show a lower prevalence of *H. pylori* infection in IBD patients across various populations and settings. The fact that such findings are replicated across different study designs and regions strengthens the validity of this association. Together, the accumulated evidence points to a meaningful biological link that warrants further investigation.

4. Discussion

The coexistence of *Helicobacter pylori* infection and Inflammatory Bowel Disease (IBD) presents a unique set of challenges that complicate both diagnosis and management. While *H. pylori* is a recognized pathogen implicated in significant gastric morbidity, its relationship with IBD remains controversial. The lower prevalence of *H. pylori* in IBD patients, consistently reported across multiple studies, raises questions about potential protective roles or interactions between the bacterium and host immunity [11,12,23,31,33–35,37–39,43,44,46–52,55–63]. This phenomenon has been attributed to

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several factors, including extensive antibiotic use in IBD management, immune modulation associated with chronic inflammation, and dysbiosis of the gut microbiota. The frequent use of antibiotics, particularly broad-spectrum agents during IBD flares or for perioperative prophylaxis in Crohn's disease, likely contributes to the observed lower colonization rates. However, this reduced prevalence may not uniformly translate into clinical benefit, as it introduces unique diagnostic and therapeutic challenges.

From a diagnostic perspective, the accuracy of non-invasive tests for *H. pylori*, such as the urea breath test (UBT) and stool antigen test, is diminished in IBD patients due to confounding factors such as active intestinal inflammation and the use of proton pump inhibitors (PPIs). These medications, commonly prescribed for upper GI symptoms in IBD patients, suppress bacterial load and gastric acidity, leading to false-negative test results. Endoscopic biopsy remains the gold standard for diagnosis, offering the opportunity for histological examination and culture, but the invasive nature of this procedure poses risks for IBD patients, particularly during active disease. Moreover, in patients with Crohn's disease involving the upper GI tract, the differentiation between *H. pylori*-related gastritis and Crohn's-associated gastroduodenitis adds an additional layer of complexity.

Therapeutically, *H. pylori* eradication in IBD patients necessitates a nuanced approach, balancing the benefits of eradication against the potential risks of exacerbating IBD symptoms. Therapy consisting of a PPI, clarithromycin, and amoxicillin, achieves eradication rates of approximately 70–80% in the general population. However, rising rates of antibiotic resistance, particularly to clarithromycin and metronidazole, reduce the efficacy of these regimens in IBD patients, many of whom have been exposed to antibiotics for disease management [64]. Bismuth-containing quadruple therapy or regimens tailored based on antibiotic susceptibility testing may be required in these cases.

A critical concern in IBD patients undergoing *H. pylori* eradication therapy is the potential for antibiotic-induced gut microbiota disruption. Dysbiosis, a hallmark of IBD, may be exacerbated by the broad-spectrum antibiotics used in eradication therapy, leading to disease flares or worsening symptoms. Oral supplementation with a narrow spectrum of Gram-positive bacteria has shown clinical improvement in *H. pylori*-related symptoms, yet microbiota alterations may predispose individuals to intestinal or systemic diseases later in life. Emerging evidence suggests that using multi-strain probiotics or paraprobiotics, rather than single-strain formulations, may help reduce the incidence of metabolic disturbances associated with dysbiosis [65].

Considering the diverse effects of different bacterial strains, high-throughput sequencing technologies are essential for characterizing microbiota changes at the strain level and personalizing probiotic interventions. Furthermore, next-generation probiotics and genetically modified microorganisms are being explored to enhance clinical outcomes, either by restoring disease-specific bacterial taxa or by producing therapeutic compounds such as antimicrobial peptides. Innovations such as microencapsulation and nanotechnology are also being developed to optimize probiotic delivery and minimize adverse metabolic effects. These advances may offer promising adjuncts in managing *H. pylori* eradication in the context of IBD [66]. Additionally, PPIs-an essential component of *H. pylori* therapy-may interact with immunosuppressive agents such as azathioprine, methotrexate, or biologics, potentially altering their pharmacokinetics and efficacy. The impact of *H. pylori* eradication on IBD activity remains debated. Some articles suggest that *H. pylori* colonization may exert an immunomodulatory effect by reducing pro-inflammatory cytokine production and promoting regulatory T-cell activity [67,68]. Consequently, eradication might remove this protective mechanism and exacerbate IBD symptoms. Conversely, *H. pylori* may aggravate upper GI symptoms in IBD patients, including dyspepsia or gastric ulceration, thereby impairing quality of life and complicating disease management.

