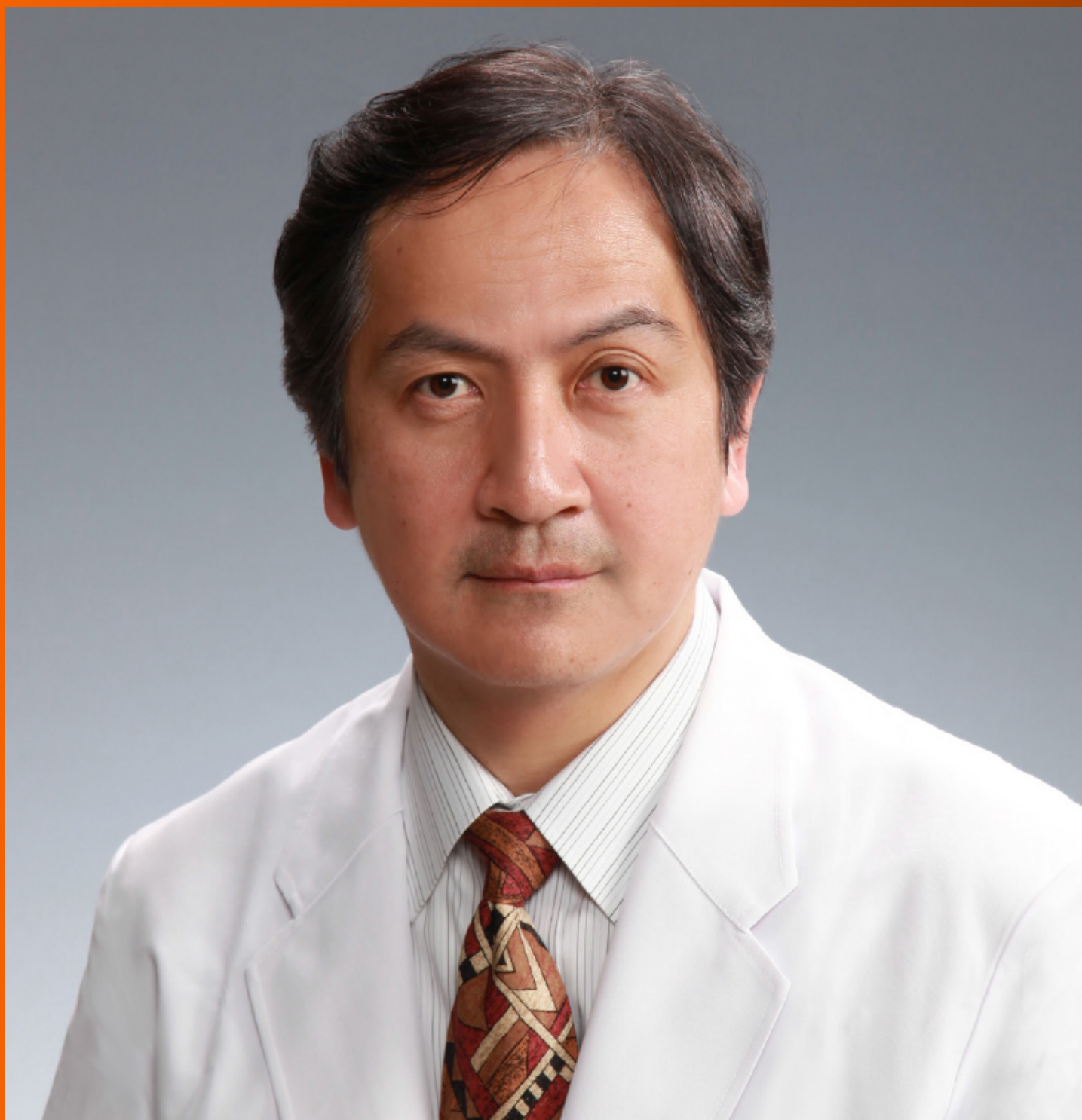


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Helicobacter pylori eradication: Exploring its impacts on the gastric mucosa

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Abstract

Helicobacter pylori (*H. pylori*) infects approximately 50% of all humans globally. Persistent *H. pylori* infection causes multiple gastric and extragastric diseases, indicating the importance of early diagnosis and timely treatment. *H. pylori* eradication produces dramatic changes in the gastric mucosa, resulting in restored function. Consequently, to better understand the importance of *H. pylori* eradication and clarify the subsequent recovery of gastric mucosal functions after eradication, we summarize histological, endoscopic, and gastric microbiota changes to assess the therapeutic effects on the gastric mucosa.

Key Words: *Helicobacter pylori*; Gastric mucosa; Histology; Endoscopic findings; Gastrointestinal microbiota; Eradication therapy

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Core Tip: Eradication of *Helicobacter pylori* (*H. pylori*) is important. Multiple gastrointestinal diseases and extragastric diseases would emerge if *H. pylori* infection persists, whereas they would improve after *H. pylori* eradication. Thus, *H. pylori* eradication produces dramatic changes in the gastric mucosa. This review highlights the most recent literature and presents a comprehensive evaluation about the impact of *H. pylori* eradication on the gastric mucosa.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) represents a type of Gram-negative microaerophilic bacterium with a helical shape, generally infecting humans in early childhood[1,2]. O'Connor et al[3] have generated a table with some of the latest epidemiological findings about *H. pylori* infection, whose rate remains high, especially in certain parts of China as well as some Eastern European and South American countries. *H. pylori* infects ~50% of the global population[4]. Some researchers have reported that *H. pylori* infection rate is associated with socioeconomic status, including educational resources and living conditions, indicating that elevated *H. pylori* prevalence is more likely to happen in underdeveloped countries[5,6]. *H. pylori* is transmitted via iatrogenic, fecal-oral, and oral-oral routes[7].

