

Review

***Helicobacter pylori*: present status and future prospects in Japan**

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The discovery of *Helicobacter pylori* has already changed the natural history of peptic ulcer disease, with most patients being cured at their first presentation. Similarly, the incidence of gastric cancer and other diseases related to *H. pylori* are likely to be greatly reduced in the near future. Isolation of the spiral intra-gastric bacterium *H. pylori* totally reversed the false dogma that the stomach was sterile, and it taught us that chronic infectious disease can still exist in modern society. *Helicobacter pylori*'s unique location, persistence, and evasion of the immune system offer important insights into the pathophysiology of the gut. Also, the fact that it was overlooked for so long encourages us to think "outside the box" when investigating other diseases with obscure etiologies. We should consider such provocative scientific ideas as bridges to the future disease control.

Key words: *H. pylori* diagnosis, *H. pylori* eradication, peptic ulcer, gastritis, gastric cancer

Introduction

Background

In recent years, research groups have concentrated on the molecular structures whereby *Helicobacter pylori* survives in the hostile gastric environment and persists in spite of the host's immune response. Epidemiologic studies have also provided convincing evidence that *H. pylori* is associated not only with gastroduodenal diseases, including chronic gastritis, peptic ulcer diseases, low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and noncardiac gastric adenocarcinoma,^{1–6} but also with extragut diseases.^{7–12}

The initial advance that facilitated the explosion of research related to *H. pylori* was the development of microaerobic cultivation methods for this bacterium. Then, it was shown that intentional infection of a volunteer led to gastritis.¹³ Classical bacteriology demonstrated that *H. pylori* is a Gram-negative, flagellated organism that produces a number of enzymes, including catalase and urease, which help neutralize host responses and favor colonization.^{14,15} One of the early benefits gained from this basic research was the demonstration that urease is produced by virtually all strains of *H. pylori*. This led to the development of accurate diagnostic tests, including the rapid urease test and the urea breath test. A stool antigen test has also emerged as an informative, noninvasive means by which to diagnose infection via detection of bacterial antigen.¹⁶ In addition, the ability to culture *H. pylori* provided a diagnostic test that allowed assessment of antibiotic susceptibility.

Before the modern discovery of intragastric bacteria 25 years ago,¹⁷ several reports dealt with spiral gastric bacteria as long ago as 1890. The modern discovery of *H. pylori* might have been delayed because in 1954, Palmer¹⁸ denied the existence of microorganisms in the human stomach, claiming that spiral bacteria were seen only post-mortem because microorganisms could not survive in the acidic gastric environment. However, microorganisms had been described in the gastric mucosa since the 1890s.¹⁹ For example, in Japan, Kasai and Kobayashi²⁰ of the Kitasato Institute reported propagation of a spirochete-like organism, probably *Helicobacter felis*, from the stomach of dogs and cats, but not from laboratory animals (Fig. 1). They showed that when rabbits infected with these spirochetes were also inoculated with the *virus fixe* (attenuated rabies virus), marked hemorrhagic lesions occurred in the gastric mucosa.²⁰ They also demonstrated that spirochetes inoculated into the gastric mucosa of the mouse could be eradicated by arsaminol²⁰ (a modern equivalent of arsaminol is thought to be bismuth, a close relative of ar-

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Fig. 1. Rokuzo Kobayashi (1887–1969), at his desk in the office of Keio University, Tokyo, Japan. Photo taken in 1935. Adopted from “Kobayashi Rokuzo” published by Dr. Rokuzo Kobayashi Memorial Association, 1971

senic).^{21,22} Seventy years then elapsed before scientists again attempted to treat gastric diseases associated with “spirochetes,” that is, *Helicobacter* infection.

Present status

Epidemiology

Most new *H. pylori* infections occur in children; however, in the absence of specific clinical signs associated with infection, the mode of transmission is difficult to define. Vomitus, saliva, and feces are the presumed sources of direct transmission, particularly in crowded housing conditions. Generally, infection correlates inversely with socioeconomic conditions,²³ with lifetime infection rates in affluent countries dropping toward 10%, while rates in countries with emerging economies approach 80%–90%.^{16,24,25} Most infected individuals experience asymptomatic gastritis, although recurrent gastroduodenal ulceration may occur in 10%–15% of the infected population. The incidence of gastric cancer is lower, with approximately 1%–5% of infected individuals developing adenocarcinoma and even fewer experiencing gastric MALT lymphoma.^{1,2,26–29}

Initially *H. pylori* depends on its urease enzyme to survive in an acid environment, and then on its spiral shape and motility to reach the gastric epithelium, where it sticks to cells through the various specific adhesion molecules. Once attached, most organisms then deliver damaging toxins to the mucosa.

Pathogenesis

The most investigated of these toxins stem from a segment of bacterial DNA referred to as the *cag* pathogenicity island (*cag* PAI). The presence of the *cag* PAI is usually associated with presence of the *s1m1* (more harmful) subtype of the vacuolating cytotoxin VacA. Genes within the *cag* PAI encode proteins such as CagE, an ATPase that drives a type IV secretion apparatus that allows bacterial macromolecules, especially CagA toxin, to translocate into the host cell.^{3,30} The intact *cag* PAI of *H. pylori* plays a significant role in the pathogenesis of gastritis in humans, since *H. pylori* carrying the *cag* PAI is associated with increased chemokine expression in gastric mucosal specimens³¹ and stronger inflammation.

