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Impacts of *Helicobacter pylori* infection and eradication on gastrointestinal microbiota: An up-to-date critical review and future perspectives

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Abstract

Helicobacter pylori (*H. pylori*) infects approximately half of the population worldwide and causes chronic gastritis, peptic ulcers, and gastric cancer. Test-and-treat strategies have been recommended for the prevention of *H. pylori*-associated diseases. Advancements in high-throughput sequencing technologies have broadened our understanding of the complex gastrointestinal (GI) microbiota and its role in maintaining host homeostasis. Recently, an increasing number of studies have indicated that the colonization of *H. pylori* induces dramatic alterations in the gastric microbiota, with a predominance of *H. pylori* and a reduction in microbial diversity. Dysbiosis of the gut microbiome has also been observed after *H. pylori* infection, which may play a role in the development of colorectal cancer. However, there is concern regarding the impact of antibiotics on the gut microbiota during *H. pylori* eradication. In this review, we summarize the current literature concerning how *H. pylori* infection reshapes the GI microbiota and the underlying mechanisms, including changes in the gastric environment, immune responses, and persistent inflammation. Additionally, the impacts of *H. pylori* eradication on GI microbial homeostasis and the use of probiotics as adjuvant therapy are also discussed. The shifts in the GI microbiota and their crosstalk with *H. pylori* may provide potential targets for *H. pylori*-related gastric diseases and extragastric manifestations.

Keywords: *Helicobacter pylori*; Gastrointestinal microbiota; Gastric cancer; *Helicobacter pylori* eradication therapy; Probiotic supplementation

Introduction

Trillions of microorganisms, including bacteria, archaea, viruses, and some parasites, reside in the gastrointestinal (GI) tracts of mammals and develop symbiotic relationships with the host. The complex microbiota–host interaction network plays a vital role in the regulation of body health and is associated with various biological activities, such as metabolic, immune, and neuroendocrine processes.[1,2] Recently, increasing evidence has indicated that dysbiosis of the GI microbiota may be closely related to the pathogenesis of obesity, diabetes mellitus (DM), inflammatory bowel disease, cardiovascular diseases, and cancer.[3] Thus, a better understanding of the GI microbiota and its variation might offer novel targets for the prevention and treatment of diseases.

Although once thought to be sterile, the stomach has been an excellent example to illustrate bacterium-induced pathologies since the first discovery of *Helicobacter pylori* (*H. pylori*) by Warren and Marshall in 1983.[4] As one of the most studied bacteria, *H. pylori* has coevolved with humans for thousands of years and has infected approximately half of the population worldwide. It is generally recognized that *H. pylori* infection can cause asymptomatic gastritis in most individuals, and approximately 10% of infected individuals develop peptic ulcers, atrophic gastritis (AG), gastric cancer (GC), or mucosa-associated lymphoid tumors.[5] The eradication of *H. pylori* has been proven to effectively reduce the risk of GC in *H. pylori*-infected individuals.[6] With advancements in sequencing technologies, accumulating evidence has demonstrated that *H. pylori* infection can reshape the structure of the GI microbiota in humans and animal models, as it connects the GI tract through its gastro–oral, oral–oral, and

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fecal–oral transmission routes.[7] However, there are still debates on whether such alterations can be reversed by *H. pylori* eradication. Moreover, several concerns have been raised regarding antibiotic-based eradication therapy, including the prevalence of antibiotic resistance and perturbations in the gut microbiota following *H. pylori* eradication. Here, we review the current perspectives on the impacts of *H. pylori* infection on the GI microbiota and its correlation with the progression of *H. pylori*-associated diseases.

Search Strategy

In this review, we used the Web of Science Core Collection (WoSCC), one of the most influential scientific literature databases, to search for relevant studies. The search strategy was a combination of the following keywords and terms: (*Helicobacter pylori* OR *H. pylori*) AND (Microbiota OR Microbiome OR Microbe OR Bacteria OR Microflora OR Flora). The publication language was restricted to English, and the time span was from 2001 (January 01, 2001) to 2024 (March 31, 2024). We primarily summarized the studies published in the past five years.

Effect of *H. pylori* Infection on the Gastric Microbiota

Initial research on the gastric microbiota was limited, partially because of the difficulties in culturing commensal microorganisms in the stomach. The advent of culture-independent methods, particularly next-generation sequencing (NGS) technology, has broadened our horizons in microbial research. In the stomachs of healthy subjects, Actinobacteria, Bacteroidetes, Firmicutes, Fusobacteria, Proteobacteria, Spirochetes, Tenericutes, and Saccharibacteria (TM7) are common bacteria at the phylum level, whereas *Prevotella*, *Streptococcus*, *Veillonella*, *Neisseria*, *Fusobacterium*, and *Haemophilus* are detected frequently at the genus level. Generally, studies have shown that *H. pylori* infection significantly reduces the alpha diversity of the gastric microbiota, which could be largely due to the compositional predominance of *H. pylori* [Supplementary Table 1, http://links.lww.com/CM9/C234].[8] Analysis of beta diversity revealed that *H. pylori*-positive individuals had distinct microbial structures compared with their negative counterparts.[9]

