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Every gastroenterologist deserves a gastrointestinal pathologist
Robert M. Genta, Richard H. Lash

The impact of biopsy number and site on the accuracy of intestinal metaplasia detection in the stomach. A morphometric study based on virtual biopsies
L. Mastracci, S. Bruno, P. Spaggiari, P. Ceppa, R. Fiocca

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Abstract

Background. Helicobacter pylori colonizes the stomach of more than half of the world’s population, and the infection continues to play a key role in the pathogenesis of a number of gastroduodenal diseases. Colonization of the gastric mucosa with Helicobacter pylori results in the development of chronic gastritis in all infected individuals and in a subset of patients chronic gastritis progresses to complications (i.e. ulcer disease, gastric neoplasias, some distinct extragastric disorders). The clinical outcome of the disease is dependent on many variables, including Helicobacter pylori genotype, innate host physiology, genetic predisposition and environmental factors. Helicobacter pylori eradication decreases the incidence of gastroduodenal ulcer and prevents its recurrence. Helicobacter pylori eradication for gastric cancer prevention has been suggested by preclinical research and clinical trials, showing even reversibility of precancerous lesions (atrophic gastritis and intestinal metaplasia) after Helicobacter pylori eradication.

Aims. To review the current literature about H. pylori and its related pathologies.

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Conclusion. At present, several clinical manifestations are recognized to be causally linked to *Helicobacter pylori* infection, and most of them can be cured by *Helicobacter pylori* eradication. Besides the relationship of *Helicobacter pylori* and gastroduodenal diseases, it has been well established that *Helicobacter pylori* infection is also involved in some extragastrointestinal diseases.

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Keywords: *H. pylori*; Peptic ulcer disease; NSAIDs; Gastric cancer

1. Introduction

More than 20 years after its discovery, *H. pylori* infection remains the main cause of gastric and duodenal diseases. Epidemiologic and clinical studies have provided convincing evidence that *H. pylori* infection is the cause of chronic gastritis, peptic ulcer disease, low grade gastric mucosa associated lymphoid tissue (MALT) lymphoma and gastric adenocarcinoma [1–3].

This review focuses on the role of *H. pylori* in gastrointestinal diseases including functional dyspepsia, peptic ulcer disease and nonsteroidal anti-inflammatory drug (NSAID) associated ulcers, GERD, gastric adenocarcinoma and MALT lymphoma, as well as in some extragastrointestinal diseases such as idiopathic thrombocytic purpura, iron deficiency anaemia and allergic diseases.

2. *H. pylori* and dyspepsia

Dyspepsia is a frequent disorder that at least sporadically affects up to 25% of the population. The cause can be organic (i.e. ulcer) but most of the time the nature of the disease is functional. Dyspepsia is defined as epigastric pain or discomfort in the upper abdomen. Patients who undergo endoscopy for upper gastrointestinal complaints with no abnormalities detected (and no organ pathologies in the ultrasound as well) are defined as functional dyspepsia. For the clinical management, the absence of alarm features is reassuring [4]. Patients presenting with the first onset of alarm symptoms or patients over 45 years of age do deserve prompt endoscopy [5].

2.1. Alarm features

- Anaemia or evidence of acute/chronic bleeding.
- Odynophagia.
- Dysphagia.
- Recurrent or persistent vomiting.
- Unintentional weight loss.
- Previous history of peptic ulcer.

The Maastricht III consensus guidelines have reemphasized the validity of a test-and-treat strategy in patients with dyspepsia under the age of 45 years (Fig. 1) [6]. The test-and-treat strategies have recently been validated by the large and excellent designed Canadian CADET-Hp trial on uninvestigated dyspeptic patients. A total of 294 patients were randomized for *H. pylori* eradication therapy for 7 days or treatment with a proton pump inhibitor (PPI) and placebo antibiotics. The results demonstrated no or minimal symptoms in 50% of those patients who received one week of eradication therapy compared to those patients who received placebo (36%). The study clearly indicated a significant benefit for a *H. pylori* test-and-treat strategy for patients with dyspepsia in the primary care setting [7]. A well performed meta-analysis and Cochrane Database systematic review also revealed a modest but significant benefit of *H. pylori* eradication.

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Fig. 1. Algorithm for the management of uninvestigated dyspepsia according to American College of Gastroenterology (ACG) and Maastricht III Consensus Report.
cation in non-ulcer dyspepsia with a number needed to treat of 15 patients [8,9].