CagA is injected into epithelial cells by the type IV secretory system, possibly as a mechanism to reduce the stress of gastric acid on the bacterium, since its transcription is increased at low pH.³² VacA is a pore-forming protein, which causes epithelial cells to vacuolate in vitro. Retrospective analyses of samples from gastric cancer patients have suggested an association with the *cagA*⁺/*vacA*⁺-positive genotype.³³ Further studies have confirmed that a risk for both cancer and peptic ulcer is associated particularly with the *cagA*/*vacA s1m1* genotype, but rarely with strains carrying the *vacA s2m2* polymorphism.^{34,35} However, the *cagA* gene does not act alone, because delivery of the CagA protein into epithelial cells appears to be dependent on a secretion system encoded for by the adjacent cluster of genes, the *cag* PAI.³⁶ After the CagA protein is injected into the host cell cytoplasm, it is tyrosine phosphorylated by host Src kinases and subsequently changes the epithelial morphology.^{37–41} CagA in strains from distinct geographic populations appears to be phosphorylated to a different degree, resulting in graded effects on intracellular signaling.^{42,43}

Oxygen-derived free radicals, which are released from activated neutrophils, are considered to be one of the potential toxic factors involving *H. pylori*-induced gastric mucosal injury, since *H. pylori* exhibits chemotactic activity for neutrophils.^{44,45} Neutrophil infiltration of the gastric mucosa leads to development of the initial lesion in *H. pylori*-associated gastritis and remains a hallmark of active bacterial infection. In response to the activation of neutrophils, NADPH oxidase (Nox) in the neutrophils' cell membranes becomes activated; an electron transfer takes place from NADPH in cells to

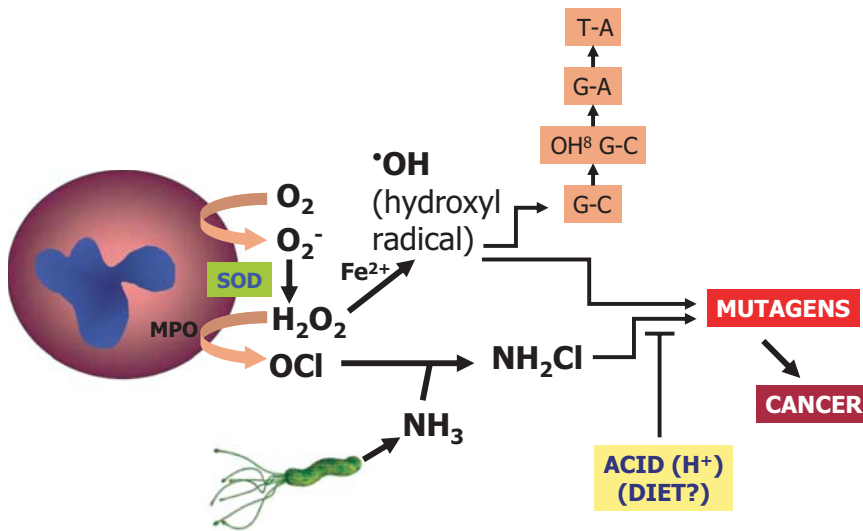


Fig. 2. *Helicobacter pylori*-associated gastric oxidative injury; monochloramine pathway. MPO, myeloperoxidase; SOD, superoxide dismutase

oxygen inside and outside of cells, and the oxygen molecules that receive an electron become superoxide radicals (O_2^-), which are rapidly converted to hydrogen peroxides (H_2O_2) by spontaneous dismutation, or to enzymatic superoxide dismutase (SOD) and hydroxyl radicals ($\cdot OH$), which are formed nonenzymatically in the presence of Fe^{2+} . In neutrophils, myeloperoxidase (MPO) also results in the formation of a potent oxidant, the hypochlorous anion (OCl^-), from H_2O_2 in the presence of Cl^- . This hypochlorous anion reacts with ammonia, derived from urea by *H. pylori*-associated urease, and yields cytotoxic oxidant, monochloramine (NH_2Cl)⁴⁶ with its lipophilic property, allowing it to freely penetrate biological membranes to oxidize intracellular components⁴⁷ (Fig. 2).

8-Hydroxy-2-deoxyguanosine (8-OHdG) is one of the most abundant lesions in DNA induced by reactive oxygen species.⁴⁸ It results from an attack by a singlet hydroxyl or oxygen radical on guanine (Fig. 2). Patients with *cagA*-positive *H. pylori* strains have higher 8-OHdG levels than both *cagA*-negative and *H. pylori*-negative patients.⁴⁹ The *cagA*-positive patients are characterized by greater oxidative DNA damage overall and at a younger age, in the presence of multifocal atrophy.⁴⁹

The preferred animal model for studying *H. pylori* gastritis is the Mongolian gerbil (*Meriones unguiculatus*).⁵⁰⁻⁵³ In one study, gerbils infected with a mutated strain lacking *cagE* exhibited a substantially reduced severity of gastritis.⁵⁴ Gastric ulceration developed in all of the gerbils infected with the wild-type strain but in none of those infected with the *cagE* mutant strain. In addition, intestinal metaplasia and gastric cancer developed in some gerbils with wild-type infection but not in animals infected with the *cagE*-negative mutant.⁵⁴ These

findings were confirmed by showing that the repaired *cagE*-positive *H. pylori* strain induced severe gastric inflammation, gastric mucosal atrophy, and gastric ulcer formation.⁵⁵ Recently, the nucleotide sequences of cDNAs encoding preproghrelin, a precursor of ghrelin (an appetite-promoting endocrine peptide produced mainly from A-like cells in the gastric fundus)^{52,56} and sonic hedgehog, a morphogen that may regulate and organize fundic gland epithelial differentiation, have been identified in the Mongolian gerbil.^{53,57} Preproghrelin and sonic hedgehog mRNA expression is significantly reduced in the gastric mucosa of Mongolian gerbils with persistent *H. pylori* colonization.^{52,53}

After reaching the mucosa and attaching by means of its lectins, *H. pylori* applies toxin to the gastric mucosa (Fig. 3). Then, the cells change their morphology and migrate, some detach, and sometimes apoptosis occurs. The healing process involves proliferation of adjacent, more healthy cells. Gastric epithelial cell turnover is regulated by the balance between cell death (apoptosis) and cell proliferation (Fig. 3). Such a regulated cell turnover by apoptosis and proliferation is essential for maintaining healthy gastric mucosal integrity. Some cells differentiate into intestinal tissue, a transformation called intestinal metaplasia. This may be somewhat protective in that *H. pylori* is unable to attach to these cells, allowing inflammatory processes to become quiet in these areas. However, extensive metaplasia is associated with decreased acid secretion, which may allow other commensal bacteria to colonize and carcinogen formation to occur. Proliferation by itself is not carcinogenic, but mutagens, such as monochloramine, may be formed in the presence of ammonia and hypochlorous anion. These cause errors in transcription to occur.