The compositional analysis of recent research has demonstrated that *H. pylori*-positive and *H. pylori*-negative individuals are dominated by the same phyla but with different proportions of relative abundance. The abundance of Proteobacteria was strikingly increased, as *H. pylori* itself belongs to the Proteobacteria phylum and *Helicobacter* genus, whereas lower abundances of Firmicutes, Actinobacteria, and Bacteroidetes were observed in gastric biopsies after *H. pylori* infection.[10] The metagenomic sequencing data of gastric tissues confirmed that infected patients were heavily dominated by *H. pylori*.[11] In gastric juice, the relative abundance of Proteobacteria increased, whereas the relative abundances of *Actinomycetes*, *Haemophilus*, *Streptococcus*, and *Prevotella* decreased.[12] Brawner *et al*[13] examined the gastric fluid samples of 86 children and adults and reported that the stomachs of *H. pylori*-infected children harbored more diverse microbiota, a smaller abundance of Firmicutes, and a greater abundance of Proteobacteria and several lower taxonomic groups, including *Rothia*, than did the stomachs of *H. pylori*-infected adults. Furthermore, striking changes in the functional mode of the gastric microbiota were observed after *H. pylori* infection. *H. pylori*-specific genes, including virulence factors such as *vacA*, *cagA*, and urease, were significantly enriched in *H. pylori*-positive biopsy samples, whereas carbohydrate and amino acid metabolism genes were enriched in *H. pylori*-negative samples.[10]

H. pylori can employ several mechanisms to regulate gastric microecology. By downregulating the expression of proton pumps, *H. pylori* can inhibit gastric acid secretion, thus changing the acidic environment and creating proper conditions for the colonization of other microorganisms.[14] In addition, *H. pylori* can induce the production of cytokines and antimicrobial peptides, therefore leading to chronic gastritis and the inhibition of other local microbes.[15] The development of T regulatory-mediated tolerance to other bacteria and the suppression of the T-cell response induced by *H. pylori* are also likely to affect other microbial members. Specifically, *H. pylori* alters immune responses and manipulates the innate immune system to exert long-term impacts, including interacting with pattern recognition receptors and thus triggering the activation of conserved signaling cascades such as those mediated by nuclear factor κB (NF-κB), mitogen-activated protein kinase (MAPK), and caspase-dependent signaling pathways.[16] Moreover, *H. pylori* can alter the diet and lifestyle of the host, which is an important influencing factor in the microecosystem.

Dysbiosis of Gastric Microbiota in *H. pylori*-Associated GC

In 2019, there were 499.2 million cases of digestive system diseases in China, resulting in 1,557,310 deaths. GC is the top disease associated with mortality.[17] In general, it is believed that GC develops through a predictable progression from superficial gastritis to AG, intestinal metaplasia (IM), and subsequently to cancer. This multistep progression cascade is often initiated by *H. pylori* infection, which is recognized as a class I carcinogen for GC.[18] The virulence of *H. pylori*, duration of infection, host genetics, and environmental factors all contribute to the development of disease. Although the specific mechanism is not completely understood, imbalances in the gastric microbiota during gastric carcinogenesis have been observed in both human and animal models.

In the past decade, the role of changes in the gastric microbiota in the pathogenesis of GC has been increasingly studied [Figure 1A]. The causal association between the gastric microbiota and GC has been verified in germ-free (GF) mice. Major histopathological features of premalignant changes, including parietal cell loss, metaplasia development, and expansion of the proliferating epithelial zone, are reproducible in GF mice transplanted with the gastric microbiota from patients with IM or GC.[19] As *H. pylori* is a component of the gastric microbiota, *H. pylori* infection plays an initial role in the cascade of AG,