Gastrointestinal diseases develop if *H. pylori* infection persists, including acute and chronic gastritis, gastric and duodenal ulcers[8], gastric mucosa-associated lymphoid tissue lymphoma (MALToma)[9], and autoimmune gastritis (AIG)[10]. Several studies have reported that *H. pylori* infection plays a role in extragastric diseases, including immune thrombocytopenia, unexplained iron-deficiency anemia, and Alzheimer's disease[11-15]. Moreover, the World Health Organization has included *H. pylori* among group 1 carcinogens for its critical role in gastric cancer (GC) etiology[16,17].

Besides curing gastritis, complete eradication of *H. pylori* can permanently cure peptic ulcers[18] and induce MALToma regression[19]. Additional evidence also suggests that *H. pylori* eradication treatment decreases precancerous lesions[20] and successfully prevents GC development[21,22], even after resection of early GC[23]. There is an urgent need to clearly assess the importance and necessity of *H. pylori* eradication. Therefore, the purpose of this review is to examine the impact on the gastric mucosa of *H. pylori* eradication to better understand the importance of *H. pylori* eradication.

GASTRIC MUCOSAL CHANGES AFTER *H. PYLORI* ERADICATION

The gastric mucosa, the innermost layer of the stomach, consists of the epithelium, lamina propria, and muscularis mucosae, constituting three protective mucosal barriers. The most important barrier is called epithelial-bicarbonate barrier, the first line of defense of the gastric mucosa[24]. On the one hand, long-term *H. pylori* infection induces a sequence of histopathological changes, from gastritis (acute, chronic, and atrophic), intestinal metaplasia (IM), dysplasia, and ultimately to neoplasia according to the classical Correa sequence[25,26]. On the other hand, after anti-*H. pylori* therapy using antibiotics and proton pump inhibitors (PPIs)[27], the gastric mucosa undergoes various changes.

HISTOLOGICAL CHANGES UPON *H. PYLORI* ERADICATION

With *H. pylori* infection, the histological changes in the gastric mucosa, such as gastritis, are among the important and obvious manifestations. Evaluation of the extent of gastritis was proposed and revised based on the Sydney System[28] and/or the Updated Sydney System[29], comprising endoscopic and pathological findings. However, the *H. pylori* eradication efficiency can be also evaluated by histological indicators of activity (neutrophil polymorph density), inflammation (lymphocyte and plasma cell elevations), atrophy, and IM.

Changes of inflammation and activity

Regarding changes in histological indicators of gastric mucosal activity and inflammation, comparable trends of improvement have been reported[30-35]. Activity was improved in all studies. In addition, several studies have reported neutrophil

disappearance early after *H. pylori* eradication; consequently, activity score is considered a highly sensitive index for assessing *H. pylori* presence. Meanwhile, the inflammatory index PGII declines rapidly within 1–2 mo after successful *H. pylori* eradication[36,37]. Furthermore, inflammation is cleared at a significantly reduced rate, but with overt improvement[38].

Changes in atrophy and IM

Atrophic gastritis (AG) and IM are premalignant conditions for GC. It remains controversial whether *H. pylori* eradication reverses AG and IM.

Various parts of the stomach exhibit different histological recoverability. With a 1-year follow-up, Sung *et al*[34] carried out a study in 2000, screening 587 *H. pylori*-positive subjects, randomizing them to the omeprazole, amoxicillin and clarithromycin ($n = 295$) or placebo ($n = 292$), and indicating that GA and IM in the antrum and corpus could be alleviated by *H. pylori* eradication, as did other studies by Annibale *et al*[39] and Ohkusa *et al*[40]. However, a recent study performed by Sung *et al*[35] in 2020 corrected the above results, demonstrating that GA is improved significantly with radical treatment of *H. pylori* in the antrum and corpus, while IM did not follow the same trend. With 3 years of follow-up, our team previously assessed 197 *H. pylori*-infected patients, including 92 receiving *H. pylori* eradication therapy and 87 control patients, and found markedly decreased atrophy in individuals with successful *H. pylori* eradication[33]. However, Kang *et al*[41] found that AG was improved in the corpus but not in the antrum. Furthermore, Kodama *et al*[42] showed that atrophy was markedly reduced after *H. pylori* eradication, both in the antrum and corpus after 5–13 years of follow-up. At the same time, IM was significantly decreased in the corpus but not in the antrum, with no differences observed in the untreated group. With 10 years of follow-up, Kodama *et al*[43] evaluated the gastric mucosa at five points based on the Updated Sydney System, revealing that atrophy at every site in the stomach and IM in the lesser curvature of the corpus showed continuous and significant decreases. In addition, Hwang *et al*[44] prospectively assessed patients with a 10-year follow-up, demonstrating that AG and IM in the antrum and corpus were gradually alleviated and reached a point at which they were comparable to those of *H. pylori*-negative individuals. There are three meta-analyses[45–47] concerning improvements of AG and IM. The first[45] assessed the long-term impact of *H. pylori* eradication on histological features in the stomach, and demonstrated that eradicating *H. pylori* improved atrophy but not IM, a finding similar to that of another meta-analysis[46]. However, Kong *et al*[47] reported that IM improvement only occurred in the gastric antrum and not in the corpus.

