

Gastrointestinal microbiome and *Helicobacter pylori*: Eradicate, leave it as it is, or take a personalized benefit–risk approach?

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Abstract

Helicobacter pylori (*H. pylori*) is generally regarded as a human pathogen and a class 1 carcinogen, etiologically related to gastric and duodenal ulcers, gastric cancer, and mucosa-associated lymphoid tissue lymphoma. However, *H. pylori* can also be regarded as a commensal symbiont. Unlike other pathogenic/opportunistic bacteria, *H. pylori* colonization in infancy is facilitated by T helper type 2 immunity and leads to the development of immune tolerance. Fucosylated gastric mucin glycans, which are an important part of the innate and adaptive immune system, mediate the adhesion of *H. pylori* to the surface of the gastric epithelium, contributing to successful colonization. *H. pylori* may have beneficial effects on the host by regulating gastrointestinal (GI) microbiota and protecting against some allergic and autoimmune disorders and inflammatory bowel disease. The potential protective role against inflammatory bowel disease may be related to both modulation of the gut microbiota and the immunomodulatory properties of *H. pylori*. The inverse association between *H. pylori* and some potentially proinflammatory and/or procarcinogenic bacteria may suggest it regulates the GI microbiota. Eradication of *H. pylori* can cause various adverse effects and alter the GI microbiota, leading to short-term or long-term dysbiosis.

Overall, studies have shown that gastric Actinobacteria decrease after *H. pylori* eradication, Proteobacteria increase during short-term follow-up and then return to baseline levels, and Enterobacteriaceae and *Enterococcus* increase in the short-term and interim follow-up. Various gastric mucosal bacteria (*Actinomyces*, *Granulicatella*, *Parvimonas*, *Peptostreptococcus*, *Prevotella*, *Rothia*, *Streptococcus*, *Rhodococcus*, and *Lactobacillus*) may contribute to precancerous gastric lesions and cancer itself after *H. pylori* eradication. *H. pylori* eradication can also lead to dysbiosis of the gut microbiota, with increased Proteobacteria and decreased Bacteroidetes and Actinobacteria. The increase in gut Proteobacteria may contribute to adverse effects during and after eradication. The decrease in Actinobacteria, which are pivotal in the maintenance of gut homeostasis, can persist for > 6 mo after *H. pylori* eradication. Furthermore, *H. pylori* eradication can alter the metabolism of gastric and intestinal bacteria. Given the available data, eradication cannot be an unconditional recommendation in every case of *H. pylori* infection, and the decision to eradicate *H. pylori* should be based on an assessment of the benefit-risk ratio for the individual patient. Thus, the current guidelines based on the unconditional “test-and-treat” strategy should be revised. The most cautious and careful approach should be taken in elderly patients with multiple eradication failures since repeated eradication can cause antibiotic-associated diarrhea, including severe *Clostridioides difficile*-associated diarrhea and colitis and antibiotic-associated hemorrhagic colitis due to *Klebsiella oxytoca*. Furthermore, since eradication therapy with antibiotics and proton pump inhibitors can lead to serious adverse effects and/or dysbiosis of the GI microbiota, supplementation of probiotics, prebiotics, and microbial metabolites (e.g., butyrate + inulin) should be considered to decrease the negative effects of eradication.

Key Words: *Helicobacter pylori*; Eradication; Gastrointestinal microbiota; Dysbiosis; Fucosylated glycan; Inflammatory bowel disease

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Core Tip: *Helicobacter pylori* (*H. pylori*) is generally regarded as a human pathogen, but it can act as a commensal symbiont. *H. pylori* colonization may have beneficial effects on the host by regulating gastrointestinal microbiota and protecting against some allergic and autoimmune disorders and inflammatory bowel disease. *H. pylori* eradication can cause various adverse effects and alter the gastrointestinal microbiota, leading to dysbiosis. Therefore, eradication cannot be an unconditional recommendation in every case of *H. pylori* infection, and the therapeutic decision should be based on a personalized assessment of the benefit vs risk.