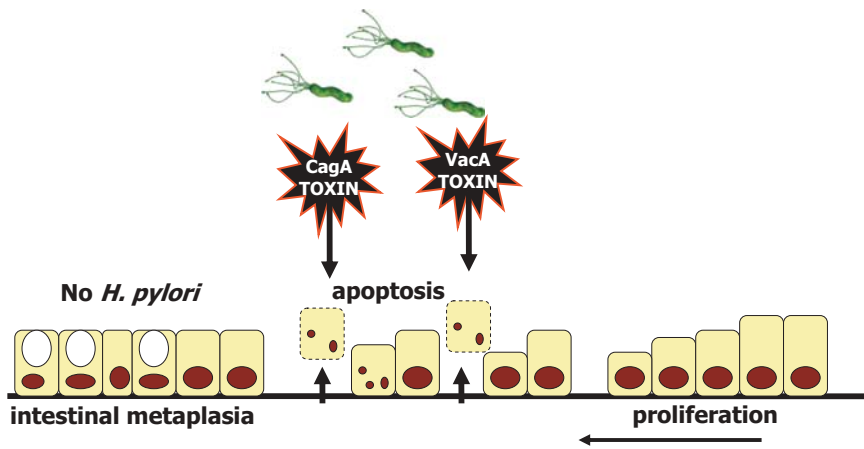


Fig. 3. After reaching the mucosa and attaching by means of its lectins, *H. pylori* applies toxin to the gastric mucosa. Cells change their morphology and migrate, some detach, and sometimes apoptosis occurs. The healing process involves proliferation of adjacent, more healthy cells. Proliferation by itself is not carcinogenic, but mutagens, such as monochloramine, may be formed in the presence of ammonia and hypochlorous anion. These cause errors in transcription. Some cells differentiate into intestinal tissue, a transformation called intestinal metaplasia

Table 1. Duodenal ulcer recurrence rate 1 year after *H. pylori* eradication

Authors	Year	Noneradication group % (95% CI)	Eradication group % (95% CI)	<i>P</i> value
Marshall et al. ⁶⁶	1988	55 (34–75)	21 (3–40)	0.029
Hentschel et al. ⁶⁵	1993	86 (76–96)	8 (0.4–15)	<0.001
Penston ⁶⁷	1994	67 (62–72)	7 (5–10)	—
Tytgat ⁶⁸	1995	58 (55–61)	2.6 (2–4)	—
Hopkins et al. ⁶⁹	1996	67 (63–72)	6 (4–9)	0.002
Laine et al. ⁷⁰	1998	56 (50–61)	20 (14–24)	<0.001

CI, confidence interval

At an earlier phase after bacterial inoculation, an initial transient enhancement of cell apoptosis (2–4 weeks) and a later increase in cell proliferation (16–20 weeks) occur in the *H. pylori*-colonized gastric mucosa of gerbils.⁵⁸ While the level of apoptosis increases as *H. pylori*-evoked gastric mucosal inflammation advances in mice, the enhanced level of apoptosis is significantly attenuated in *H. pylori*-colonized gastric mucosa of gerbils with enhanced inflammation and epithelial proliferation in the gastric mucosa during longer term colonization,⁵⁹ suggesting a possible link between attenuated gastric mucosal apoptosis and a specific carcinogenesis in gerbils after *H. pylori* colonization.^{60,61}

Peptic ulcer disease

The strongest association of *H. pylori* infection is with peptic ulcer disease;⁶² 95% of duodenal ulcers and 70% of gastric ulcers are related to *H. pylori* infection. Several cohort studies have estimated that the lifetime risk of ulcer disease in *H. pylori*-positive subjects is three to ten times that in *H. pylori*-negative subjects.⁶³ Introduction of *H. pylori* eradication regimens has completed the evidence for a causal relation between *H. pylori* and

peptic ulcer disease because *H. pylori* eradication has been shown to strongly reduce the risk of ulcer recurrence.⁶⁴ In prospective controlled studies of duodenal ulcer recurrence, ulcers recurred in 55%–86% of patients in *H. pylori*-positive cohorts, in contrast to a rate of 3%–21% in *H. pylori*-negative (successfully eradicated) cohorts^{65–70} (Table 1). Gastric ulcers typically recurred in 46%–71% of patients in *H. pylori*-positive cohorts, contrasting with ulcer recurrence rates of 10% or less in *H. pylori*-negative (successfully eradicated) cohorts^{71–76} (Table 2).

The meta-analytic results of a North American study by Laine et al.⁷⁰ have shown that *H. pylori* eradication markedly decreases ulcer recurrence. Nevertheless, ulcers recurred in 20% of patients in these studies within 6 months, despite a successful cure of infection and no reported use of nonsteroidal anti-inflammatory drugs (NSAIDs), suggesting that non-*H. pylori*, non-NSAID ulcers may be more common in the United States than previously believed.