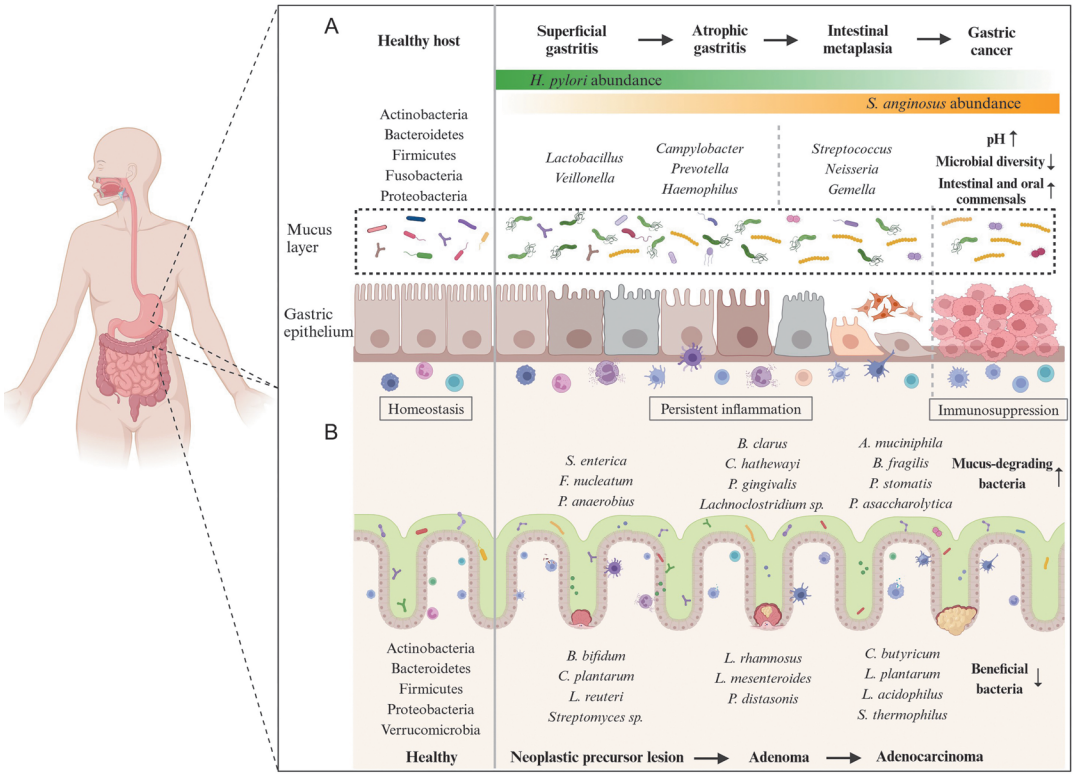

Figure 1: Influence of *H. pylori* infection on the GI microbiota. (A) Compared with those of healthy hosts, the gastric mucosa of *H. pylori*-positive patients with superficial or AG were dominated by *Helicobacter*, while the abundances of other bacteria were decreased, resulting in reduced microbial diversity. Chronic *H. pylori* infection can progress from AG to GC, which may be associated with an increase in pH, an altered immune response, and increased intestinal and oral microbiota. (B) *H. pylori* infection can promote the development of CRC through the regulation of the gut microbiota, with increases in mucus-degrading bacteria and decreases in beneficial bacteria. AG: Atrophic gastritis; CRC: Colorectal cancer; GC: Gastric cancer; GI: Gastrointestinal; *H. pylori*: *Helicobacter pylori*.

IM, and GC. Previous studies confirmed that *H. pylori* infection leads to inflammation of the gastric mucosa and destruction of the hydrochloric acid-secreting glands of the stomach, ultimately resulting in a condition known as AG.[20] It has been hypothesized that the hypochlorydia associated with AG allows the stomach to be colonized by oral and lower bowel microbes that are not typically present under normal, harshly acidic conditions.[21]

Early studies employing an insulin–gastrin (INS–GAS) transgenic mouse model demonstrated that *H. pylori*-infected GF INS–GAS mice took longer to develop gastric lesions than did *H. pylori*-infected mice and colonized complex gastric microbiota, indicating that changes in the non-*H. pylori* gastric microbiota composition might promote GI intraepithelial neoplasia.[22] The roles of other non-*H. pylori* gastric microbiota in the development of GC have been widely investigated. Researchers reported that, compared with initial gastritis status, the bacterial diversity of gastric mucosal samples decreased continuously from gastritis to GC, and the microbial community structure was significantly altered across disease stages.[23] Similarly, a study conducted on a large cohort of Chinese patients (21 with superficial gastritis, 23 with AG, 17 with IM, and 20 with GC) demonstrated that the bacterial diversity in patients with IM and GC was significantly lower than that in patients with superficial gastritis.[24] However, studies have also suggested increased microbial diversity and richness in patients with GC compared with controls. A previous study examined the gastric mucosa-associated microbiota of 31 Korean patients and reported that both the evenness and diversity of the gastric microbiota in the GC group were greater than those in the chronic gastritis and IM groups.[25] Liu *et al*[26] explored the bacterial diversity and richness of normal, peritumoral, and tumoral tissues from patients with GC and noted decreased diversity and richness in peritumoral and tumoral microhabitats compared with normal gastric tissue. These findings indicate that gastric microbial diversity varies among different microhabitats, even within the same individual. Patients with GC are characterized by the predominance of non-indigenous colonizers, which are primarily derived from the oral cavity and intestine. For example, the oral microbes *Peptostreptococcus stomatis*, *Streptococcus anginosus*, *Parvimonas micra*, *Slackia exigua*, and *Dialister pneumosintes* were found to be significantly enriched in the stomachs of patients with GC compared with patients in precancerous stages and could be used as biomarkers for GC diagnosis.[24] Another study reported that *Prevotella melaninogenica*, *S. anginosus*, and *Propionibacterium acnes* were more abundant in the tumoral microhabitats than in the peritumoral tissues of patients with GC.[26] Additionally, Ferreira *et al*[23] reported a remarkable overrepresentation of intestinal commensals, including *Citrobacter*, *Clostridium*, *Lactobacillus*, *Achromobacter*, and *Rhodococcus*, in the gastric mucosa of patients with GC. Dysbiosis of the gastric microbiota was also identified in the precancerous stages.