The discrepant responses of AG and IM to *H. pylori* eradication may have several reasons. On the one hand, the methods of histological assessment of biopsy specimens, sample sizes, and amounts of biopsy specimens are different across studies. On the other hand, progression from AG to serious AG, IM, and GC takes decades, indicating that a longer follow-up period could better mimic the actual situation[48,49]. Moreover, different risk factors for AG and IM, such as bile reflux, other bacterial infections, age, and dietary structure, could also influence the final results[33,50].

Different follow-up times result in different recoverability degrees of AG and IM. Since follow-up is tightly associated with improvement data in the majority of studies, follow-up times were divided into three groups for further assessment of AG and IM, including short (< 3 years), medium (3–10 years), and long (≥ 10 years) terms (Table 1). Activity and inflammation improvements following *H. pylori* eradication were consistent. However, whether AG and IM can be completely cured upon *H. pylori* eradication remains debatable. It is worth noting that a research team in Colombia conducted a large trial with long-term follow-up in the 1990s. After 6 years[51], 12 years[32], 16 years[52], and 20 years[53], the results indicated that *H. pylori* infection increased histological progression, and anti-*H. pylori* treatment significantly induced histological improvement and disease regression, and reduced progression of precancerous lesions of GC. Therefore, AG could be reversed, and even IM, with prolonged follow-up.

The above findings suggest that *H. pylori* eradication improves AG and IM, and anti-*H. pylori* treatment confers long-term benefits in decreasing the progression of precancerous lesions. The earlier the *H. pylori* eradication, the greater the benefits.

CHANGES IN ENDOSCOPIC FINDINGS AFTER *H. PYLORI* ERADICATION

Endoscopy is an important gastrointestinal examination method. The Kyoto Classi-

Table 1 Major features of the eight trials examining for histological parameters

Ref.	Study arm, <i>n</i>				Methods	Histologic parameter																	
	Eradicated	Not eradicated	Follow-up, yr	Medication		1 = OS	AG											IM					
						2 = RCT	Antrum			Corpus			Antrum			Corpus							
							Before	After	<i>P</i> value	Before	After	<i>P</i> value	Before	After	<i>P</i> value	Before	After	<i>P</i> value					
Sung <i>et al</i> [34]	226	245	1	OAC	2	0.64 ± 0.78	0.70 ± 0.82	<i>P</i> = 0.627	0.06 ± 0.31	0.02 ± 0.18	<i>P</i> = 0.682	0.78 ± 0.98	0.61 ± 0.94	<i>P</i> = 0.014	0.04 ± 0.32	0.06 ± 0.30	<i>P</i> = 0.391						
Annibale <i>et al</i> [39]	25	7	0.5	BAM	1	0.56 ± 0.24	0.5 ± 0.2	NS	1.64 ± 0.11	1.36 ± 0.18	NS	0.58 ± 0.25	0.53 ± 0.23	NS	0.52 ± 0.13	0.76 ± 0.16	NS						
Ohkusa <i>et al</i> [40]	115	48	1-1.25	PPI/A/C	1	0.8 ± 1	At 1–3 mo: 0.8 ± 1	<i>P</i> > 0.2	0.5 ± 0	At 1–3 mo: 0.3 ± 0	<i>P</i> = 0.020	0.7 ± 0	At 1–3 mo: 0.6 ± 0	<i>P</i> = 0.14	0.0 ± 0.0	At 1–3 mo: 0.2 ± 0	<i>P</i> = 0.022						
							At 12–15 mo: 0.9 ± 1	<i>P</i> = 0.15		At 12–15 mo: 0.2 ± 0	<i>P</i> = 0.001		At 12–15 mo: 0.4 ± 0	<i>P</i> < 0.001		At 12–15 mo: 0.1 ± 0	<i>P</i> > 0.2						
Lu <i>et al</i> [33]	92	62	3	O/LAC	1	1.25 ± 0.44	0.97 ± 0.83	<i>P</i> < 0.01	NA	NA	NA	0.64 ± 0.76	0.73 ± 0.77	NS	NA	NA	NA						
Kang <i>et al</i> [41]	210	16	3	PPI/A/C	1	0.85 ± 0.06	1 yr: 0.83 ± 0.06	NS	0.70 ± 0.07	1 yr: 0.42 ± 0.06	<i>P</i> < 0.001	0.91 ± 0.07	1 yr: 0.83 ± 0.06	NS	0.60 ± 0.07	1 yr: 0.54 ± 0.06	NS						
	54	16	3	PPI/A/C	1	0.96 ± 0.14	3 yr: 1.32 ± 0.20	NS	0.91 ± 0.20	3 yr: 0.45 ± 0.15	<i>P</i> = 0.033	1.02 ± 0.14	3 yr: 1.29 ± 0.14	NS	0.68 ± 0.15	3 yr: 0.83 ± 0.14	NS						
Kodama <i>et al</i> [42]	118	21	8.6	PPI/A/C	1	1.60 ± 0.09	1.02 ± 0.08	<i>P</i> < 0.001	0.71 ± 0.10	0.02 ± 0.02	<i>P</i> < 0.001	0.60 ± 0.11	0.43 ± 0.09	NS	0.17 ± 0.12	0.00 ± 0.00	<i>P</i> < 0.05						
Kodama <i>et al</i> [43]	176	21	10	PPI/A/C	1	AI: 1.39 ± 0.07	6 yr: 0.90 ± 0.09	<i>P</i> < 0.05	B1: 1.08 ± 0.08	1 yr: 0.78 ± 0.11	<i>P</i> < 0.05	A1: 1.14 ± 0.10	NA	NS	B1: 0.97 ± 0.09	6y: 0.42 ± 0.17	<i>P</i> < 0.05						
						A2: 1.39 ± 0.06	1 yr: 1.06 ± 0.08	<i>P</i> < 0.01	B2: 0.52 ± 0.06	0.6 mo: 0.29 ± 0.07	<i>P</i> < 0.05	A2: 0.50 ± 0.07	NA	NS	B2: 0.13 ± 0.04	NA	NS						
						IA: 1.51 ± 0.08	1 yr: 1.24 ± 0.09	<i>P</i> < 0.05				A1: 1.04 ± 0.09	NA	NS									
Hwang <i>et al</i> [44]	442	91	10	PPI/A/C E/A/C/M	1	<i>n</i> = 178	<i>n</i> = 89 (50.0)	<i>P</i> = 0.002	<i>n</i> = 105	<i>n</i> = 72 (68.8)	<i>P</i> = 0.01	<i>n</i> = 221	<i>n</i> = 45 (20.4)	<i>P</i> = 0.002	<i>n</i> = 142	<i>n</i> = 31 (21.8)	<i>P</i> = 0.01						