According to a recent systematic review of 56 randomized controlled trials of treatment for peptic ulcer disease in *H. pylori*-positive adults,⁷⁷ a 1 to 2 weeks' course of *H. pylori* eradication therapy is an effective treatment. Namely, in duodenal ulcer (DU) healing,

Table 2. Gastric ulcer recurrence rate 1 year after *H. pylori* eradication

Authors	Year	Noneradication	Eradication	P value
		group % (n)	group % (n)	
Fukuda et al. ⁷²	1995	71 (42/59)	0 (0/24)	<0.001
Seppala et al. ⁷⁵	1995	47 (60/128)	7 (2/29)	<0.001
Sung et al. ⁷⁶	1995	58 (11/19)	8 (2/26)	<0.001
Kato et al. ⁷³	1996	46 (18/39)	0 (0/11)	<0.001
Axon et al. ⁷¹	1997	48 (30/63)	7 (3/44)	<0.001
Lazzaroni et al. ⁷⁴	1997	63 (20/32)	10 (2/20)	<0.001

eradication therapy was superior to several weeks of ulcer healing drugs [34 trials, 3910 patients, relative risk (RR) of ulcer persisting = 0.66] or no treatment (2 trials, 207 patients, RR = 0.37). In gastric ulcer (GU) healing, no significant differences were detected between eradication therapy and administration of an ulcer healing drug (14 trials, 1572 patients, RR = 1.25). For preventing DU recurrence, no significant differences were detected between eradication therapy and maintenance therapy with an ulcer healing drug (4 trials, 319 patients, RR = 0.73), but eradication therapy was superior to no treatment (27 trials, 2509 patients, RR = 0.20). For preventing GU recurrence, eradication therapy was superior to no treatment (11 trials, 1104 patients, RR = 0.29).

The incidence of peptic ulcers has steadily decreased in Western countries in the last two decades. The decreasing prevalence of peptic ulcers is thought to result both from contraction of the formerly large pool of patients with recurrent ulcer disease by *H. pylori* eradication at first presentation and from the decreasing prevalence of *H. pylori* infection in the population.^{24,78,79} The latter is related to several factors, such as improved hygiene and living conditions, decreased family sizes, and the use of antimicrobial therapy for other purposes.

Helicobacter pylori and NSAIDs are the two major causes of peptic ulcer disease. Their potential interaction in the induction of ulcer disease remains controversial. A thorough analysis of interaction data has revealed that the ulcer-inducing effects of both risk factors are cumulative.⁸⁰ Eradication of *H. pylori* in chronic NSAID users does no harm, and in some studies has decreased the incidence of ulcer disease. In a study from Hong Kong, patients starting with NSAID maintenance therapy were randomized to eradication therapy or placebo. After 6 months of follow-up, the incidence of ulcers was 12.1% in the eradication group and 34.4% in the placebo group ($P = 0.0085$). The corresponding probabilities of complicated ulcers after 6 months were 4.2% and 27.1% ($P = 0.0026$), respectively.⁸¹ These data show that, at least in an Asian population, screening and

treatment for *H. pylori* infection significantly reduces the risk of ulcers in patients starting long-term NSAID treatment, but also that eradication alone is insufficient to totally prevent ulcers and ulcer complications. In several studies, *H. pylori* eradication was inferior to omeprazole maintenance treatment for prevention of recurrent NSAID-associated ulcer bleeding.^{82,83} An overall synthesis of these data suggests that NSAIDs and *H. pylori* are independent, but not necessarily additive, causes of peptic ulcer. The wise choice might be to address both issues in all patients with ulcer complications: supplement NSAID users at risk with a second agent, consider the option of selective cyclooxygenase-2 (cox-2) inhibitors, and eradicate *H. pylori* as well.

Functional dyspepsia

Recently, the “Rome III” classification for functional gastrointestinal disorders was defined.⁸⁴ In this classification, functional dyspepsia (FD) is included in the subcategory of functional gastroduodenal disorders.⁸⁵ Four types of functional gastroduodenal disorders are distinguished: FD [B1, comprising postprandial distress syndrome (B1a) and epigastric pain syndrome (B1b)]; belching disorders (B2); functional nausea and vomiting disorders, functional vomiting, and cyclic vomiting syndrome (B3); and rumination syndrome (B4).^{85,86}

Of patients with functional dyspepsia, 30%–60% carry *H. pylori*, but this prevalence is not much different from that in the unaffected population.⁸⁷ Various studies have focused on the effect of *H. pylori* eradication in patients with both functional and uninvestigated dyspepsia. A meta-analysis of 13 randomized studies of nonulcer dyspepsia showed that when dyspepsia outcomes are dichotomized into minimal/resolved versus same/worse symptoms, *H. pylori* eradication is associated with an 8% RR reduction compared with placebo.⁸⁸ The calculated number-needed-to-treat to cure one case of dyspepsia is 18. Apart from the focus on cure of symptoms, cost efficiency is also an issue when treating large groups of patients. Given this reported number-

needed-to-treat, it remains unclear whether *H. pylori* eradication is a cost-effective strategy. In a Canadian primary care study, however, *H. pylori* eradication was reported to be more cost-effective after 1 year of follow-up than empirical diagnosis and treatment.^{89,90} In another interesting study, Sonnenberg and Townsend⁹¹ found that, for some reason, expenditure on many other aspects of health care decreased after patients had eradicated *H. pylori*.