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TO THE EDITOR

We read with great interest the article by Niu et al[1], which showed that the effectiveness of quadruple *Helicobacter pylori* (*H. pylori*) eradication therapy containing bismuth depended on the gastric microbiota, and a high rate of *H. pylori* eradication was associated with the presence of *Rhodococcus*, *Lactobacillus*, and *Sphingomonas*, which were significantly enriched in the gastric mucosa in the successful eradication group[1]. The role of lactobacilli, mainly beneficial bacteria, in *H. pylori* infection, including eradication, has been well studied[2]. However, the authors showed for the first time the importance of *Rhodococcus* and *Sphingomonas*, which are more likely to be opportunistic or pathobiont species with unclear functions in the human gastrointestinal (GI) tract[3,4], in successful eradication of *H. pylori*[1]. It is noteworthy that in gastric cancer (GC), when the abundance of *H. pylori* decreased, several taxa (including *Rhodococcus* and *Lactobacillus*, discussed by Niu et al[1]) in the gastric mucosa significantly increased, which may indicate their potential involvement in GC after *H. pylori* infection[5]. In addition, *H. pylori* was negatively correlated with some opportunistic bacteria/pathobionts such as *Haemophilus*, *Streptococcus*, *Neisseria*, and *Fusobacterium* in the success group[1]. The results obtained by Niu et al[1] may suggest that *H. pylori* competes not so much with beneficial bacteria as with pathobionts, and eradication may ultimately worsen the gastric microbiota.

Indeed, not only does the composition of the gastric microbiota affect *H. pylori* eradication, but eradication significantly affects the microbiota of both the stomach and intestine, which can lead to marked and long-term dysbiotic changes. Dysbiosis of the microbiota after *H. pylori* eradication can be caused by many factors: by the action of antibiotics and proton pump inhibitors; by the loss of *H. pylori* leading to changes in the immune response of the GI mucosa; and by changes in the microenvironment of the GI tract, including those in microbial metabolic pathways and changes in gastric acidity associated with both pharmacotherapy and loss of *H. pylori*[6,7]. Features of the dysbiotic changes, their duration, and the rate of restoration of the disturbed microbiota vary greatly in different studies.

Diverse effects of *H. pylori* eradication on gastric and intestinal microbiota

Recent studies have demonstrated not only short-term but also long-term (≥ 6 mo) changes in the gastric microbiota after *H. pylori* eradication. In about half of cases (52.3%), eradication led to the predominance of proinflammatory *Acinetobacter* in gastric corpus mucosa with a decrease in microbial diversity in patients with endoscopic follow-up for > 1 year[8]. An earlier study showed that *Acinetobacter* was enriched in patients with persistent gastric inflammation 1 year after *H. pylori* eradication[9]. Moreover, some bacteria in the gastric mucosa (*Actinomyces*, *Granulicatella*, *Parvimonas*, *Peptostreptococcus*, *Prevotella*, *Rothia*, and *Streptococcus*), which are predominantly of oral origin, were associated with precancerous gastric lesions (atrophy and/or intestinal metaplasia) 1 year after *H. pylori* eradication[9]. *Actinomyces*, whose abundance can increase in the absence of *H. pylori*, might significantly increase the risk of GC [10]. Thus, some studies demonstrated a contribution of various gastric bacteria to precancerous gastric lesions after *H. pylori* eradication[9]. In general, Actinobacteria decreased after *H. pylori* eradication, Proteobacteria increased during short-term follow-up and then returned to baseline levels, and Enterobacteriaceae and *Enterococcus* increased in the short-term and interim follow-up[11]. Alternatively, it has been shown that in regions with high GC risk, *H. pylori* is one of the main factors in gastric dysbiosis and successful eradication can lead to the restoration of gastric microbiota[12].