To assess the long-term effectiveness of the test-and-treat strategy, a small study by Patchett et al. reviewed patients with non-ulcer dyspepsia after _H. pylori_ eradication after a follow-up of 5 years. This study demonstrated that successfully treated patients were almost asymptomatic [10].

The aim of the test-and-treat strategy is to separate _H. pylori_ positive from _H. pylori_ negative dyspepsia patients using a non-invasive diagnostic test. The urea breath test and the stool antigen test are the most accurate non-invasive tests with sensitivity and specificity rates of 93–95% each [11,12]. The value of non-invasive testing depends on the positive and negative predictive value, which is related to _H. pylori_ prevalence in the population. The current guidelines recommend test-and-treat strategy in populations with high _H. pylori_ prevalence (>20%). _H. pylori_ treatment leads to symptom improvement in non-ulcer dyspepsia; it also reduces the risk of peptic ulcers, atrophic gastritis and the development of gastric cancer. In areas with low _H. pylori_ prevalence (<20%) empirical use of proton pump inhibitors is considered to be an equal option in symptom relief [13], but _H. pylori_ test-and-treat strategy leads to reduced endoscopic workload and was demonstrated to be more cost effective compared to the use of empiric antisecretory therapy [14].

### 3. Peptic ulcer disease

#### 3.1. Non-NSAID-related peptic ulcer disease

The strong correlation between the colonization of _H. pylori_ and peptic ulcer disease is well established by an abundance of studies. The clinical outcome of _H. pylori_ infection is highly variable and depends on host, environmental and bacterial virulence factors. The pattern of colonization and distribution of gastritis strongly correlates with the clinical manifestation. Antral-predominant gastritis shows a strong correlation to the development of duodenal ulcers, whereas patients with corpus-predominant gastritis are known to have a higher risk for developing gastric ulcers, gastric atrophy, intestinal metaplasia and finally gastric adenocarcinoma [15,16]. In _H. pylori_ infected patients the lifetime risk for developing peptic ulcer disease ranges from 3 to 25% [17]. Eradication of _H. pylori_ dramatically reduces the relapse of _H. pylori_-related peptic ulcers and leads to long-term remission of peptic ulcer disease [18].

Although _H. pylori_ eradication leads to better symptom relief in patients with peptic ulcers compared to those with non-ulcer dyspepsia, dyspeptic symptoms may still persist in up to 30% of peptic ulcer patients after eradication therapy [19]. This suggests that part of the symptoms is not ulcer dependent. Eradication of _H. pylori_ infection is cost effective and often allows the discontinuation of acid suppressive therapy in many patients [20]. The benefit from eradication therapy is lasting for at least 6 years [21].

#### 3.2. NSAID-related peptic ulcer disease

The interaction between _H. pylori_, NSAIDs and aspirin during gastrointestinal epithelial damage and the pathogenesis of ulceration is complex and still remains a topic of clinical importance and research interest. Both _H. pylori_ and NSAIDs are independent risk factors for the development of peptic ulcer disease and peptic ulcer bleeding. An excellent systematic review reported a significantly increased risk of peptic ulcer bleeding in _H. pylori_ infected patients (OR 6.1; 95% confidence interval [CI] 3.9–9.6) compared to _H. pylori_ negative subjects on NSAID treatment (OR 4.8; 95% CI 3.8–6.2) [22].

The results of the ongoing research keep raising controversies regarding the effect of _H. pylori_ eradication in patients under NSAID medication. In a pivotal study by Chan et al. in 1997, gastric ulcers were significantly prevented by eradication in NSAID naïve subjects before taking NSAIDs [23]. These results were confirmed by another trial of the same group that randomized _H. pylori_ positive, NSAID naïve patients with dyspeptic syndromes or history of peptic ulcer to eradication or placebo before taking NSAIDs [24]. During a six-month follow-up, peptic ulcers were reported to be more frequent in the placebo (34%) compared to the eradication group (12%). Those findings were already part of the recommendations of the Maastricht 2–2000 Consensus Report [25].