A: Amoxicillin; A1: Lesser curvature of the antrum; A2: Greater curvature of the antrum; B1: Lesser curvature of the corpus; B2: Greater curvature of the corpus; B: Bismuth subcitrate; C: Clarithromycin; E: Esomeprazole; GA: Gastric atrophy; IA: Lesser curvature of the angulus; IM: Intestinal metaplasia; L: lansoprazole; M: Metronidazole; NA: Not applied; NS: Not significant; O: Omeprazole; OS: Observational study; PPI: Proton pump inhibitor; RCT: Randomized controlled trial; data are presented as *n* (%) or the median ± standard deviation or mean ± SE/median.

fication of Gastritis, categorizing *H. pylori* infection into three phases (non-gastritis, active gastritis, and inactive gastritis[54]), was proposed to better assess the status of *H. pylori* infection and GC risk by endoscopy[55] (Figure 1). In a healthy stomach, an easily detectable feature, non-gastritis, was the regular arrangement of collecting venules (RAC), featured as small red spots on the mucosal surface[56,57]. However, after being infected with *H. pylori*, the stomach was characterized as irregular arrangement or absence of the so-called collecting venules[58]. AG after infection by *H. pylori* presents with diffuse redness, spotty redness, mucosal edema, and enlarged folds. This phenomenon can decrease and disappear after *H. pylori* eradication[59-61]. In addition, with *H. pylori* eradication, nodular gastritis (NG), whose endoscopic character is “goose flesh” in the antrum, can also disappear with the passage of time [62,63].

After a period of *H. pylori* infection, AG turns into inactive gastritis upon eradication therapy or spontaneously disappears because of advanced atrophy, featuring map-like redness, and flat or depressed erythematous tumors, which is the characteristic change of AG after *H. pylori* eradication, *i.e.*, nonatrophied areas dissipate the inflammation, and the atrophied areas are relatively red compared to the nonatrophied areas. Using white-light imaging (WLI) and linked color imaging (LCI), Majima *et al*[64] found that map-like redness is closely associated with GC occurrence upon effective *H. pylori* eradication. Another study also revealed map-like redness upon *H. pylori* eradication as the sole predictive factor for metachronous cancer[65]. With *H. pylori* infection, atrophic change expands from the antrum to the fundus, and is improved after eradication[66,67]. Another characteristic was described as mottled patchy erythema (MPE) after *H. pylori* infection, showing many flat/slightly depressed erythematous lesions detected by white light endoscopy, and highly predicting the impact of *H. pylori* eradication.

The typical endoscopic finding of IM is mixed patchy pink and pale mucosal areas surrounding grayish slightly elevated plaques generating an irregular, uneven surface. Moreover, villus-like structures, whitish mucosa, and rough mucosal surface can help diagnose IM by endoscopy[68,69]. In addition, endoscopic IM contributes to recognition of current and past *H. pylori* infections, similar to endoscopic atrophy[70]. *H. pylori* eradication reduces the development of hyperplastic polyps (HPPs); either sessile or pedunculated polyps result from *H. pylori* infection[71]. Gastric xanthoma (GX) is a typical endoscopic manifestation of *H. pylori* infection that persists upon *H. pylori* eradication, showing one or more yellowish well-delineated nodules or plaques of 1-10 mm in diameter[72]. However, GX may be a precancerous lesion of GC[72,73]. After treatment with PPI, the endoscopic phenomena of multiple white elevated lesions and cobblestone-like mucosa became more evident in comparison with PPI nonusers[74].

Overall, endoscopic features represent additional indexes for evaluating *H. pylori* therapy for efficacy. Atrophy, IM, HPPs, and fundic gland polyps are detected in active and inactive gastritis. In addition, atrophy boundaries are unclear with map-like redness observed upon *H. pylori* eradication[75]. However, endoscopic atrophy and IM may show no rapid improvement[76,77], and prolonged follow-up is required for detecting gastric mucosal changes endoscopically following *H. pylori* eradication[78].