A distinct cluster of oral bacteria, including *Peptostreptococcus*, *Streptococcus*, *Parvimonas*, *Prevotella*, *Rothia*, and *Granulicatella*, was associated with the emergence and persistence of atrophy and IM, whereas the probiotic *Faecalibacterium prausnitzii* was depleted.[27] A meta-analysis that reanalyzed 16S rRNA sequencing data from 825 samples from six independent studies revealed comprehensive and generalizable gastric microbial features associated with the histological stages of gastric carcinogenesis, including the influence of GC-associated bacteria and *H. pylori*.[28] Our previous study revealed convergent dysbiosis of mucosal and fluid microbiota during stomach carcinogenesis, which suggests that the destruction of the mucosal barrier facilitates the colonization of non-indigenous microbiota.[8] The results were consistent with those of a previous meta-analysis that revealed significantly enriched oral microbes in GC and convergent dysbiosis of gastric fluid and the mucosal microbiome during gastric disease progression when *H. pylori* reads were removed from the analyses.[29] Fu *et al*[30] reported that *S. anginosus* induced gastritis–atrophy–metaplasia–dysplasia in mice and promoted carcinogenesis through its surface protein membrane-associated lipoprotein of *T. pallidum* (TMPC) binding through the Annexin-2 and MAPK signaling cascades. Another study by Li *et al*[31] demonstrated the potential role of *Propionibacterium* in the progression of GC through the promotion of M2 polarization of macrophages via TLR4/PI3K/Akt signaling. Moreover, non-*H. pylori* stomach microbiota, including *Staphylococcus epidermidis* and *Streptococcus salivarius*, had a demonstrable effect on *H. pylori*-induced gastritis in the GF INS–GAS mouse model. Coinfection with *H. pylori* and *S. salivarius* resulted in significantly higher pathological scores than infection with *H. pylori* alone.[32] Our previous study revealed that probiotic combinations (containing *Lactobacillus salivarius* and *Lactobacillus rhamnosus*) protected against *H. pylori*-associated carcinogenesis, probably through remodeling the GI microbiota.[33]

Lee *et al*[34] treated INS–GAS mice with triple therapy (metronidazole, omeprazole, and clarithromycin) and reported that *H. pylori* eradication reduced the severity of gastric dysplasia several weeks postinfection. Interestingly, they also treated INS–GAS mice with no prior *H. pylori* infection with triple therapy and reported that doing so also reduced the severity of dysplasia in these mice. These data suggest that antibiotic treatment potentially affects microorganisms other than *H. pylori*. Given that this study focused primarily on the role of *H. pylori* eradication in the development of GC, the investigators did not measure changes in microbial diversity or the abundances of specific microbial taxa following triple therapy treatment. Nevertheless, given that antibiotic-based treatment affects the composition of the microbiota in the colon and stomach, the effects of *H. pylori* eradication on the composition of non-*H. pylori* microbiota in uninfected mice is associated with reduced gastric dysplasia.

Effect of *H. pylori* Infection on Gut Microbiota

Compared with studies on the effects of *H. pylori* infection on the gastric microbiota, fewer studies have investigated the impact of *H. pylori* infection on the gut microbiota, and the structure of the gut microbiota varies after *H. pylori* infection. Most studies have reported either unchanged or even greater alpha diversity of the gut microbiota in *H. pylori*-positive individuals than in *H. pylori*-negative controls, which might be largely due to the altered gastric acid environment permitting more microorganisms to reach the gut.[35,36] Another possible explanation is that *H. pylori* infection strengthens host resilience against GI microbiota perturbations, resulting in increased fecal microbiota diversity. A significant difference in beta diversity was reported in most studies between *H. pylori*-positive and *H. pylori*-negative subjects. *H. pylori* infection may influence the gut microbiota through direct interactions, changes in the acidic environment of the stomach, or crosstalk with the host immune system. In a transgenic *Drosophila* model that heterogeneously expressed the *H. pylori* virulence factor *CagA*, the expression of *CagA* was able to induce gut microbiota dysbiosis, with an increase in *Lactobacillus brevis*, a species that can promote epithelial proliferation in *Drosophila*.[37] Hypochlorhydria and hypergastrinemia of the stomach induced by *H. pylori* infection are other factors suggested to be responsible for the changes in the gut microbiota, allowing the entrance of acid-sensitive bacteria into the distal GI tract. Immune responses may also be employed by *H. pylori* to modulate the gut microbiota. In the intestine, especially in Peyer's patches and mesenteric lymph nodes, *H. pylori* infection disrupts the homeostasis of conventional and regulatory $CD4^+$ T cells, which allows life-long persistence of *H. pylori* by counteracting the initial proinflammatory Th1/Th17 response. In a previous study by Heimesaat *et al*,[38] Mongolian gerbils were infected with *H. pylori* for 14 months, and distinct shifts in the composition of the gut microbiota with increased $CD3^+$ T-cell infiltration were reported, indicating that *H. pylori* is an immunoregulator of T cells that affects the distal gut microbiota. The imbalance between proinflammatory $CD3^+$ T cells and reduced Treg cells might be responsible for the consequences of *H. pylori* infection on intestinal immunity and inflammation. In addition to affecting $CD4^+$ T-cell responses, *H. pylori* infection also controls systemic $CD8^+$ T-cell functions. Previous studies have indicated that *H. pylori* systemically dampens the $CD8^+$ T-cell response, which, along with the variation in the gut microbiota, may have implications for colon carcinogenesis.[39]