Another Cochrane meta-analysis compared treatment strategies for uninvestigated dyspepsia.⁹² Individual strategies consisted of initial pharmacological therapy (with endoscopy for treatment failures), early endoscopy, testing for *H. pylori* and endoscopy only for those testing positive, or *H. pylori* eradication therapy with or without prior testing. The analysis showed that proton-pump inhibitors (PPIs) are effective in the treatment of dyspepsia. Early investigation by endoscopy or *H. pylori* testing benefited some patients with dyspepsia but was not cost-effective as part of an overall management strategy.⁹² A meta-analysis of five studies comparing prompt endoscopy followed by targeted treatment versus an *H. pylori* test-and-treat strategy without further investigation reported that endoscopy was associated with a small symptom benefit at 1 year (RR, 0.95), but this strategy was not cost-effective.⁹³ In summary, *H. pylori* play a role in the etiology of dyspeptic symptoms; thus, *H. pylori* test-and-treat strategies are effective for a subgroup of patients with dyspepsia. For patients with uninvestigated dyspepsia, an *H. pylori* test-and-treat strategy is an appropriate option, although empirical acid-suppressive therapy can be more efficient in populations with a low *H. pylori* prevalence. Also, in patients with investigated FD, *H. pylori* eradication is a relevant option. In both situations, patients must be aware that symptom resolution may take months after completion of therapy.

Atrophic gastritis, intestinal metaplasia, and gastric cancer

Thirty years ago, Correa et al.⁹⁴ proposed that gastritis could progress to gastric cancer, which made the identification of *H. pylori* as a major cause of gastritis even more relevant. Chronic *H. pylori*-induced inflammation can eventually lead to loss of the normal gastric mucosal architecture, with destruction of gastric glands and replacement by intestinal metaplasia. This process of atrophic gastritis and intestinal metaplasia occurs in approximately half of the *H. pylori*-colonized population, first in those subjects and at those sites where inflammation is most severe.⁹⁵ Because not everyone infected with *H. pylori* develops gastric cancer, several modifiers have been identified. Currently, the perception is that gastric cancer arises from multiple “hits,” which include

oxidative stress and environmental toxins, which increase mutation rates. Diet, bacterial factors, and genes regulating the host response likely affect the degree of oxidative stress and DNA damage.⁹⁶ Host polymorphisms in the regions controlling interleukin (IL)-1 have been reported to be associated with an increased incidence of hypochlorhydria and gastric cancer,^{97–102} probably because these regions regulate the inflammatory response to bacterial infections. Areas of gland loss and intestinal metaplasia extend with time multifocally, and although they do not give rise to any specific symptoms, they increase the risk for gastric cancer by five- to 90-fold, depending on the extent and severity of atrophy.¹⁰³

Evidence that *H. pylori* increases the risk of gastric cancer development via the sequence of metaplasia and atrophy originates from various studies that showed that *H. pylori*-positive subjects develop these conditions far more often than do uninfected controls.¹⁰⁴ This finding is supported by data that show geographical associations between the prevalence of *H. pylori* and the incidence of gastric cancer.^{105,106} On the basis of these findings, it has been estimated that *H. pylori* colonization increases the risk of gastric cancer approximately tenfold, and *H. pylori* has been designated a class I carcinogen by WHO.¹⁰⁷ Later case-control studies that looked more extensively into signs of previous *H. pylori* infection in gastric cancer patients and controls reported even higher odds ratios, up to 68, for development of distal gastric cancer in the presence of *H. pylori* infection.¹⁰⁸ This result is supported by data from animal models, most notably the Mongolian gerbil model, in which *H. pylori* infection induces atrophic gastritis and gastric dysplasia.^{60,61,109} The risk of development of atrophy and cancer in the presence of *H. pylori* is again related to host and bacterial factors, which influence the severity of the chronic inflammatory response and the amount of gastric mucosa involved. As such, the risk is increased not only in subjects colonized with *cagA*-positive strains^{110,111} but also in those with a genetic predisposition to higher IL-1 production in response to colonization.⁹⁷ In the developed world, 60% to 80% of gastric cancers are therefore related to the long-term presence of *H. pylori*.

Interestingly, the incidence of gastric cancer has significantly decreased over the past decades in Western countries. This decrease preceded the aforementioned decrease in the prevalence of *H. pylori*. As a slow process over decades, however, this decrease is not relevant to an individual subject who is *H. pylori*-positive. Furthermore, in spite of the decline in gastric cancer incidence in Western countries, gastric cancer is still the fourth most common cancer in the world, as its incidence remains very high in large areas of the world, particularly in parts of East Asia and South America.¹¹² Much

research now focuses on the cancer-preventive effect of *H. pylori* eradication, aimed at both the general population and patients with preneoplastic conditions, particularly atrophic gastritis and intestinal metaplasia. In the case of the latter, several placebo-controlled randomized studies have now reported that *H. pylori* eradication can induce to some extent regression of atrophy.^{113–117} The effect of these interventions on gastric cancer prevention is, however, less obvious than the historical cancer incidence might suggest. In several studies, *H. pylori* eradication had in the first years of follow-up no significant effect on gastric cancer incidence.^{114,116,118} In all of these studies, the difference between the eradication and placebo groups with respect to the incidence of gastric cancer in the first 4 to 12 years after treatment was not significant. The striking observation in all of these studies, however, was that those gastric cancers that occurred after eradication treatment were confined to those subjects who already had atrophic gastritis and intestinal metaplasia at baseline, suggesting that the major cancer-preventive effect of *H. pylori* eradication is to be expected in subjects without those precancerous conditions; patients with those conditions may at least in part have already passed the point of no return. If confirmed by other studies, this result means that the observed regression of the severity of atrophy is of no direct relevance with respect to cancer risk. One study differed from the others in that it did observe a significant preventive effect of *H. pylori* eradication on gastric cancer development.¹¹⁹ The investigators monitored 1120 patients in a nonrandomized study for a mean of 3.4 years (range, 1–8 years) after *H. pylori* eradication treatment. Gastric cancer developed in 8 of 944 patients cured of infection and in 4 of 176 who had persistent infection ($P = 0.04$). The remarkable observation was that gastric cancers occurred only in patients with previous gastric ulcers and not in those who had duodenal ulcers ($P = 0.005$).¹¹⁹ This result is consistent with the hypothesis that gastric ulcer patients, in contrast to duodenal ulcer patients, are characterized by reduced gastric acid secretion, corpus-predominant gastritis, and accelerated progression toward atrophic gastritis and intestinal metaplasia. Similarly, previous studies have also shown that gastric ulcer patients are at higher risk for gastric cancer than are duodenal ulcer patients.²⁶ The above-mentioned preventive studies, taken together, described cancer development in 29 (1.5%) of 1896 subjects receiving placebo and in 25 (0.9%) of 2754 subjects receiving eradication treatment, corresponding to an odds ratio of 0.54 for cancer development after *H. pylori* eradication compared with placebo, suggesting that *H. pylori* eradication may decrease the risk for development of distal gastric cancer. Further studies are being performed in this field, the results of which will allow a more precise determination of the cancer-preventive