H. pylori eradication also affects the gut microbiota. Bismuth quadruple therapy leads to short-term dysbiosis of the gut microbiota with an increased abundance of Proteobacteria and decreased abundances of Bacteroidetes and Actinobacteria. The increase in gut Proteobacteria may contribute to adverse effects during eradication therapy[13]. In another study, *H. pylori* eradication was associated with significant alterations in the gut microbiota that did not completely recover 6 wk after treatment [7]. In general, there was a decrease in Actinobacteria, which are pivotal in the maintenance of gut homeostasis, compared with baseline throughout the follow-up (> 6 mo) after eradication[11]. Furthermore, eradication therapy alters microbial functional pathways and the metabolism of gastric and gut bacteria[9,14].

Conversely, other studies showed that successful *H. pylori* eradication exerts beneficial effects on gut microbiota, including increased probiotic *Bifidobacterium* and downregulation of drug-resistance mechanisms[12]. Liou *et al*[15] generally confirmed the long-term safety of *H. pylori* eradication therapy but reported incomplete restoration of microbial diversity after 1 year and clinically irrelevant but significant increases in body mass index (BMI) and body weight at that time.

Interestingly, an increase in body weight/body mass index after *H. pylori* eradication had been identified earlier[16]. Suggested mechanisms of this effect range from an improvement in the symptoms of postprandial dyspepsia[16] to changes in the regulation of leptin and ghrelin[17] mediated by antibiotic-associated changes in the microbiota (especially by the imbalance between bacterial producers of lactate and acetate)[18]. In general, however, the data in various studies are contradictory and indicate weight gain, weight loss, or the absence of an effect of *H. pylori* eradication on body weight; this may be due to differences in the characteristics of the studied populations, such as age, nosology, and composition of the GI microbiota[19]. Further in-depth study of the microbiome-mediated effects of *H. pylori* and eradication therapy on human host metabolism, including nutrient uptake, energy homeostasis, bodyweight, hormone secretion, lipid profile, and glucose homeostasis/glycemic control, will provide clinically important findings for the management of *H. pylori* infection.

***H. pylori* status and the human gut microbiome**

The presence or absence of gastric *H. pylori* can significantly affect the gut microbiota. For example, Nitrospirae were found exclusively in *H. pylori*-negative patients. The role of this phylum, containing nitrite-oxidizing bacteria, in the human microbiome is unclear. In a study by Wang *et al*[20], Nitrospirae were found in the gastric mucosa in all patients with GC but not in patients with chronic gastritis. The authors suggested that these bacteria may be involved in carcinogenesis through enhanced production of N-nitroso compounds. A recent study demonstrated a possible pathogenetic link between enriched colonic Nitrospirae and drug-resistant epilepsy, implying that Nitrospirae can increase nitrite toxicity and cause blood-brain barrier dysfunction[21].

Proinflammatory *Bacteroides ovatus* and *Fusobacterium varium*, associated with ulcerative colitis and adenomatous polyps[22,23] as well as trimethylamine-producing *Clostridium* sp. AT5[24] were enriched in *H. pylori*-negative samples, while *Bacteroides plebeius*, characteristic of the healthy groups (*vs* patients with adenomatous polyps)[23] and butyrate-producing *Eubacterium ramulus* were enriched in *H. pylori*-positive samples[7].