A randomized, placebo controlled trial by Hawkey et al. demonstrated that _H. pylori_ eradication was not superior to PPI therapy for prevention of peptic ulcer reoccurrence in patients on long-term NSAID medication [26]. Another trial reported even a higher ulcer recurrence rate in patients with a previous ulcer bleeding and naproxen medication in the group randomized to _H. pylori_ eradication compared to those patients who received long-term PPI therapy (absolute difference 14%; 95% CI 4–24%) [27]. However, in the same study, patients on aspirin remained protected by _H. pylori_ eradication with no further PPI therapy. _H. pylori_ eradication followed by lansoprazole treatment was shown to be more effective in the prevention of recurrent ulcer disease in persistent NSAID/aspirin users compared to _H. pylori_ eradication alone [28]. A further published study demonstrated that eradication of _H. pylori_ did not reduce the incidence of gastroduodenal ulcers in patients on long-term NSAID treatment [29].

The reason for those conflicting results is the different pathogenic mechanism by which _H. pylori_ and NSAIDs induce epithelial damage and ulceration. Thus, the effects of _H. pylori_ eradication vary depending on distribution of _H. pylori_-induced ulcers in the studied population. Another important issue is the duration of NSAID medication. In a huge hospital-based, case–control study Lanas et al. demonstrated an increased risk of peptic ulcer bleeding in patients taking NSAID over 1–30 and 31–90 days (RR 7.6; 95% CI 6.0–9.5 and RR 7.3; 95% CI 4.0–13.2) compared to long-term NSAID users (RR 2.5; 95% CI 1.8–3.4) [30].
Based on the evidence of the studies mentioned above, the current guidelines favour *H. pylori* test-and-treat-strategy in naive NSAID users to prevent peptic ulcer disease. In patients who receive long-term PPI medication to prevent NSAID-induced ulcers, *H. pylori* eradication is indicated to reduce the PPI-*H. pylori*-related corpus-predominant gastritis, loss of specialized glands and accelerated development of atrophic gastritis [31,32]. This is in particular the case in patients with reflux disease that are on long-term acid suppression with PPI therapy.

4. *H. pylori* and gastroesophageal reflux disease (GERD)

The interaction between colonization of *H. pylori* and GERD is another topic of dispute over the past years. The prevalence of *H. pylori* was found to be lower among patients suffering from GERD [33,34]. The falling prevalence of *H. pylori* and related diseases in developed countries over the past decades with the inverse correlation to an increase of GERD has prompted the speculation of *H. pylori* as a protecting factor for the esophagus, while others argued that [35–40] *H. pylori* eradication does neither cause GERD nor exacerbate existing GERD symptoms, independently of PPI treatment [41,42]. A population-based study of more than 10,000 people found no effect of *H. pylori* eradication on the overall prevalence of heartburn (OR 0.99; 95% CI 0.88–1.12) or regurgitation (OR 1.04; 95% CI 0.91–1.19) and no improvement of pre-existing symptoms [43]. The issue for *H. pylori* eradication is of particular relevance in patients suffering from GERD who need a long-term maintenance PPI therapy. In *H. pylori* infected patients, PPI therapy is associated with the development of a corpus-predominant pangastritis and thus with an acceleration towards atrophic gastritis [31,32]. In contrast, *H. pylori* eradication in those patients induced regression of corpus glandular atrophy [44]. In the current guidelines, *H. pylori* is not considered as a relevant factor in GERD pathogenesis. *H. pylori* should be searched for and treated in patients receiving long-term maintenance PPI therapy, but a routine testing in all GERD patients is not recommended.

5. *H. pylori* and MALT lymphoma

*H. pylori* has been clearly defined as a causative agent for the development of MALT lymphoma. MALT lymphoma is a unique and distinct form of marginal zone B-cell-non-Hodgkin’s lymphoma. MALT lymphomas account for approximately 7–8% of all non-Hodgkin’s lymphomas, and the gastrointestinal tract is the most common site of the disease [45]. The association between *H. pylori* infection and MALT lymphoma has been provided by various studies and a pathogenic link has been confirmed. MALT lymphoma development results from a chronic T-cell antigenic stimulation and is a good example for the close relationship between chronic inflammation and lymphangiogenesis [46,47]. The most compelling evidence for the causal relationship of *H. pylori* infection and MALT lymphoma is that 62% of the patients with low grade gastric MALT lymphoma have complete remission after *H. pylori* eradication within 12 months [48,49]. Those data have strengthened the indication for *H. pylori* eradication therapy in gastric MALT lymphoma. Several predictors of response to eradication therapy have been recognized: *H. pylori* positivity; Lugano classification stage I; lymphoma confined to the stomach; gastric wall invasion confined to mucosa/submucosa and the absence of gene t (11,18) and (q21; q21) translocation with fusion of API2 and MALTI. The fusion of the two genes may promote the survival of lymphomatous B-cell clones via anti-apoptotic effects and strongly predicts failure to respond to eradication therapy.