effect of *H. pylori* eradication, of whether atrophy and metaplasia are conditions beyond the point of no return, and of the side effects and costs of such preventive measures.

The Japan Collaborative Cohort Study Group for Evaluation of Cancer Risk reported that women with a family history of gastric cancer and *H. pylori* infection were associated with a 5.1-fold greater risk for gastric cancer compared with women without a family history of gastric cancer and who did not have *H. pylori* infection.¹²⁰ In contrast, family history and *H. pylori* infection were not found to be significant risk factors for gastric cancer in male patients in their report, where the investigation of *H. pylori* infection was performed only by using *H. pylori* antibodies. Recently, results of a large nested case-control study within a prospective cohort have been reported in Japan.¹²¹ Among 123 576 subjects that were followed up from 1990 to 2004, 511 gastric cancer cases matched to 511 controls were used in this analysis. The adjusted odds ratio of gastric cancer associated with *H. pylori* infection was 5.1. In addition, if anti-CagA positivity was used as an indicator of previous or current infection, the risk was reached 12.5.

Gastric MALT lymphoma

Nearly all MALT lymphoma patients are *H. pylori* positive,¹²² and *H. pylori*-positive subjects have a significantly increased risk for the development of gastric MALT lymphoma.¹²³ Because of diagnostic controversies and the relative rarity of this disorder, the exact incidence in *H. pylori*-positive subjects is unknown, but MALT lymphomas occur in fewer than 0.1% of *H. pylori*-positive subjects.¹²⁴ Randomized trials to determine the effect of *H. pylori* eradication in MALT lymphoma patients are therefore not feasible, but various case series have reported that eradication can lead to complete remission in patients with low-grade gastric MALT lymphoma.^{125–128} Overall, approximately 60%–80% of these patients reach complete remission following *H. pylori* eradication, some 10% continue to have signs of minimal residual disease, and the remainder show no response or disease progression. The variation in response among different series may be due in part to different criteria for the diagnosis of MALT lymphoma, potentially including some patients with benign lymphoid aggregates. Of those who initially reach complete remission after *H. pylori* eradication, 10%–35% show recurrent disease during further follow-up. For that reason, long-term follow-up of MALT lymphoma patients is mandatory.¹²⁹ A major predictor of the response appears to be the presence of a t(11;18) (q21;q21) translocation. This translocation is associated with *API2-MALT1* fusion, the former being involved in regulation of apoptosis and the latter resembling a

caspase-like protein, with an as yet unknown biological function. Together, the fusion leads to suppression of apoptosis. Several studies have reported that MALT lymphomas with this translocation respond only rarely or not at all to *H. pylori* eradication.^{130,131}

Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) has long been considered to occur independently of *H. pylori* colonization; that is, it occurs with the same frequency and severity in *H. pylori*-positive and -negative subjects. This opinion is based on cross-sectional observations that suggest that the prevalence of *H. pylori* among GERD patients is similar to that among controls.¹³² However, further studies have suggested that *H. pylori* might protect against the development of GERD and by that means might be of benefit to its hosts. This slowly emerging concept derives from repeated observations of a low prevalence of *H. pylori* among GERD patients, particularly of the more virulent strains;¹³³ reciprocal time and geographical trends for *H. pylori* prevalence compared with the incidence of GERD and its complications; a potentially increased incidence of GERD after *H. pylori* eradication;¹³⁴ and the recognition that *H. pylori*-induced corpus gastritis reduces acid secretion. However, no evidence suggests that *H. pylori* eradication has a considerable impact on either the new development of GERD,¹³⁵ the worsening of preexisting GERD when treatment has been withdrawn during disease remission,¹³⁶ or preexistent GERD in remission during PPI maintenance therapy.^{113,117} Together, these data show that although epidemiologic data suggest that there may be an inverse relation between *H. pylori* and GERD, the risk for new development or worsening of preexistent GERD is not an issue when deciding whether to treat *H. pylori*.

Diagnosis of H. pylori infection

Diagnostic methods for *H. pylori* infection are categorized as invasive or noninvasive tests.¹³⁷ Invasive tests involve endoscopic biopsy of gastric mucosal samples, whereas noninvasive tests do not require an endoscopic procedure. The invasive tests are histology,¹³⁸ rapid urease test (RUT),¹³⁹ and microaerobic bacterial culture.¹⁷ The advantage of the RUT is that it is inexpensive, easy-to-use, and rapid. The advantages of culture are its specificity of 100% (direct demonstration of the presence of *H. pylori*) and that it allows further characterization of the organism (determining its sensitivity to antibiotics, investigating its virulence factors, etc). Noninvasive tests are the urea breath test,¹⁴⁰ antibody tests of sera^{141–143} or of urine,^{144,145} and the *H. pylori* stool antigen test.^{146–149}

H. pylori eradication therapy

During the 20 years since the World Gastroenterology Organization (WGO-OMGE) consensus conference, international or domestic consensus conferences for *H. pylori* eradication have been held all over the world, including in Europe, America, and Asia (Fig. 4). Most recently, on 22 November 2006, the Japanese Society for *Helicobacter* Research held a “Current Consensus—2006” (Management of *H. pylori* infection in Japan) meeting in Tokyo. In this consensus meeting, one of the main topics was whether Japan will become the first *H. pylori*-free country.