Compositional analysis revealed that at the phylum level, the abundance of Proteobacteria increased significantly in samples aspirated from the descending duodenum of *H. pylori*-infected individuals, possibly because of the translocation of *Helicobacter* from the stomach to the gut lumen.[40] Notably, the Bacteroidetes:Firmicutes (B:F) ratio, which is related to lipid metabolism and energy homeostasis in the host, was observed to be relatively high in *H. pylori*-positive individuals.[41] At the genus level, *H. pylori* infection is accompanied by an increase in *Prevotella* and decreases in beneficial bacteria, including *Bifidobacterium* and *Bacteroides*, in fecal samples.[42] Several studies have shown that *H. pylori*-positive individuals present a decreased prevalence of *Roseburia*, which produces short-chain fatty acids (SCFAs) that

contribute to the maintenance of intestinal homeostasis.[42] The suppressed level of SCFAs after *H. pylori* infection might be detrimental to human health. A previous study sequenced 16S rRNA genes in biopsies from the proximal duodenum of *H. pylori*-positive and *H. pylori*-negative participants, and the results revealed that the relative abundances of *Haemophilus*, *Neisseria*, *Prevotella pallens*, *Prevotella 7,* and *Streptococcus* were greater in patients with *H. pylori* infection than in healthy controls.[43] The source of microbiome specimens is a crucial determinant for microbial composition analysis.[40] Although the aim of relevant studies is to investigate the effects of *H. pylori* infection on the gut microbiota, the majority of researchers have performed sequencing analysis on fecal samples. Given that the profiles of the fecal microbiota only partially represent those of the mucosal microbiota, further research on intestinal biopsies is still needed to provide a comprehensive profile of the gut microbiota upon *H. pylori* infection.

Interaction Between *H. pylori* Infection and Gut Microbiota in Patients with Colorectal Cancer (CRC)

Recent studies have suggested a potential link between *H. pylori* infection and the development and progression of CRC.[44] Additionally, an increasing number of epidemiological studies have shown a positive correlation between *H. pylori* infection and the risk of CRC.[45] As the intriguing host–microbiota interaction is vital for the maintenance of intestinal homeostasis, changes in the gut bacterial structure and function have been proposed to be involved in CRC development [Figure 1B]. Although the exact mechanisms have not yet been elucidated, *H. pylori*-induced dysbiosis of the gut microbiota, proinflammatory immune responses, and dysfunction of the intestinal epithelial barrier may explain the increased *H. pylori*-associated CRC risk.

A recent study demonstrated that *H. pylori*-induced alterations in gut homeostasis that contributed to colorectal carcinogenesis, and these changes were reversible after *H. pylori* eradication.[44] Compared with non-infected controls, the abundances of *Akkermansia* spp. and *Ruminococcus* spp. were enriched in *H. pylori*-infected mice, both of which have been described as mucus-degrading taxa. The utilization of GF mice and fecal microbiota transplantation further confirmed the crucial role of pro-inflammatory and pro-carcinogenic microbial signatures induced by *H. pylori* in promoting intestinal tumor growth. Meanwhile, an increase in CRC-associated taxa was observed in *H. pylori*-positive patients, including *Prevotellaceae* and *Peptostreptococcales*, proving the pro-carcinogenic role of reshaped gut microbiota after *H. pylori* infection. In line with these findings, Yang *et al*[46] found that the relative abundance of *Prevotellaceae*, a taxa described as pro-carcinogenic, was significantly increased in patients with *H. pylori* infection by metagenomic sequencing. In addition to gut bacteria, disruptions in the gut virome have been demonstrated to play a role in *H. pylori* infection-induced CRC.[47] An expansion of temperate phages was observed in *H. pylori*-infected mice, and some of the phages were predicted to infect bacteria associated with CRC, including *Enterococcus faecalis*.[48]

H. pylori Infection and Oral Microbiota

H. pylori can be transmitted through oral–oral and fecal–oral routes, thus reshaping the microbial ecosystem in both habitats and participating in the pathogenesis of different diseases.[49] The oral cavity is a complex habitat for more than 700 species of microorganisms in the human body. In the oral sites of healthy subjects, Actinobacteria, Bacteroidetes, Firmicutes, Proteobacteria, Spirochetes, and TM7 are common at the phylum level, and *Streptococcus*, *Haemophilus*, *Neisseria*, *Prevotella*, and *Veillonella* are frequently detected at the genus level.[50] Notably, *Streptococcus* is the most abundant genus, accounting for 12–66% of the total genera detected in the oral cavity.[51]