According to the Maastricht III Consensus Report, *H. pylori* eradication is the treatment of first choice for *H. pylori* infected individuals with stage I low grade gastric MALT lymphoma [6].

6. Gastric adenocarcinoma

Despite a decline of the incidence of gastric cancer in developed countries, gastric cancer remains the fifth most common cancer and shows responsibility for the death of more than 100,000 each year in Europe [50]. The etiology of gastric carcinoogenesis has been demonstrated to be multifactorial. The most important risk factor is the infection with *H. pylori*. Host genetic elements, such as a pro-inflammatory cytokine profile and/or a positive family history as well as bacterial virulence factors further increase the risk of developing gastric cancer [51]. Furthermore environmental factors, like nutrition and socioeconomic factors are suggested to be additionally important [52].

The example of *H. pylori* infection as the cause of gastric cancer displays a classical model to study the cancer development as the consequence of a microbial infection and chronic inflammation. Because of the strong association between gastric cancer and *H. pylori* infection, the WHO classified *H. pylori* as a class I carcinogen already in 1994 [53]. Although *H. pylori* significantly increases the risk to develop both subtypes of gastric adenocarcinoma, the mechanisms underlying the development of intestinal-type cancer are better characterized. The intestinal type adenocarcinoma progresses in a well defined series of histological steps [15]. Intestinal type gastric adenocarcinoma development seems to be a slow progress, beginning with the acquisition of *H. pylori* and subsequent development of chronic active gastritis, which occurs in all infected individuals. After the initiation by *H. pylori* and the influence of variable environmental and host factors, chronic active gastritis may progressively evolve to atrophic gastritis and intestinal metaplasia. In some individuals the metaplastic epithelium will undergo further genomic and phenotypic changes, resulting in gastric dysplasia and finally ending in
adenocarcinoma. This Correa’s multistep model has been clearly reproduced in Mongolian gerbils infected with \textit{H. pylori} [54,55].

The association of \textit{H. pylori} and gastric cancer has been confirmed by large-scale epidemiological studies, meta-analysis of case control studies and experimental studies.

Epidemiological studies suggest a strong association between \textit{H. pylori} infection and distal gastric cancer. One estimate attributed 70% of non-cardiac gastric adenocarcinoma to \textit{H. pylori} infection [56]. A more recent study by Huang et al. focused on the association between \textit{H. pylori} CagA positive strains and the risk for gastric cancer. It has been clearly demonstrated that CagA positive \textit{H. pylori} strains are more virulent and associated with higher grades of inflammation compared to CagA negative strains. This meta-analysis showed that among \textit{H. pylori} infected populations, infection with CagA positive strains increased the risk for gastric cancer by 1.64-fold (95% CI, 1.21–2.24) overall and by 2.01-fold (95% CI, 1.21–3.32) for non-cardiac gastric cancer [57].

