

Helicobacter pylori and Non-Malignant Diseases

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Abstract

The prevalence of *Helicobacter pylori*-associated peptic ulcers, in particular duodenal ulcers, is decreasing following decreasing prevalence of *H. pylori* infection, while the frequency of non-steroidal anti-inflammatory drugs (NSAIDs)-induced and *H. pylori*-negative idiopathic ulcers is increasing. The incidence of bleeding ulcers has been stable during the last decades. Several putative *H. pylori* virulence genes, i.e., *cag*, *vacA*, *babA*, or *dupA*, as well as host-related genetic factors like IL-1 β and TNF α -gene polymorphism, have been proposed as risk factors for duodenal ulcer. *H. pylori* eradication may prevent NSAID complications, in particular, when it is performed before introduction of NSAIDs. There is a complex association between *H. pylori* and gastroesophageal reflux disease (GERD), and the impact of *H. pylori* eradication on the appearance of GERD symptoms depends on various host- and bacteria-related factors. Eradication of *H. pylori* in GERD is recommended in patients before instauration of a long-term PPI treatment to prevent the development of gastric atrophy. A small proportion (10%) of non-ulcer dyspepsia cases may be attributed to *H. pylori* and may benefit from eradication treatment. A test-and-treat strategy is more cost-effective than prompt endoscopy in the initial management of dyspepsia.

Peptic Ulcer Disease

The prevalence of peptic ulcer disease (PUD) has been decreasing for decades. A 10-year retrospective study analyzed the changing demographics of PUD in a total of 2182 patients with PUD admitted to a predominantly immigrant public hospital in the USA, 1173 in the early period (1995–1999) and 1009 in the recent period (2000–2004). This study showed that incidence of PUD was only modestly decreasing, male predominance was disappearing, and gastric ulcer was more prevalent than duodenal ulcer [1]. Lassen et al. compared the incidence of PUD in four Danish counties between 1993 and 2002. The incidence of uncomplicated duodenal or gastric ulcer decreased by 37 and 29%, respectively. The incidence of perforated ulcer diminished by 43%. In contrast, the incidence of bleeding peptic ulcer was stable on this period [2]. A Swedish study explored the prevalence, symptomatology, and risk factors for PUD in a random sample (n = 3000) of a general adult population surveyed between December 1998 and June 2001. Smoking, aspirin

use, and obesity were risk factors for gastric ulcer, whereas smoking, low-dose aspirin use, and *Helicobacter pylori* infection were risk factors for duodenal ulcer. Peptic ulcer often coexisted with atypical symptoms, and idiopathic duodenal ulcer was more common (19%) than anticipated [3]. Another retrospective survey, comparing PUD prevalence in patients referred for upper gastrointestinal endoscopy in two Italian hospitals in the pre-*Helicobacter* era (1986–1987) and 10 years after the progressive diffusion of eradication therapy (1995–1996), confirmed a significant reduction in PUD prevalence (from 8.8 to 4.8%, $p < .001$ for duodenal ulcer, and from 3.9 to 1.5%, $p < .001$, for gastric ulcer) which may be attributed to decreasing of *H. pylori* infection [4]. An increasing frequency of *H. pylori*-negative idiopathic ulcers was also confirmed in a prospective cohort study including consecutive patients with bleeding gastroduodenal ulcers from January to December 2000. In Hong Kong out of 638 patients with bleeding ulcers, 213 (33.4%) had *H. pylori*-positive ulcers and 120 (18.8%) had *H. pylori*-negative idiopathic ulcers. The corresponding figures for the time

period 1997–1998 were 480 (50.3%) and 40 (4.2%), respectively ($p < .001$) [5]. Eradication of *H. pylori* reduces the relapse rate. Ford et al. analyzed 56 trials from the Cochrane Central Register of Controlled Trials to compare the effect of *H. pylori* eradication therapy to that of placebo or ulcer healing therapy on ulcer healing and relapse rate following successful healing. In duodenal ulcer healing, eradication therapy was superior to ulcer healing therapy and in preventing gastric ulcer recurrence, eradication therapy was superior to no treatment, confirming that eradication therapy is an effective treatment for *H. pylori*-positive PUD disease [6].