The variations in the oral microbiota may differ among various oral samples and host health statuses. In the absence of oral and GI diseases, *H. pylori* infection has different effects on the composition of the microbiota in different oral ecological niches. By detecting bacterial 16S rDNA V3-V4 hypervariable regions in saliva samples, Ji *et al*[52] reported that the alpha diversity of *H. pylori*-infected subjects was similar to that of uninfected subjects and that the beta diversity was distinctly different between the two groups. At the genus level, *H. pylori* infection significantly increased the abundances of *Acinetobacter*, *Ralstonia,* and *Oribacterium* and decreased the abundances of *Alloprevotella*, *Klebsiella,* and *Fusobacterium*. In another study employing swab samples, reduced alpha diversity and significantly different beta diversity were observed in *H. pylori*-positive cohorts compared with their negative counterparts. At the phylum level, *H. pylori* infection was characterized by an increase in Proteobacteria and decreases in Fusobacteria and Firmicutes. At the genus level, the abundances of *Pseudomonas* and *Roseomonas* significantly increased, whereas those of *Fusobacterium*, *Haemophilus*, and *Streptococcus* strikingly decreased.[53] These results demonstrated that *H. pylori* infection has different influences on niches of the oral cavity. *H. pylori* infection can disrupt the homeostasis of the oral microbiota in three main interactive ways: coaggregation, endosymbiosis, and symbiotic biofilm formation.[54] For example, the major cariogenic bacterium *Streptococcus mutans* can form a symbiotic biofilm with *H. pylori* and contribute to the colonization of *H. pylori* in the mouth.[55]

The alterations in oral microorganisms after *H. pylori* infection can also differ from those in patients with oral or GI diseases. For example, in patients with oral lichen planus, there were positive correlations between *H. pylori* infection and the relative abundances of the Bacteroidetes phylum and the *Alloprevotella* and *Haemophilus* genera.[56] In a study assessing tongue-coating microbiomes from patients with superficial gastritis and GC, the composition of the microbiota was unrelated to gastric diseases and *H. pylori* infection status.[57] However, in another study including patients with gastritis, an increase in the *Treponema* genus and a decrease in *Haemophilus* were observed, indicating the different impacts of the interactions between *H. pylori* and other diseases on the structure of the oral microbiota.[58]

H. pylori Eradication and Gastric Microbiota

Since the discovery of the pathologic role of *H. pylori* in gastric diseases such as gastritis and gastric carcinogenesis, the eradication of *H. pylori* has been widely adopted in clinical practice. The recommended strategies for *H. pylori* eradication include traditional bismuth quadruple therapy, concomitant non-bismuth quadruple therapy, and proton pump inhibitor (PPI) triple therapy. The latest guidelines published by China, which has a high prevalence of *H. pylori*, suggest that bismuth quadruple therapy is the preferred choice for initial and rescue treatment. In addition, high-dose dual therapy is equally effective as bismuth quadruple therapy in empirical treatment.[59] Currently, the impact of *H. pylori* eradication on the gastric microbiota has gained attention, and an increasing number of studies have focused on whether *H. pylori*-shaped gastric microbiota can be restored to the uninfected state [Figure 2A]. According to studies focused on quadruple therapy, the alpha diversity increased dramatically, and significant differences in the gastric microbial community structure were reported after *H. pylori* eradication in the short term.[60] With respect to long-term changes, studies revealed that alpha diversity could be fully restored to the level of negative controls after *H. pylori* eradication, and higher alpha diversity indices were observed than those of their negative counterparts.[61] However, there is controversy regarding whether significant differences exist between the posteradication group and the negative control group.

Guo *et al*[62] investigated microbial alterations in gastric biopsy samples from 58 subjects in whom eradication was successful, and the results revealed significantly different community structures 6 months after successful eradication. Another study recruiting children revealed that the microbial structure of endoscopic gastric mucosal biopsy samples in the posteradication group was similar to that in the *H. pylori*-negative group.[63] An increase in alpha diversity indices and a significant difference in beta diversity were observed in the short- and long-term follow-up after *H. pylori* eradication.[60] Interestingly, compared with that in gastric mucosal samples, the alpha diversity of the gastric juice microbiota in *H. pylori*-positive samples was lower than that in *H. pylori*-negative samples.[64] Gastric compositional analysis of mucosal samples revealed that the relative abundances of *H. pylori*-related taxa, such as Proteobacteria at the phylum level and *Helicobacter* at the genus level, decreased strikingly,[65] whereas the abundances of other major phyla, including Actinobacteria, Bacteroidetes, Firmicutes, and Fusobacteria, and two widely known beneficial bacteria, *Bifidobacterium* and *Lactobacillus*, increased after successful treatment.[60,66] Serrano *et al*[67] reported that clearing *H. pylori* restored the gastric microbial composition to resemble the community structure found in non-infected children, suggesting that *H. pylori* eradication had an impact on the associated microbiota. Functional analysis revealed that several normal function-related pathways, including those related to gastric acid secretion, protein digestion and absorption, and amino acid metabolism, which may be partially restored by eradication therapies, were upregulated.[27]

H. pylori Eradication and Gut Microbiota

Bismuth-containing quadruple therapy, including PPIs, bismuth, and two antibiotics, has been recognized as the first-line regimen for *H. pylori* eradication. Given the adverse effects of PPIs and antibiotics on the gut microbiota, there is increasing concern about the dysbiosis of the gut microbiota during *H. pylori* eradication [Supplementary Table 2, http://links.lww.com/CM9/C234 and Figure 2B]. Generally, the alpha diversity of the gut