EFFECT OF *H. PYLORI* ERADICATION THERAPY ON GASTRIC MICROBIOTA

There are many microorganisms in the human stomach, constituting alongside *H. pylori* the so-called gastric microbiota[79], whose balance and stability are indispensable for normal gastric mucosal digestion and metabolism. With more advanced techniques, such as culture-free molecular methods (*e.g.*, 16S rDNA sequencing), the human stomach is currently known to host multiple resident microbes. Based on such techniques, many reports have shown that *H. pylori*-negative individuals have a greatly diverse gastric microbiome with four dominating phyla, including Proteobacteria (including *H. pylori*), Firmicutes, Bacteroidetes, and Actinobacteria; the commonest genera are *Streptococcus*, *Lactobacillus*, and *Propionibacterium*[80-85].

Upon *H. pylori* infection, changes in gastric microorganisms arise, including gastric microbial diversity, composition, and predictive pathways[86], leading to various diseases[87-89]. Generally, colonization by *H. pylori* is associated with significantly reduced alpha and beta diversities (representing inter-sample and in-sample diversities, respectively)[90-92]. Additionally, several studies have revealed that *H.*

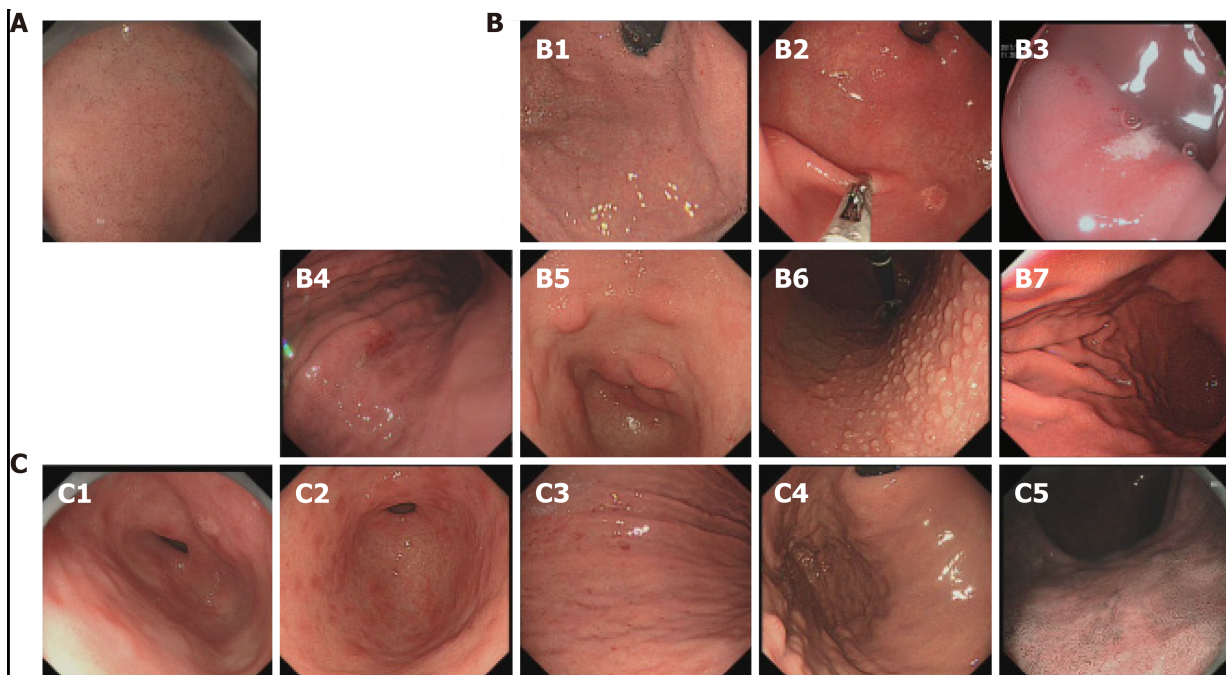


Figure 1 Endoscopic features for *Helicobacter pylori* infection. A: Normal gastric mucosa. Regular arrangement of collecting venules is seen; B: Infected gastric mucosa. B1: Spotty redness; B2: Gastric xanthoma; B3: Erosion; B4: Multiple redness and erosion; B5: Hyperplastic polyp; B6: Nodular gastritis; B7: Intestinal metaplasia; C: Gastric mucosa after eradication. C1: Patchy redness; C2: Map-like redness; C3: Redness; C4: Atrophy; C5: Intestinal metaplasia.

pylori-infected individuals have different community structures in comparison with their *H. pylori*-negative counterparts[93-96]. Compositionally, Proteobacteria often dominate the gastric mucosa upon *H. pylori* infection, becoming the single most abundant bacteria and almost reaching 90% abundance at the phylum level, while other phyla (Actinobacteria, Bacteroidetes, Firmicutes, and Fusobacteria) show reduced numbers[82,90,92-94,96,97].

After anti-*H. pylori* treatment, the gastric microbiome undergoes major reshaping (Table 2). Mounting evidence indicates that gastric microbial diversity markedly increases upon effective *H. pylori* eradication but does not improve if treatment fails [35,82,86,93,98,99]. Recovery may take some time as microbial diversity increases gradually from week 0 to weeks 6 and 26[86]. Additionally, alpha diversity can regain the level of uninfected individuals following effective eradication[98]. Although the community structure can also be partly restored upon *H. pylori* eradication, whether in post-eradication groups it can be restored to that of healthy control groups appeared to be age related. Specifically, several studies indicated that the adult specimens from 6 mo after successful treatment still showed altered community structure *vs* the negative control group[98], while others recruiting children reported the close community structures between the eradication and *H. pylori*-negative groups at 4 wk post-therapy [99] and the restored gastric microbiota composition in individuals administered with anti-*H. pylori* therapy at 2 mo post-treatment[82]. We believe that in adult patients, further research is needed to see whether the recovery in microbial composition can be observed over a longer observation period.