Conversely, *Butyricimonas* spp., including *Butyricimonas virosa*, associated with bacteremia in patients with GI cancer (colon and duodenal adenocarcinomas) and diverticulitis[25] as well as *Bacteroides coprophilus*, specifically enriched in ankylosing spondylitis[26], were enriched in *H. pylori*-positive individuals[7]. Proinflammatory *Prevotella copri*, associated with rheumatoid arthritis and microscopic colitis as well as *Enterobacter cloacae* and *Klebsiella pneumoniae*, pathogens commonly associated with hospital infections, were also enriched in *H. pylori*-positive individuals[27]. Moreover, gut microbial vitamin B₁₂ biosynthesis was significantly lower in *H. pylori*-positive individuals compared with *H. pylori*-negative individuals[27]. Dash et al[28] showed that the gut microbiota of *H. pylori*-infected individuals was characterized by a significantly increased abundance of *Succinivibrio*, Coriobacteriaceae, Enterococcaceae and Rikenellaceae as well as *Candida glabrata* and other unclassified fungi. The authors suggested a possible role for these *H. pylori*-associated changes in the gut microbiota in intestinal barrier disruption and development of colorectal carcinoma[28].

Potential protective and regulatory role of commensal *H. pylori*

Currently, *H. pylori* is generally regarded as a human pathogen and a class 1 carcinogen[29], responsible for 15% of the total cancer burden globally and up to 89% of all GC cases[30]. *H. pylori* is etiologically related to gastric and duodenal ulcers and mucosa-associated lymphoid tissue lymphoma. According to current guidelines, it is almost always subject to unconditional eradication based on the “test-and-treat” strategy[31]. However, although *H. pylori* is present in > 50% of the world’s population, sequelae of infection occur in only 20% of infected individuals, and malignant complications, such as GC, occur in < 3% of infected people[7]. Therefore, there is also an alternative point of view that *H. pylori* is a commensal symbiont[32,33]. Back in 1998, Blaser[32] wrote that, “*H. pylori* can thus be regarded as indigenous or ‘normal’ flora, which most humans acquire within the first few years of childhood and then carry for life.”

Unlike other pathogenic/opportunistic bacteria, *H. pylori* colonization of newborns/infants is facilitated by T helper type 2 immunity and leads to the development of immune tolerance[34]. Most likely, the co-evolution of *H. pylori* and the human host over millennia has led to the fact that this bacterium is considered a commensal symbiont, not a pathogen, by the host’s immune system. This is indirectly confirmed by the fact that α 1,2-fucosylated glycans of the GI epithelium, which are an important part of the innate and adaptive immune system (they create a symbiotic environment for the host and microbiota and protect against pathogens), mediate the adhesion of *H. pylori* to the surface of the gastric epithelium, contributing to successful colonization[35]. As a result, early colonization of *H. pylori* can have a positive effect on the host, for example on the regulation of the hormones leptin and ghrelin as well as on protection against some allergic (e.g., asthma) and autoimmune diseases and against inflammatory bowel disease (IBD)[36,34]. The inverse association between *H. pylori* and some potentially proinflammatory and/or procarcinogenic bacteria found in various studies[20,22-24] may suggest a regulatory function of *H. pylori* toward the GI microbiota. The available evidence for beneficial effects of *H. pylori* toward the GI microbiota, as well as potential protective effects against certain diseases, should not be ignored by the gastroenterological community.

Presence of *H. pylori* infection and reduced risk of IBD: Is there a causal relationship? The potential protective role of *H. pylori* in the development of IBD, shown in some studies[37], may be related to both modulation of the gut microbiota and the immunomodulatory properties of *H. pylori*. An inverse association between *H. pylori* and potentially proinflammatory microbes (*Bacteroides ovatus*, *Fusobacterium varium*, *Rhodococcus*, *Sphingomonas*) supports a microbiome-modulating mechanism, while an immunomodulatory mechanism of protection against IBD may involve the activation of colonic mucus production by *H. pylori* via the NLRP3/caspase-1/interleukin-18 axis[38].