One of the challenges in *H. pylori* research is identification of disease-specific *H. pylori* virulence factors predictive of the outcome of infection. Although a number of putative *H. pylori* virulence genes such as the *cag* pathogenicity island (PAI), *VacA*, *BabA*, *OipA*, and *HrgA* have been associated with increased risks of PUD or gastric cancer, none could be clearly linked to a specific disease. Lu et al. examined 500 *H. pylori* strains from East Asia and South America associated with different gastric pathologies and found that a gene named *dupA* (duodenal ulcer-promoting gene) situated in the plasticity region of *H. pylori* genome was specifically associated with duodenal ulcer versus gastritis (42 versus 21%, respectively) [7]. The frequency and genotype of *babA2*, a gene encoding a blood-group antigen-binding adhesin mediating attachment of *H. pylori* to human Lewis(b) antigens on gastric epithelial cells, and other virulence factors, were studied in *H. pylori* strains in Brazilian patients with PUD. Although *babA2* genotype was frequently found (70%), no significant correlation was observed between *babA2* and *vacAs1* genotypes or between *babA2* and *cagA* status and intensity of gastritis in these patients [8]. Interleukin 1 β (IL-1 β) and tumor necrosis factor alpha (TNF α) may play a role in the genetic predisposition to duodenal ulcer upon *H. pylori* infection by modulating the host immune response. Several studies evaluated a possible association between IL-1 β and TNF α -gene polymorphism and risk of duodenal ulcer. In the Korean study including 1360 subjects, the frequencies of IL-1 β -511 C/T and T carrier were lower in the *H. pylori*-positive patients with benign gastric ulcer as compared to controls, suggesting that the IL-1 β -511T-carrier polymorphism has a preventive effect on the development of gastric ulcer [9]. In a case control study including 310 *H. pylori*-infected individuals from eastern India, analysis of genotype frequency revealed a significantly higher frequency of IL-1 β -511TT and -31CC genotypes in individuals with duodenal ulcer compared to those with normal mucosa [10]. IL-1 β gene cluster polymorphisms was also studied in 437 Brazilian children, 209 of whom were *H. pylori* positive and showed that in these infected children, the presence of ILRN*2 allele and *cagA*-positive

status were independently associated with duodenal ulcer [11]. In contrast, Garcia et al. did not find an association between allelic variants of IL-1 and TNF gene and the susceptibility to duodenal ulcer [12].

Non-Steroidal Anti-Inflammatory Drug Consumption

An epidemiologic study from Hong Kong evaluated trends in the prevalence of PUD from 1997 to 2003 based on all upper endoscopies performed in a single endoscopy unit. A decreasing trend in PUD prevalence, mainly due to a decrease in duodenal ulcer, parallel to a decrease in the prevalence of *H. pylori* infection and non-steroidal anti-inflammatory drug (NSAID) use, was observed [13]. A case control study from the Netherlands evaluated NSAID use and the prevalence of *H. pylori* infection in patients hospitalized during the year 2000 for peptic ulcer bleeding. Among 361 cases collected from 14 hospitals deserving an area of 1.68 million inhabitants, the overall incidence of peptic ulcer bleeding was 21.5/100,000 persons. NSAID use was found in 52%, including 17% who were taking ulcer-preventing treatment. Among the 64% tested for *H. pylori*, 43% were positive. According to these results, half of the complicated ulcers could be related to NSAID use, and *H. pylori* may not be actually implicated in the majority of cases [14].

Ulcer prevalence was evaluated endoscopically in 187 patients taking low doses of aspirin for prevention of cardiovascular events. At inclusion, the ulcer prevalence was 11% and no association was found between dyspeptic symptoms and ulcers. At another endoscopy performed on 113 patients after 3 months, 7% had developed an ulcer. The factors associated with the risk of duodenal ulcer were *H. pylori* infection and age over 70 years [15]. Similar results were obtained in complicated ulcers in a retrospective study based on 128 patients who had surgery for PUD performed in a 5-year time period in a department of surgery in Dallas, Texas, USA. The mean age of the patients was 60 years and two-thirds of the total number of patients had comorbidity. Use of NSAID was found in 54% and 47% were *H. pylori* positive. In 81% of cases, surgery was performed in emergency for ulcer bleeding or perforation [16]. NSAID treatment in patient at high risk for peptic ulcer requires a preventive treatment, which has not been yet defined.

Lai et al. compared the incidence of complicated ulcers in patients treated either by COX-2 inhibitors monotherapy or by a non-selective NSAID treatment associated with proton pump inhibitors (PPIs). Patients who developed ulcer complication after NSAID treatment were recruited and received, if needed, *H. pylori* eradication treatment. Randomization defined a group of patients treated by celecoxib and another treated by naproxen

associated with lansoprazole for 24 weeks. In the follow-up, complicated ulcer was observed in 3.7% in the celecoxib group and in 6.3% in the lansoprazole group, the difference being non-statistically significant. More patients experienced dyspepsia in the celecoxib group (15.0%) than in the lansoprazole group (5.7%) [17].