Compositionally, the relative abundance of *H. pylori* starkly decreases post-treatment, although it remains the dominant bacterium[86,93]. Meanwhile, Actinobacteria, Firmicutes, Bacteroidetes, and Fusobacteria are significantly enriched after successful eradication[82,90,93,98]. At the genus level, the probiotics *Lactobacillus* and *Bifidobacterium* are markedly increased post-therapy[86]. Functional analysis was performed in multiple studies[82,86,98]. The activities of disease-associated categories in *H. pylori* infection (lipopolysaccharide biosynthesis, bacterial motility proteins, *etc.*) were more pronounced[82,98]. In addition, the metabolic pathways (protein digestion and absorption, gastric acid secretion, and carbohydrate digestion and absorption) in the presence of *H. pylori* were downregulated[100]. After eradication therapy, these functions might be partly restored[86].

H. pylori infection is associated with reduced bacterial diversity and causes a shift in bacterial structure. Clearance of *H. pylori* significantly increases bacterial diversity. The relative abundance of *Helicobacter* decreases after therapy, while other phyla are increased, partly restoring bacterial structure and improving microbiota functions,

Table 2 Major features of five meta-analyses

Ref.	Year	Total No. of study	Eradication group			Control group			OR/RR	95%CI
			Total No.	Total events	Incidence rate	Total No.	Total events	Incidence rate		
Sugimoto <i>et al</i> [118]	2020	4RCTs	2731	73	2.7%	2733	49	1.80%	0.67	0.47–0.96
Sugano <i>et al</i> [119]	2019	32	16301	316	1.90%	14805	535	3.60%	0.46	0.39–0.55
Doorakkers <i>et al</i> [120]	2016	8 Cohort	12899	119	0.90%	18654	208	1.10%	0.46	0.32–0.66
Chen <i>et al</i> [121]	2016	8RCTs	3992	74	1.90%	3962	116	2.90%	0.64	0.48–0.85
Ford <i>et al</i> [104]	2014	6RCTs	3294	51	1.60%	3203	76	2.40%	0.66	0.46–0.95

RR: Risk ratio; OR: Odds ratio; 95% C: 95% confidence interval.

such as metabolism.

CHANGES IN GC AFTER *H. PYLORI* ERADICATION

Many studies have confirmed that *H. pylori* infection is the main etiological agent of GC[101,102], whose risk can be reduced by *H. pylori* eradication[103–108].

To explore this, Wong *et al*[109] performed a study demonstrating that GC incidence rates were comparable in the treatment and placebo groups (7 cases in either group), which may have been due to a underpowered design despite the 7.5-year follow-up of 1630 participants. However, with the follow-up time gradually extended, the incidence rates of GC in both groups gradually showed differences. Another study demonstrated significantly decreased GC incidence after 6 years of follow-up after *H. pylori* eradication, and the standardized incidence ratio (SIR) was 1.62 in the initial 5 years but was reduced thereafter to reach 0.14[21]. A Swedish cohort study found significantly decreased risks of gastric adenocarcinoma and non-cardia gastric adenocarcinoma upon cure of *H. pylori* infection (SIRs were 8.65 in 1–3 years, 2.02 in 3–5 years, and 0.31 in 5–7.5 years)[22,109]. After *H. pylori* treatment, the risk was 39% lower over an extended follow-up of 15 years and 52% over an extended follow-up of 22 years among individuals with *H. pylori* eradication compared with those showing persistent infection, whereas there was no difference during the initial 7.3-year follow-up[20,110,111]. Having a first-degree relative with diagnosed GC doubles or triples GC risk[112]. In *H. pylori*-infected individuals with a first-degree relative diagnosed with GC, eradication of *H. pylori* also reduces GC risk[106,113]. A South Korean study utilized a prospective randomized design (832 and 844 in the cure and placebo groups, respectively, of first-degree relatives of GC cases). GC risk was reduced by 55% after *H. pylori* eradication *vs* the placebo group, with an average follow-up of 9.2 years. Of note, GC risk was 73% lower upon *H. pylori* eradication compared with the placebo group.

GC, as the end point of gastric disease, is also inextricably linked to *H. pylori*. Choi and collaborators[114] found that *H. pylori* eradication had no significant relationship with metachronous GC (MGC) incidence within an average follow-up of 3 years, whereas *H. pylori* eradication markedly reduced MGC incidence with a median follow-up duration of 71.6 mo[115]. A recent randomized trial involving early GC cases (a population that usually has severe atrophic alterations in the gastric mucosa) demonstrated that treating *H. pylori* infection reduced MGC risk by half[106]. A similar effect was also reported in another Chinese trial[116]. Successful eradication therapy cannot completely eliminate the development of GC. Take *et al*[117] performed a retrospective cohort trial in Japan, including 2737 patients treated for *H. pylori* infection with yearly endoscopic follow-up for 21.4 years. The degree of atrophy was related to a high yearly risk of GC. They also found an elevated risk of diffuse-type GC in individuals with mild to moderate gastric atrophy at baseline. The above findings suggest that endoscopic monitoring for GC should continue beyond 10 years post-*H. pylori* eradication regardless of the degree of gastric mucosal atrophy at the time of eradication treatment[117].