We suggest another possibility for the association between *H. pylori* infection and IBD, a non-causal relationship, which relates to the fucosylation status of host mucin glycans in the GIT. Individuals with a non-functional α (1,2)-fucosyltransferase 2 (*FUT2*) gene (they are termed non-secretors), who have loss-of-function mutations, cannot express α (1,2)-fucosylated glycans in the GI mucosa. Non-secretors (about 20% of the population) are more susceptible to infection by some pathogens (*Escherichia coli*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Candida albicans*) and have aberrant gut microbiota, with a reduction of beneficial *Bifidobacterium* spp. The *FUT2* non-secretor phenotype increases susceptibility to Crohn’s disease, ulcerative colitis, primary sclerosing cholangitis, celiac disease, psoriasis, Behçet’s disease, type 1 diabetes, and so on but at the same time protects against *H. pylori*, which requires fucosylated glycans in the gastric mucosa for adhesion[35,39,40].

A recent study showed that patients with ulcerative colitis and Crohn’s disease had decreased *FUT2* expression and α 1,2-fucosylation in the colon[41]. In addition, *Fut2* deficiency in the intestinal epithelium exacerbated colitis in epithelium-specific *Fut2* knockout (*Fut2*^{IEC}) mice, promoted the release of proinflammatory cytokines, and aggravated epithelial barrier damage[41]. The authors demonstrated for the first time that epithelium-specific *Fut2* deficiency increased susceptibility to IBD through modulation of the gut microbiome and microbiota-mediated lysophosphatidylcholine generation. Lysophosphatidylcholine may have deleterious effects on the colon by promoting the release of proinflammatory cytokines, damaging the tight junctions and epithelial barrier in the colon epithelium, and exacerbating colonic inflammation in *Fut2*^{IEC} mice[41].

In turn, upregulation of *FUT2*-mediated fucosylation in the intestinal epithelium, for example by exogenous L-fucose, can protect the intestinal barrier, enhance tight junctions, and alleviate intestinal inflammation[42]. Similar to the colon, increased expression of the fucosyltransferase genes *FUT2* and *FUT1* in the gastric epithelium promotes *H. pylori* adhesion and ultimately infection[43]. Thus, we suggest that increased expression of *FUT2* in the gastrointestinal mucosa can simultaneously mediate both *H. pylori* infection and protection against IBD *via* an *H. pylori*-independent mechanism. In this case, a causal relationship between the presence of *H. pylori* and a reduced risk of IBD is unlikely. However, it cannot be ruled out that *H. pylori* mediates the protective effect of fucosylation against IBD by modulation of the gut microbiota or through an immunomodulatory mechanism[38].

Concluding remarks

Given the available data, eradication cannot be an unconditional recommendation in every case of *H. pylori* infection, as in the vast majority of people *H. pylori* is most likely a commensal[32,33], possibly beneficial in mutualistic interaction with the host (for example protecting against some allergic and autoimmune diseases[36]). We join the opinion of Chen *et al*[7] that the decision to eradicate *H. pylori* should be based on an assessment of the benefit–risk ratio for the individual patient. We also support the position of Miller and Williams[44] that “universal eradication” of *H. pylori* may cause more harm than good for the infected persons. Thus, the current guidelines based on the unconditional “test-and-treat” strategy[31] should be revised, including to reduce the excessive number of indications for eradication and to avoid empirical eradication therapy without a previous diagnostic test for *H. pylori* infection.

It may be worth recommending unconditional eradication only in patients with concomitant mucosa-associated lymphoid tissue lymphoma[45] and/or in individuals at high risk of GC, for example in groups of high familial (hereditary) risk[46] or in high-risk areas/populations where eradication effectively reduces the risk of GC[47]. In the latter case, the advisability of such an approach is unquestionable, if it is evidence-based. For example, a recent systematic review and meta-analysis provided moderate-certainty evidence that searching for and eradicating *H. pylori* can reduce the subsequent incidence of GC and death from GC in healthy asymptomatic infected people; the risk of GC decreased by 46% after eradication therapy[48]. However, the authors concluded that as all but one of the eligible trials were conducted in East Asian populations (in China, Japan, or South Korea), and the only trial conducted in a non-Asian population (in Colombia) did not demonstrate any benefit of such an approach, the results of the systematic review cannot be extrapolated to populations outside East Asia [48].