A meta-analysis evaluated the effect of *H. pylori* eradication on the prevention of peptic ulcer in patients taking NSAIDs. Analysis included 939 patients in five studies. Eradication of *H. pylori* was associated with a reduced risk of peptic ulcer (odds ratio (OR): 0.43). A significant reduction of risk was found by sub-analysis in patients not previously treated by NSAID (OR: 0.26) as compared to patients already treated. These results suggest that eradication prevents complicated ulcers especially in patients not previously treated by NSAID. In patients already treated, prevention by PPI is more effective than eradication alone [18]. The effects of *H. pylori* eradication on NSAID-related gastrointestinal symptoms were reported in a randomized, case-control study. *H. pylori*-positive patients who had NSAID prescription for at least 2 weeks were randomized to receive either eradication treatment or placebo. Non-infected patients recognized by a negative serology, were taken as the control group. The overall prevalence of gastrointestinal symptoms decreased from 43% at 2 weeks to 10% at 12 weeks. No difference in symptoms prevalence was seen between the patients who received eradication therapy and those who did not receive therapy or were *H. pylori* negative. However, at the 12 weeks evaluation, symptoms tended to be lower in the *H. pylori*-eradicated group, suggesting that eradication may provide a long-term beneficial effect on NSAID-related symptoms [19].

Gastroesophageal Reflux Disease

The association between *H. pylori* infection and gastroesophageal reflux disease (GERD) is controversial. Some studies suggested a protective role of *H. pylori* with respect to GERD and its complications, while the others did not confirm this finding. A trend in prevalence of reflux esophagitis parallel to a trend in lower prevalence of *H. pylori* infection was demonstrated in a large series of 16,375 patients referred for upper endoscopy in Singapore from 1992 to 2001 [20]. In this study, both increase in the prevalence of endoscopic esophagitis (RR 1.99, 95%CI, 1.18–3.36, $p < .009$) and its inverse relationship with urease test results (RR 0.991, 95%CI 0.983–0.999, $p < .04$) were significant. A Japanese study, in which the effect of *H. pylori* eradication on the development of reflux esophagitis was studied in a 5- to 6-year follow-up, showed that the frequency of reflux was higher in *H. pylori*-treated patients than in *H. pylori*-positive patients [21]. Some previous studies suggested that *H. pylori*

eradication may reduce the efficacy of PPIs in GERD. This issue was revisited by Giral et al. who evaluated intragastric pH before and after administration of lansoprazole for 8 days in 10 *H. pylori*-positive patients with reflux esophagitis before and after *H. pylori* eradication. Intragastric pH was significantly higher in the presence of *H. pylori*, whereas baseline pH remained unchanged after *H. pylori* eradication [22]. Similarly, Calleja et al. evaluated the effect of *H. pylori* infection on healing and symptoms relief in 227 patients with proven esophagitis treated for 8 weeks with pantoprazole. Comparison of healing and symptoms relief rates between *H. pylori*-positive and *H. pylori*-negative patients showed that at 8 weeks, patients with erosive esophagitis and *H. pylori* infection exhibited a significantly better response to pantoprazole through complete heartburn relief, although no difference in endoscopic healing rates between the groups was observed [23]. One of the potential mechanisms by which *H. pylori* could protect against development of GERD is induction of gastric atrophy since it is well recognized that GERD is associated with increased exposure to gastric acidity. Since proinflammatory IL-1 β polymorphisms increase the risk of hypochlorhydria and gastric atrophy, the association between these polymorphisms, presence of gastric atrophy, and risk of GERD were studied in 320 *H. pylori*-positive and *H. pylori*-negative consecutive dyspeptic patients in Japan. A proinflammatory IL-1 β genotype was associated with increased risk of atrophy and decreased risk of GERD in *H. pylori*-infected subjects confirming that in some genetically predisposed individuals, *H. pylori* infection may protect against GERD through induction of gastric atrophy [24]. A large amount of data recently accumulated pleads, however, against a protective effect of *H. pylori* against GERD in the majority of cases. In a randomized, placebo-controlled trial including 157 Japanese patients with dyspepsia, Ott et al. studied the risk of reflux esophagitis after treatment for *H. pylori* infection. No difference in terms of frequency of esophagitis or heartburn symptoms was found at 3 and 12 months between the antibiotic and placebo-treated group, indicating that *H. pylori* eradication does not cause reflux esophagitis [25]. Similarly, among 102 consecutive *H. pylori*-positive patients with peptic ulcers followed 1 year after eradication, no significant difference was found in the frequency of reflux esophagitis between *H. pylori*-positive and *H. pylori*-negative individuals and the only factor positively associated with the development of GERD was the presence of hiatal hernia before therapy [26]. In elderly patients on short- and long-term treatment with PPIs, eradication of *H. pylori* did not affect the clinical outcome of esophagitis, while it improved chronic gastritis and its activity, suggesting that *H. pylori* should be