Several meta-analyses have demonstrated that the risk of GC is correlated with *H. pylori* eradication (Table 3)[104,118-121]. One meta-analysis including six randomized studies involving healthy, asymptomatic participants with *H. pylori* infection showed that GC risk was about 34% less after treatment compared with the control group [104]. Another meta-analysis also showed a reduced incidence of GC upon eradication therapy compared with control patients (pooled incidence rate ratio = 0.54)[122]. Sugano *et al* [119] and Doorakkers *et al* [120] reported that the lower odds ratio/relative risk was 0.46. A further meta-analysis demonstrated that no matter how varied the countries, conditions at baseline, and follow-up periods among studies, *H. pylori* eradication effectively reduces GC incidence. Consistent with the prediction, long-term (≥ 5 years) follow-up showed greater effects in reducing GC upon *H. pylori* eradication compared with shorter follow-up periods (< 5 years)[119]. This was consistent with other meta-analyses[104,118,120-122]. Thus, the above meta-analyses provided further robust evidence of the effect of eradication treatment.

Precancerous lesions are closely associated with GC. Consequently, whether and when *H. pylori* eradication reverses precancerous tumors has attracted increasing attention. Kiriya *et al* [123] and Wong *et al* [109] have reported that eradicating *H. pylori* did not reverse mucosal injury in IM to yield a normal gastric mucosa or prevent GC development, indicating a histological point of no return. In agreement, others have indicated that GC progression continues following *H. pylori* eradication[109,124]. However, the Taipei global consensus and Matsu Islands consensus proposed that eradicating *H. pylori* reduces GC risk[107,108], which may be due to treatment effects before a certain point for preventing GC.

In general, GC risk in *H. pylori*-infected patients is increasing. A large number of studies have shown that *H. pylori* eradication can reduce the incidence of not only GC, but also MGC. In both small and large studies (community, region, or country) examining young and old individuals, and even first-degree relatives of patients, eradication of *H. pylori* results in long-term benefits.

DISCUSSION

H. pylori infection induces a sequence of histological changes, especially AG and IM. A histological classification system (Figure 2A) was proposed by an international group of gastroenterologists and pathologists, to grade gastritis into stages with corresponding cancer risk in individual patients, termed the Operative Link on Gastritis Assessment (OLGA) scale[125]. However, disease severity and extent in OLGA are primary parameters, which leads to low interobserver agreement. Therefore, a staging system based on IM (Operative Link on Gastric Intestinal Metaplasia Assessment, OLGIM; Figure 2B) was proposed to assess the degree of IM and GC risk in 2010[126]. However, some individuals potentially at high risk of GC may be overlooked[127]. Therefore, the combination of OLGA and OLGIM more accurately predicts GC risk. Meanwhile, the AI system using deep learning (especially convolutional neural networks; CNNs) has been applied in gastroenterology[128-131]. For example, studies have reported the usefulness of CNN-based AI systems for diagnosing *H. pylori* infection and timely detecting gastric neoplasms[129,131,132].

Previous studies have found that only a small number of patients with *H. pylori* infection develop GC eventually, but *H. pylori* is one of the main causes of GC. The high risk of GC emphasizes the need for early detection and proper treatment of *H. pylori* infection. Along with standard endoscopy, new endoscopic techniques, such as magnifying endoscopy[133], endocytoscopy[134,135], magnifying narrow-band imaging (M-NBI)[136], I-Scan[137], endomicroscopy[138], and LCI[139-141], can be used to detect *H. pylori* infection. Magnifying endoscopy allows the structure of the mucosa and the subepithelial capillary network around the gastric fovea to be observed in detail. As a novel ultra-high magnification technology, endocytoscopy can recognize gastric mucosal minimal changes[134,135]. Moreover, the NBI system and I-Scan are also the recent developments in computed virtual chromoendoscopy imaging [137]. The diagnostic accuracy of M-NBI endoscopy for gastritis and magnifying I-Scan for *H. pylori* infection was 96.1% and 94.0%, respectively[136,137]. Currently, a novel imaging mode under blue laser endoscopy, LCI, plays an important role in endoscopic diagnosis of active *H. pylori* infection or distal gastric disease, through its enhanced slight differences in mucosal color[139-141]. With the assistance of computer-aided diagnosis (CAD) systems, LCI-CAD can effectively assess the gastric mucosal status of uninfected, currently infected, and post-*H. pylori* eradication patients[142-144].

Table 3 Studies on gastric microbiota alteration after eradication

Ref.	Year	Total subjects	Follow-up time	Age	Regimen	Study group		Main outcomes
				1 = Adults 2 = Children	1 = TT for 7-14 d 2 = QT for 10-14 d	HEG	<i>H. pylori</i> (-)	
Li et al [93]	2017	33	Day 0 and week 9	1	1	17	16	Bacterial diversity increased and the relative abundance of <i>Helicobacter</i> decreased, while the relative abundance of other phyla increased
Serrano et al [99]	2019	16	Day 0 and month 2	2	1	11	5	Bacterial diversity increased and the structures of the uninfected group were restored
Guo et al [98]	2020	164	Day 0 and month 6	1	2	115	49	Bacterial diversity returned to the level of the control group. The structure of the bacteria was different after treatment compared to the control group. Microbiota functional capacities were changed
He et al [86]	2019	17	Weeks 0, 6, and 26	1	2	10	NA	Bacterial diversity increased and structure and microbiota functional capacities were changed
Miao et al [82]	2020	55	Day 0 and week 4	2	1, 2 and STP	11	8	Diversity was similar compared to the control group. The bacterial structure became close to controls
Sung et al [35]	2020	102	Day 0 and 1 year	1	1	102	NA	Bacterial diversity increased and structure was changed

HEG: *Helicobacter pylori* eradication group; *H. pylori*: *Helicobacter pylori*; NA: Not applicable; QT: Quadruple therapy; TT: Triple therapy; STP: Sequential therapy with proton pump inhibitor and amoxicillin.