Originally, in 1988, Marshall et al.⁶⁶ reported that *H. pylori* had been eradicated in 27% of a colloidal bismuth substrate (CBS)/placebo group and in 70% of a CBS/tinidazole group. Furthermore, when *H. pylori* persisted, 61% of duodenal ulcers healed and 84% relapsed, whereas when *H. pylori* was cleared, 92% of ulcers healed and only 21% relapsed during the 12-month follow-up period.⁶⁶

According to a randomized, double-blind, placebo-controlled study performed by Lind et al.,¹⁵⁰ 787 patients with proven duodenal ulcer disease were randomized to treatment twice daily for 1 week with omeprazole, 20 mg (O), plus either placebo (P) or combinations of two of the following antimicrobials: amoxicillin, 1 g (A), clarithromycin, 250 or 500 mg (C250, C500), or metronidazole, 400 mg (M). Their eradication rates for the all-patients-treated analysis were 96%, OAC500; 95%, OMC250; 90%, OMC500; 84%, OAC250; 79%, OAM; and 1%, OP. These results suggest that omeprazole-based triple therapies given twice daily for 1 week produce high eradication rates, are well-tolerated, and are associated with high patient compliance.

In terms of second-line treatment, Matsuhisa et al.¹⁵¹ examined the eradication rate of a PPI, amoxicillin, and metronidazole (PPI/AM) regimen in 228 patients with *H. pylori* infection, in whom the first-line therapy with a PPI, amoxicillin, and clarithromycin administered for 1 week had failed. Their eradication rates for PPI/AM(500) and PPI/AM(750) were 90.6% and 88.6%, respectively, suggesting that PPI/AM administered for 1 week may be a highly effective second-line regimen.

In terms of third-line regimens, Gisbert et al.¹⁵² performed a third eradication treatment with levofloxacin (500 mg), amoxicillin (1 g), and omeprazole (20 mg), each twice daily for 10 days ($n = 100$), which resulted in per-protocol and intention-to-treat eradication rates of 66% and 60%. Although such fluoroquinolone-based rescue therapy constitutes an encouraging empirical third-line strategy after multiple previous *H. pylori* eradication failures,¹⁵² a high resistance rate (47.9%) to fluoroquinolone has been observed in *H. pylori* strains

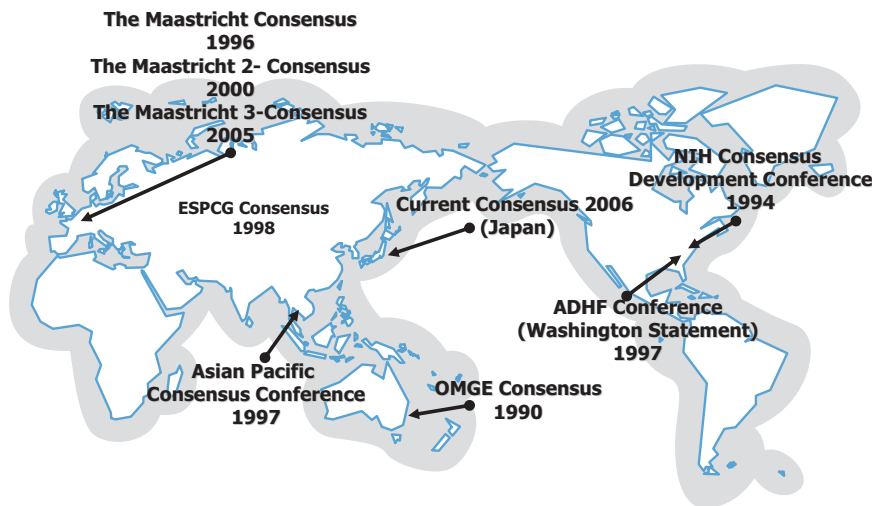


Fig. 4. Worldwide consensus conferences on *H. pylori* eradication therapy. *ESPCG*, European Society for Primary Care Gastroenterology; *NIH*, National Institutes of Health; *ADHF*, American Digestive Health Foundation; *OMGE*, Organisation Mondiale de Gastro-Entérologie (World Gastroenterology Organization)

from Japanese patients after unsuccessful *H. pylori* eradication. Therefore, the choice of this antibiotic for the third-line treatment should be made only after drug susceptibility testing.^{153,154}

Side effects and contraindications for *H. pylori* eradication

Side effects of *H. pylori* eradication are reported in up to 50% of patients taking the triple agent regimen.^{155,156} The adverse effects are usually mild; fewer than 10% of patients stop treatment due to side effects.¹⁵⁵ The common side effects are dysgeusia and diarrhea. Amoxicillin can cause diarrhea or an allergic reaction with skin rash. Clarithromycin can cause dysgeusia, vomiting, nausea, abdominal pain, and rarely QT prolongation. Metronidazole can cause seizures, peripheral neuropathy, and a disulfiram-like reaction with ethanol, and it can increase the toxicity of anticoagulants, lithium, and phenytoin. Acute gastrointestinal mucosal lesions have been demonstrated to be an adverse event after eradication therapy. Acute duodenal erosions were observed in 13.5% of patients who received eradication therapy;¹⁵⁷ erosions were transient and asymptomatic in the early phase after eradication. Acute gastric erosions showed the same clinical characteristics, but acute gastric ulcers with severe symptoms rarely occurred. The acute mucosal lesions that occurred were probably attributable to an increase in acid secretion associated with the resolution of gastric mucosal inflammation.⁶ On the other hand, the occurrence of mild reflux esophagitis at a late phase after eradication is controversial. *Helicobacter pylori* infection is an environmental factor that has declined as GERD has increased.¹⁵⁸ However, a systematic review¹⁵⁹ of randomized trials did not show any role of *H. pylori* eradication in causing GERD.