In light of these complexities, a tailored approach to managing *H. pylori* infection in IBD patients is essential. Routine screening may not be justified in asymptomatic individuals, but targeted testing should be performed in patients with upper GI symptoms, a history of peptic ulcer disease, or those requiring long-term PPI use. Whenever possible, eradication therapy should be timed during IBD

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remission to minimize the risk of flares. A multidisciplinary approach involving gastroenterologists, microbiologists, and clinical pharmacologists is recommended to optimize outcomes and mitigate risks.

Future research should focus on the long-term impact of *H. pylori* eradication on IBD progression, microbiota composition, and patient quality of life. Large-scale studies using germ-free mice colonized with human microbiota, as well as clinical trials combining broad-spectrum antibiotic regimens with targeted probiotic interventions, are needed to better understand the role of microbiome modulation in this population. The integration of novel diagnostic tools and personalized medicine strategies holds the potential to transform the management of *H. pylori* in the context of IBD and improve clinical outcomes for this unique patient group.

5. Conclusions

While *Helicobacter pylori* eradication offers clear oncological benefits-most notably in the primary and secondary prevention of gastric cancer-it presents a distinct set of challenges in patients with inflammatory bowel disease (IBD). Among the most pressing concerns is the possibility of triggering de novo IBD or exacerbating existing disease following eradication therapy. Although an association has been reported in several observational studies, the causal relationship and underlying mechanisms remain poorly defined. Notably, current international guidelines do not offer specific recommendations regarding *H. pylori* management in patients with IBD (10). This omission highlights a significant gap in clinical guidance and underscores the importance of further research in this area, particularly given the increasing global burden of IBD and the widespread implementation of *H. pylori* screening and treatment programs. An important, yet often overlooked, aspect is the disease stage at the time of eradication. Patients in clinical or endoscopic remission may respond differently to microbiota-altering antibiotic regimens compared to those with active inflammation. The degree of mucosal integrity, immune activation, and underlying dysbiosis likely modifies the host response to such perturbations. In clinical practice, this makes timing a critical variable that should be factored into therapeutic decision-making. The patient's current IBD treatment regimen also warrants close attention. Use of corticosteroids, immunomodulators, or biologic agents could influence not only the immune response to eradication therapy but also the risk of opportunistic infections such as *Clostridioides difficile (27).* Furthermore, these treatments might dampen typical clinical signs of infection or inflammation, complicating post-eradication monitoring. Another important consideration is the history of prior *H. pylori* eradication attempts. Whether the current therapy is first-line or a salvage regimen will influence the selection of antibiotics, resistance profiles, and the expected degree of microbiota disruption. These variables are not trivial; they may significantly affect IBD stability, symptom recurrence, or the risk of treatment-related adverse events. From a clinical and research standpoint, it is essential to move beyond population-level data and adopt a more individualized approach. Future studies should stratify patients based on IBD phenotype, disease activity, current immunosuppression, and eradication history. Rigorous prospective trials using validated clinical, endoscopic, and biochemical endpoints are urgently needed to elucidate risk profiles and optimize treatment strategies. In countries where *H. pylori* screening is employed as a public health measure to reduce gastric cancer incidence, clinical guidelines must be adapted for patients with IBD. These should incorporate stratification models that account not only for cancer risk but also for potential immunological and microbiome-mediated effects unique to this population. Clinicians also need practical tools to differentiate between genuine IBD flares and predictable adverse effects of eradication therapy. Conversely, decisions to withhold *H. pylori* treatment due to concerns about disease destabilization or *C. difficile* infection must be supported by robust, patient-specific risk–benefit assessments. Ultimately, the management of *H. pylori* in the context of IBD sits at the intersection of gastroenterology, microbiology, and immunology. It demands a nuanced approach, informed by both high-quality evidence and careful clinical judgment. This evolving field offers significant opportunities-not only to improve outcomes

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for a vulnerable subgroup of patients, but also to deepen our understanding of host–microbiome interactions in immune-mediated disease.

6. Future Directions

Future research should aim to clarify the causal mechanisms underlying the inverse association between *Helicobacter pylori* infection and inflammatory bowel disease (IBD), with particular focus on the immunological and microbiome-related pathways involved. It remains important to determine whether the observed relationship reflects a true biological interaction or is influenced by confounding factors such as antibiotic use, disease severity, or treatment history. Further investigation into the role of specific *H. pylori* strains, host genetics, and environmental exposures could provide deeper insight into the variability seen among patients. Additionally, studies assessing the impact of *H. pylori* eradication on IBD activity, therapeutic response, and gut microbial balance will be essential for informed clinical management. Incorporating microbiome analysis, immune profiling, and precision medicine strategies may help identify patient subgroups that could benefit from personalized approaches. A clearer understanding of this complex interplay could ultimately refine both diagnostic and therapeutic practices in IBD care.

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