A well-known paradox, the low incidence of GC in some regions of Africa, Asia (*e.g.*, in India), and Latin America with a high prevalence of *H. pylori* infection, also requires in-depth study; this is called the African[49] or Asian/Indian enigma[50]. Although the existence of this phenomenon is sometimes disputed[51], studies have shown that *H. pylori* alone is most likely not enough for the development of GC, even with a high prevalence of highly pathogenic strains. Therefore, it is necessary to take into account not only the virulence factors of *H. pylori* and the oncogenic potential of specific strains of *H. pylori* but also the genetics and ethnicity of the human host population, their dietary habits (including antioxidant and sodium levels), smoking, alcohol consumption, socioeconomic status, and coinfection (parasitoses/helminthiasis) modulating the potentially protective T helper type 2 immune response[49, 50].

An important factor influencing the serious consequences of *H. pylori* infection appears to be the co-evolution of *H. pylori* and the human host. A recent study demonstrated that the African human ancestry showed clear signs of co-evolution with *H. pylori*, while the European ancestry was maladapted. The Asian ancestry was intermediate but closer to the African ancestry[52]. This supports the hypothesis that *H. pylori* is a commensal symbiont rather than a human pathogen. Hopefully, a series of international prevalence surveys to investigate age-specific prevalence of *H. pylori* in areas of low and high GC risk, namely ENIGMA, recently launched under the auspices of the International Agency for Research on Cancer in Africa (Uganda), Asia (Iran), and Latin America (Chile, Costa Rica), will shed light on the regional characteristics of *H. pylori* infection and identify markers for GC risk stratification to offer reasonable preventive interventions for different populations[53].

In addition, *H. pylori* eradication is likely to be recommended in patients with cancer who are on therapy with immune checkpoint inhibitors or vaccine-based immunotherapy, for example in patients with non-small-cell lung cancer[54].

In patients with diseases negatively associated with *H. pylori*, such as IBD, microscopic colitis, celiac disease, asthma, multiple sclerosis, Barrett’s esophagus, esophageal adenocarcinoma, eosinophilic esophagitis, and so on, eradication should be carried out with caution, carefully weighing the risk-to-benefit in each case. Even though *H. pylori* eradication did not affect either the healing rate or the recurrence rate of pre-existing gastroesophageal reflux disease, the possibility of developing new erosive gastroesophageal reflux disease after eradication should always be kept in mind[55].

The most cautious and careful approach should be taken in elderly patients with multiple eradication failures since repeated eradication (second-/third-line therapies) can cause antibiotic-associated diarrhea, including severe *Clostridioides difficile*-associated diarrhea and colitis[56] and antibiotic-associated hemorrhagic colitis due to *Klebsiella oxytoca*[57]. In this regard, we support the recent

conclusion of the American Gastroenterological Association experts that, “after multiple failed eradication attempts, the potential benefits of *H. pylori* eradication should be weighed carefully against the likelihood of adverse effects and inconvenience of repeated high-dose acid suppression and antibiotic exposure, particularly among individuals who are not at an identifiably higher risk of complications from persistent *H. pylori* infection (e.g., GC, peptic ulcer disease); in such scenarios, a shared decision-making approach should be seriously considered, especially in the elderly, those with frailty, and those with intolerance to antibiotics” (Best Practice Advice #9)[30].

Furthermore, since eradication therapy with antibiotics and proton pump inhibitors can lead to serious adverse effects and/or long-term dysbiotic changes in the GI microbiota, the supplementation of probiotics[58-61], prebiotics, and microbial metabolites (e.g., butyrate + inulin)[62] to reduce the negative effects of eradication should be considered[7]. In addition, alternative eradication regimens with limited or no antibiotic use, for example phage-based regimens[63], autoprobiotics[64], and natural agents and methods including traditional Chinese medicine[65], should be proposed, developed, and explored in future studies.

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