In this review, we describe the changes in gastric histology, endoscopic appearances, gastric microbiota, and decreased risk of GC and MGC [108]. Dyspeptic symptoms, AIG, and recurrence of peptic ulcer disease significantly declined after eradication of *H. pylori*. The risk of synchronous GC after endoscopic resection of early GC was also reduced. Many extragastric disorders, such as iron deficiency anemia, MALToma, and idiopathic thrombocytopenic purpura, were also associated with the presence of *H. pylori* and they were improved after eradication of *H. pylori* [8,9,10,145,146]. Therefore, consensus reports recommend eradication of *H. pylori* in infected patients, decreasing the risk of these diseases [38,147].

However, there are some potential concerns for *H. pylori* therapy due to the significantly increased antibiotic (particularly metronidazole and clarithromycin) resistance rates for *H. pylori* [148,149], and development of novel and alternative antimicrobial agents specific for *H. pylori* is urgent. These approaches are broadly divided into two main categories: (1) Novel synthetic treatment, which includes new classes of antimicrobial peptides (AMPs) and small molecule inhibitors; and (2) natural treatment options, which include the use of probiotics and phytotherapy to treat *H. pylori* infection. First, AMPs play a pivotal role in the innate immune responses to *H. pylori* in humans. AMPs can be roughly divided into nine categories: Pexiganan, tilapia piscidins, epinecidin-1, cathelicidins, defensins, bicarinalin, odorranain-HP, PGLa-AM1, and bacteriocins [150]. Among them, cathelicidins and defensins, both secreted by epithelial cells of many tissues, exhibit the key therapeutic potential [151]. SQ109, a typical representative of small molecule inhibitors for treating *H. pylori* infection, displays robust thermal and pH stability, induces low/no spontaneous drug resistance, and shows anti-*H. pylori* superiority over metronidazole and amoxicillin [152]. Second, adjuvant probiotics and phytotherapy therapy are designed to increase the eradication rate of *H. pylori* and reduce the adverse effects of treatment [153,154]. Phytotherapy, including herbs and spices, cruciferous vegetables, Korean red ginseng and green tea, and extracts of oils, resveratrol, and beta-carotene, is another naturopathic therapy. Specifically, herbal-based therapies, one of the most popular forms of phytotherapy, can act as anti-inflammatory agents to treat *H. pylori* infection [155]. Nevertheless, the active component for the majority of agents and the molecular mechanism of inhibition against *H. pylori* remain unknown. After the eradication of *H. pylori*, the risk of gastroesophageal reflux disease is increased due to the restoration of gastric acid secretion [156,157]. Alterations in gut microbiota might decrease the secretion levels of insulin, and fasting glucose, total cholesterol, and triglyceride were reduced after *H. pylori* eradication [148,158]. However, the findings remain contro-

A

Atrophy score		Corpus			
		No atroph (score 0)	Mild atrophy (score 1)	Moderate atrophy (score 2)	Severe atrophy (score 3)
Antrum (Including incisura angularis)	No atroph (score 0)	Stage 0	Stage I	Stage II	Stage II
	Mild atrophy (score 1)	Stage I	Stage I	Stage II	Stage III
	Moderate atrophy (score 2)	Stage II	Stage II	Stage III	Stage IV
	Severe atrophy (score 3)	Stage III	Stage III	Stage IV	Stage IV

B

IM score		Corpus			
		No IM (score 0)	Mild IM (score 1)	Moderate IM (score 2)	Severe IM (score 3)
Antrum (Including incisura angularis)	No IM (score 0)	Stage 0	Stage I	Stage II	Stage II
	Mild IM (score 1)	Stage I	Stage I	Stage II	Stage III
	Moderate IM (score 2)	Stage II	Stage II	Stage III	Stage IV
	Severe IM (score 3)	Stage III	Stage III	Stage IV	Stage IV

Figure 2 Operative link on gastritis assessment staging system (A) and operative link on gastric intestinal metaplasia assessment (B) staging system. IM: Intestinal metaplasia; OLGA: Operative link on gastritis assessment staging system; OLGIM: Operative link on gastric intestinal metaplasia assessment.

versial and further well-designed randomized trials are warranted to clarify the impact of *H. pylori* eradication on metabolic parameters.

More significantly, the relative immutability of IM is of concern, as the condition carries a high GC risk not only in the presence of *H. pylori* infection, but also after *H. pylori* eradication. In other words, GC can still develop even after successful eradication in the presence of IM[159]. Previous studies have indicated that the detection of map-like erythema, a histological indicator of IM, is correlated with a high risk of GC development after *H. pylori* eradication[65]. Even worse, the eradication therapy can cause some characteristics, such as a gastritis-like appearance, resulting in a difficult diagnosis of GC[160-162]. This is why post-eradication status should be distinguished from *H. pylori* negativity.

CONCLUSION

Whether *H. pylori* eradication confers long-term benefits has been debated for a long time. Obviously, eradication of *H. pylori* is more important, because the disadvantages can be avoided based on clinical experience and continuous technological development. More importantly, *H. pylori* eradication offers lifelong benefits, and the earlier it is eradicated, the better. In addition, more sensitive and accurate tools can be developed to detect *H. pylori* infection in the early and post-eradication stages. This could be a promising area of research.

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