eradicated in elderly patients with esophagitis who need maintenance treatment with PPIs [27]. A physiological study by Moschos et al. showed no effect of *H. pylori* infection on esophageal peristalsis, the lower esophageal sphincter pressure, and the acidity of refluxates into the oesophageal lumen in 59 patients with established GERD [28]. Another controversial issue is a negative association between GERD and some particularly virulent strains of *H. pylori*. In 1622 patients submitted to routine upper endoscopy in Taiwan, reflux esophagitis was found in 21.2% of patients and occurred at a significantly lower rate among *H. pylori*-positive patients harboring triple-positive virulent genotype strains (*cagA*, *babA2*, and *vacAs1*-positive) [29]. However, another study performed in Spain, did not show an increased prevalence of Barrett's esophagus, main complication of GERD, and *H. pylori* infection and in particular infection with CagA+ strains [30]. Altogether, the effect of *H. pylori* eradication on the development of GERD seems to depend on diverse individual genetic and/or environmental factors. However, because of the role of this infection in the development of distal gastric carcinoma, it seems reasonable to eradicate this bacterium in order to prevent gastric cancer, in particular in patients on a long-term PPI treatment.

Non-Ulcer Dyspepsia

Non-ulcer dyspepsia (NUD) is defined as chronic or recurrent pain/discomfort centered in the upper abdomen. Patients suffering from predominant heartburn or acid regurgitation should be considered to have GERD, until proven otherwise, according to recent guidelines [31]. Organic explanation for dyspeptic symptoms has not been found. Both Maastricht 2 and Maastricht 3 Consensus Reports advised eradication of *H. pylori* in patients with functional dyspepsia which was confirmed by the results of a meta-analysis [32]. Twenty-one randomized controlled trials were included in the systematic review. There was a 10% relative risk reduction in the *H. pylori* eradication group (95% CI 6 to 14%) compared to placebo, leading to the conclusion that eradication therapy has a small but statistically significant beneficial effect in *H. pylori*-positive functional dyspepsia [32]. The main result of the 7-year follow-up study of di Mario et al. is that dyspeptic symptoms improve after *H. pylori* eradication in 30–50% of patients over a long period of follow-up [33]. Mazzoleni et al. demonstrated, in a population with a high prevalence of *H. pylori* infection, the benefit of eradication in patients with normal endoscopy but not in those with erosive gastritis [34]. Ford et al. aimed to determine the effect of screening for *H. pylori* on dyspepsia and dyspepsia-related medical resource use over 10 years, including 2324 original participants, 1864 (80%) of whom were traced

and contacted. A significant reduction in total dyspepsia-related health-care cost was found, the savings being more important than the initial cost of *H. pylori* screening and treatment [35]. Similarly, an economic analysis of a *H. pylori* test-and-treat strategy versus a prompt endoscopy approach in primary care setting performed in the Netherlands, suggested that the former was more cost-effective than the latter in the initial management of dyspepsia in general practice [36]. It is estimated that a gastric cancer is present in 1 to 2% of patients with dyspepsia. Liou et al. from Taiwan analyzed 17,894 endoscopy results in patients with uninvestigated dyspepsia. Gastric cancer was found in 225 patients (12.6 cases per 1000 endoscopies) who presented uninvestigated dyspepsia, among whom 114 (50.7%) did not have alarm symptoms but a simple dyspepsia. About 5.3% (12/225) of gastric cancer cases would have been missed if endoscopy had been omitted in patients without alarm symptoms and aged less than 45 years, indicating that 40 years old might be an optimal age threshold for screening endoscopy for uninvestigated dyspepsia in Taiwan [37].

Conclusion

In most of the nonmalignant diseases associated with *H. pylori*, bacterial eradication has a beneficial effect. It remains still a challenge for the clinicians and researchers to better identify the patients at high risk of development of serious *H. pylori*-related diseases. In patients with GERD, although a systematic search for *H. pylori* cannot be recommended, eradication treatment is indicated in *H. pylori*-positive patients before instauration of a long-term treatment by PPIs to prevent gastric atrophy. Along with disappearance of *H. pylori* in the developed world, the paysage of gastroduodenal pathologies is changing, with a decreasing incidence of *H. pylori*-induced ulcers and an increasing incidence of GERD and NSAIDs-induced and idiopathic ulcers.

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