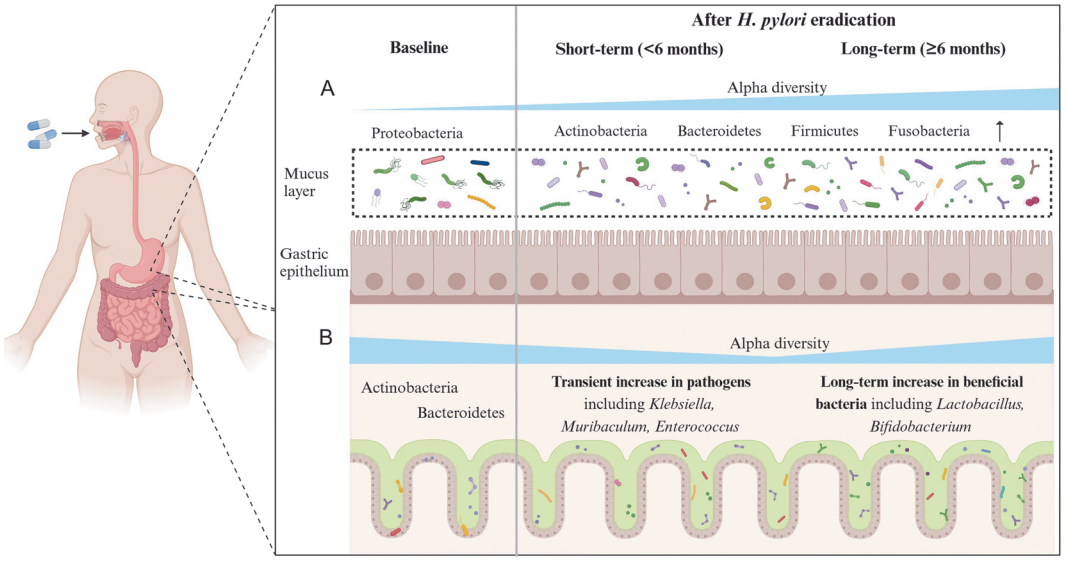

Figure 2: Influence of *H. pylori* eradication on the GI microbiota. (A) The alpha diversity of the gastric microbiota continuously increased after *H. pylori* eradication. The abundances of the *H. pylori*-related Proteobacteria taxa significantly decreased, whereas those of other phyla, including Actinobacteria, Bacteroidetes, Firmicutes, and Fusobacteria, strikingly increased. (B) The alpha diversity of the gut microbiota was significantly reduced following *H. pylori* eradication and was restored in the long term, with transient increases in pathogens such as *Klebsiella*, *Muribaculum*, and *Enterococcus*. The relative abundances of beneficial bacteria, including *Lactobacillus* and *Bifidobacterium,* dramatically increased in the later stage. GI: Gastrointestinal; *H. pylori*: *Helicobacter pylori*.

microbiota tends to decrease in the short term and is gradually restored over time.[7] Previous studies reported transient perturbation of fecal microbiota diversity and a transient increase in the antibiotic resistome, which were largely restored to the pretreatment state from 2 months to 1 year after eradication therapy.[7] Consistently, we also demonstrated that the eradication of *H. pylori* restored rather than disturbed the gut microbiota in asymptomatic young adults.[68] However, the speed and extent of restoration vary with different regimens. Liou *et al*[69] reported a significantly greater effect on alterations in the gut microbiota with concomitant therapy and bismuth quadruple therapy than with triple therapy. The time required for the restoration of alpha and beta diversity was shorter with triple therapy than with the other two regimens. Another study investigated changes in the gut microbiota after second-line *H. pylori* eradication therapy.[7] The authors noted that the recovery of diversity was slower with bismuth-based quadruple therapy for 10 days than with levofloxacin-based sequential quadruple therapy for 14 days. Recent studies have shown that the combination of vonoprazan and amoxicillin therapy achieves acceptable eradication rates for *H. pylori*, which has minimal negative effects on the gut microbiota compared with bismuth quadruple therapy.[70] In addition to gut bacteria, a recent study revealed a decrease in gut virome diversity, along with a shift in the virome community toward a greater proportion of core viruses after treatment.[71]

Compositional analysis of fecal samples revealed that *H. pylori* eradication immediately reduced the relative abundances of Bacteroidetes and Actinobacteria and increased those of Firmicutes and Proteobacteria at the phylum level, indicating a decreased B:F ratio after eradication therapy, which has been proven to be associated with obesity.[69] At the genus level, several pathobionts, including *Klebsiella*, *Proteus*, *Enterococcus*, *Muribaculum*, and *Enterocloster*, were increased immediately after exposure to treatment; these alterations did not persist and spontaneously reverted mostly to the basal state within 1 year.[7] Moreover, the abundances of *Enterococcus faecium* and *E. faecalis* notably increased after bismuth quadruple therapy, but no significant difference was observed in individuals receiving high-dose dual therapy.[72] Compared with those in the quadruple regimen group, in terms of relative abundance, a greater number of species returned to baseline levels in the dual therapy group. Importantly, alterations in the fecal microbiota after successful *H. pylori* eradication also resulted in an overrepresentation of beneficial *Bifidobacterium*.[62] A metaproteomic assessment revealed that eradication therapy reshaped the relative contributions of the functions required to produce acetate, propionate, and butyrate.[73] Notably, microbial proteins involved in antibiotic resistance and inflammation increased after therapy, whereas reductions in host proteins with known roles in inflammation and *H. pylori*-mediated carcinogenesis were observed.