There was no increase in reflux symptoms in almost 3000 patients with *H. pylori* infection who were randomly assigned eradication therapy compared with placebo.^{160,161}

Contraindications for *H. pylori* eradication are documented hypersensitivity to the eradication drugs, especially penicillin-allergy. However, alternative regimens such as bismuth/tetracycline/metronidazole combinations can be used and exhibit high cure rates.

Future prospects

Interaction between gastric stem cells and H. pylori

Cells of the gastric mucosa undergo constant renewal, the rate depending on the health of the tissue. The current evidence¹⁶² suggests that a single stem cell in every gastric gland indirectly gives rise to a clone of differentiated cells, by production of committed progenitor cells. It is most likely that this stem cell occupies a niche in the isthmus composed of mesenchymal cells and extracellular matrices. This environment regulates the function of the epithelial stem cell via mesenchymal-epithelial cross talk. Recent studies in gnotobiotic mouse models of chronic atrophic gastritis¹⁶³ have shown that parietal cell loss results in amplification of multi- and oligopotential gastric stem cells, which express sialylated glycan receptors recognized by *H. pylori* adhesions, SabA,¹⁶⁴ HpaA,¹⁶⁵ and HP0721.¹⁶⁶ DNA microarray studies indicate that 6%–7% of *H. pylori* genes are differentially expressed in response to a shift in pH from 7 to 5.¹⁶⁷ A large group of genes downregulated at pH 5, in particular, encode outer membrane proteins, including Hop family members that are predicted to be outer membrane porins and adhesins. Loss of acid-

producing parietal cells increases bacterial adhesin expression and increases the proportion of stem cells with adhesin receptors.¹⁶⁸ Another very provocative study suggests that in the mouse model of gastric cancer evoked with *Helicobacter felis* (cat *Helicobacter*), infection arises because malignant stem cells emerge from a pool of bone marrow cells that are recruited into areas of chronic gastritis.¹⁶⁹

*Other diseases of interest possibly influenced by H. pylori*¹⁷⁰

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disease that leads to thrombocytopenia as a result of increased thrombocytolysis due to the appearance of autoantibodies to platelets. The acute type frequently occurs in children, often preceded by a viral infection. It develops rapidly and shows spontaneous remission. Chronic-type ITP occurs most commonly in adults and reportedly correlates with *H. pylori* infection. In 1988, Gasbarrini et al.⁷ reported that *H. pylori* eradication therapy to eight patients with *H. pylori*-positive ITP improved thrombocytosis after the therapy. Veneri et al.,¹⁷¹ who administered *H. pylori* eradication therapy to 43 patients with *H. pylori*-positive ITP, reported the therapy to be successful in 41 of the 43 and recognized continuous improvement in 20 (48.8%) of these 41 patients on long-term observation. According to another report by the same authors,¹⁷² the frequencies of HLA-DRB 111, HLA-DRB 114, and HLA-DQB 103 as host factors were high in *H. pylori*-positive ITP, while the frequency of HLA-DRB 103 as a host factor was higher in the *H. pylori*-negative ITP group than in the *H. pylori*-positive ITP group, and HLA-DQB 103 showed favorable platelet reactivity after eradication therapy in *H. pylori*-positive ITP.¹⁷² Inaba et al.¹⁷³ administered *H. pylori* eradication therapy to 35 patients with chronic ITP (25 *H. pylori*-positive ITP patients and 10 *H. pylori*-negative ITP patients), and succeeded in eradicating the bacteria in all of the patients with *H. pylori*-positive ITP. They reported that the platelet count was improved in 11 (44%) of the 25 patients, while the platelet count was unchanged in the 10 *H. pylori*-negative ITP patients. We also administered bacterial eradication therapy to 37 patients with chronic ITP (26 *H. pylori*-positive ITP and 11 *H. pylori*-negative ITP patients) and succeeded in eradicating the bacteria in all of the *H. pylori*-positive ITP patients; we found the platelet count to be improved in 16 (62%) of the 26 patients with *H. pylori*-positive ITP, while the platelet count was unchanged in the 11 patients with *H. pylori*-negative ITP.¹² In other words, there was no improvement with bacterial eradication in *H. pylori*-negative ITP, and the effects of the antibacterial agent itself in terms of increasing the platelet count was negligible.

Many other reports show a relation between *H. pylori* infection and human diseases such as iron-deficiency anemia^{8,174–181} and chronic urticaria.^{182–184}

Final Message

While substantial progress has been made in our understanding of the role of genetic and environmental factors in the etiology of *H. pylori*-associated disease, there is still much to be learned about the epidemiology and pathogenesis of *H. pylori*. Although much knowledge of the potential association of *H. pylori* infection with human diseases has been accumulated, much of it is rather anecdotal or uncontrolled, and studies have not been consistently replicated in other centers. It is certainly true that further evidence-based studies should be performed to confirm *H. pylori* associations and the beneficial effects of eradication. On the other hand, eradication of *H. pylori* is rather simple these days and may be of no consequence in the treatment of patients with severe chronic diseases. In countries such as Japan where dreaded diseases such as gastric cancer seem to stem from *H. pylori*, the twenty-first century may be the time to totally eradicate this troublesome organism from the entire population.

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