Probiotics, which are defined as live microorganisms that exert beneficial effects on host health, have been shown to relieve the clinical symptoms of *H. pylori*-infected patients, improve the success rate of *H. pylori* eradication, and reduce the incidence of adverse events when combined with antibiotics. Studies have shown that probiotics and their metabolites, mainly SCFAs and bacteriocins, can inhibit the colonization and growth of *H. pylori*, which may be associated with changes in the GI microbiota in clinical trials.[74,75] For example, a previous multicenter, randomized, double-blind, placebo-controlled trial revealed that probiotics containing *Bifidobacterium* not only relieved the side effects caused by antibiotics but also regulated fluctuations in the GI microbiota.[65] Another study demonstrated that the recovery of microbiota composition through probiotic intervention following antibiotic administration was contingent on the replication rates of the ingested strains.[76] The decrease in alpha diversity after eradication therapy was prevented when the bacteria were supplemented with probiotics.[77] Chen *et al*[61] reported that probiotic supplementation was correlated with improved GI symptoms as well as an increased B:F ratio after *H. pylori* eradication. Additionally, probiotic supplementation inhibited the overgrowth of pathogens, including *Shigella*, *Klebsiella*, and *Streptococcus*, caused by eradication therapy and promoted the metabolism of cofactors and vitamins,[78] thereby maintaining the integrity of the mucosa and strengthening the mucosal barrier. Moreover, butyrate, an SCFA secreted by probiotics, has been shown to enhance intestinal barrier function by activating AMP-activated protein kinase (AMPK) or inhibiting claudin-2 production to stimulate the expression of tight junction proteins.[79] Probiotics may indirectly alleviate *H. pylori* infection through promoting the immune response, especially by stimulating the activity of phagocytic and natural killer cells, regulating the phenotype and cytokine pattern of dendritic cells, and increasing the secretion of anti-inflammatory cytokines.[80] Furthermore, individuals who received the probiotic *Saccharomyces boulardii* CNCM-I 745 presented significantly lower levels of antimicrobial resistance genes, which provide resistance to lincosamides, tetracyclines, and beta-lactams, than did the control group.[81] Taken together, through modifying the microbiome, reducing adverse reactions, inhibiting the overgrowth of pathogens, strengthening protective barriers, and regulating the immune response, antibiotic-based treatment combined with probiotics can effectively improve the eradication rate. Although eradication therapy supplemented with probiotics has exhibited substantial benefits, determining which probiotics are more effective for *H. pylori* eradication is still a challenge. In addition to eradication therapy combined with probiotics, berberine, a traditional Chinese medicine, has shown great safety in eradicating *H. pylori,* and a recent randomized controlled trial indicated that the efficacy of triple therapy with berberine for *H. pylori* initial treatment was comparable to that of vonoprazan quadruple therapy and rabeprazole quadruple therapy.[82] However, whether the administration of berberine triple therapy leads to alterations in the gut microbiota still needs further exploration.

H. pylori Eradication and Oral Microbiota

H. pylori eradication has also been shown to strongly affect the structure of the oral microbiota. In saliva samples from patients with no oral or GI diseases, *H. pylori*

infection decreased bacterial diversity but significantly enriched the abundances of *Streptococcus*, *Haemophilus*, and *Staphylococcus*.[83] Another study that utilized vonoprazan–amoxicillin dual therapy revealed no differences in the salivary microbiota before and after the eradication of *H. pylori*, suggesting the different influences of eradication regimens on the oral microbiota.[84] However, Peng *et al*[57] performed 16S rRNA gene sequencing of tongue coating samples and reported dramatically decreased alpha diversity after vonoprazan–amoxicillin dual therapy. More importantly, the diversity modestly increased with *H. pylori* eradication, and the abundances of Firmicutes and *Lactobacillus* were significantly reduced after *H. pylori* eradication. The above results indicate that the infection and eradication of *H. pylori* can affect the structure of the oral microbiome, thus influencing the development and progression of related diseases.

Conclusions

As one of the most studied pathogens in the GI tract, *H. pylori* infection is associated with alterations in the GI microbiota, including not only the gastric microbiota but also those inhabiting the mouth and gut. *H. pylori* infection can inhibit the secretion of gastric acid and change the gastric environment, resulting in significant differences in the microbiota of individuals and the occurrence of gastric pathology, AG, IM, and GC. Mounting evidence has suggested that dysbiosis of the gastric microbiota, especially the colonization of oral bacteria, is involved in the development of GC. Current studies have also demonstrated the complex correlations between *H. pylori* and the gut microbiota in the progression of CRC. The eradication of *H. pylori* could restore the imbalance of the GI microbiota in the long term, although transient perturbations were observed. Hence, it is advisable to proceed with treatment rather than observation upon testing positive for *H. pylori*, as the advantages of eliminating *H. pylori* outweigh the disadvantages. Further studies are needed to elucidate the roles of other bacteria in *H. pylori*-related diseases and decipher the potential mechanisms both *in vitro* and *in vivo*.

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Conflicts of interest

None.

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