6.1. Prevention of gastric cancer

\textit{H. pylori} eradication heals active gastritis and dramatically reduces the incidence and/or recurrence of peptic ulcer disease. For gastric cancer the unique opportunity is a preventive strategy against gastric cancer. The aims of \textit{H. pylori} eradication therapy are either to reverse the inflamed mucosa to normal or to prevent further progression of advanced chronic changes (atrophic gastritis, intestinal metaplasia). Although \textit{H. pylori} infection is a significant risk factor for the development of gastric cancer, there are few controlled clinical trials showing that eradication can prevent the progression from normal gastric mucosa to gastric cancer. Ultimately, a prospective randomized clinical trial would be the only reliable way to determine the effect of \textit{H. pylori} eradication. A recent theoretical model estimated that a sample size of 17,625 middle aged subjects per group would be required in a follow up over 10 years to demonstrate a 50% reduction in the expected age-dependent increase of gastric cancer [58]. Unfortunately, attempts to do this are unrealistic mainly due to logistical, methodological and financial issues. However, there is strong evidence indicating that the development of pre-neoplastic changes (atrophic gastritis and intestinal metaplasia) of the gastric mucosa can be prevented by \textit{H. pylori} eradication [6,59–61]. Several non-randomized controlled studies in animals and humans have demonstrated a reduction of the risk of gastric cancer after \textit{H. pylori} eradication [61,62]. Randomized controlled studies have shown a regression of pre-neoplastic lesions or, at least, a decrease of progression compared to control groups after eradication therapy [63–66]. Other data indicate that atrophy and metaplasia do not show progress in patients after \textit{H. pylori} eradication [32,66,67]. But it has also been demonstrated that progression of atrophic gastritis and intestinal metaplasia to gastric cancer can occur in patients after \textit{H. pylori} eradication, suggesting that other factors contribute the progression of pre-neoplastic changes [65,68]. Thus, it is necessary to define exactly the conditions where genetic and epigenetic alterations reach a point of no return when the elimination of the triggering carcinogen (\textit{H. pylori}) has no effect on the proceeding of cancer. According to the current knowledge, \textit{H. pylori} eradication should be attempted possibly before the onset of pre-neoplastic lesions (atrophy, intestinal metaplasia) [6].

Taken all direct and indirect evidences together, \textit{H. pylori} eradication has the potential to prevent gastric cancer [69]. From a clinical perspective, eradication therapy should be considered in a subset of patients at high risk, including patients with positive family history, patients after subtotal gastric resection or removal of early gastric cancer by endoscopic methods.

7. \textit{H. pylori} and extragastric diseases

As of today, among the long list of possible associations, \textit{H. pylori} infection is confirmed to play an important role in three extragastro-duodenal diseases.

7.1. Idiopathic thrombocytic purpura

The role of \textit{H. pylori} in the pathogenesis of idiopathic thrombocytic purpura (ITP) has been first described by Gasbarrini et al. [70]. The platelet count in patients with ITP returns to normal after eradication, as shown by several studies [71,72]. A possible role for CagA in the pathogenesis of ITP was assumed because of a significant reduction of the anti-CagA antibody titre in responders compared to non-responders to \textit{H. pylori} eradication therapy. Asahi et al. demonstrated that platelet recovery is a result of \textit{H. pylori} eradication therapy, and the disappearance of the bacteria is partly mediated by reduced auto-antibody production [73].

7.2. Iron deficiency anaemia

The link between \textit{H. pylori} and the pathogenesis of iron deficiency anaemia (IDA) has been well established over the past years. Different results have been reported on IDA in adults compared to children and adolescent patients. \textit{H. pylori} was highly prevalent in patients with unexplained IDA. After eradication of \textit{H. pylori} all patients achieved normalized haemoglobin levels [74]. In children and adolescents the balance of iron intake and utilization is more complex and thus the results of the studies are less valid. One interesting finding is that the soluble transferrin receptor (sTFR) is significantly elevated in \textit{H. pylori} infected children with IDA compared to non-infected children, although serum transferrin and iron showed normal levels. For this reason the authors assumed that sTFR is a much better parameter of the iron status in \textit{H. pylori} infected children than serum iron or ferritin [75,76].
7.3. Asthma, allergy and atopic diseases

Asthma, allergy and atopic diseases have been shown to have a negative association with \textit{H. pylori}. In this context Chen and Blaser reported an inverse correlation between asthma bronchiale and allergy and the prevalence of \textit{H. pylori}. Colonization with \textit{H. pylori}, especially with CagA-expressing strains was inversely correlated with the diagnosis of allergic rhinitis (OR 0.55; 95% CI 0.37–0.82) supporting the hypothesis that acquisition of \textit{H. pylori} is associated with a reduced risk of allergic diseases [77]. In accordance with those findings, the hygiene hypothesis postulates an increase in atopic diseases at least partly due to a diminished exposure to microorganisms during childhood [78]. Herbarth et al. demonstrated an inverse association between \textit{H. pylori} infection and eczema in children that were not predisposed to atopy (aOR 0.31; \( P = 0.006 \)). In contrast, chronic bronchitis leads to an increased risk for eczema (aOR 1.98; \( P < 0.001 \)). Other serological studies enhance a higher prevalence of \textit{H. pylori} in patients with chronic obstructive lung diseases [79]. The authors concluded a protective role of intestinal bacterial colonization (\textit{H. pylori}) for the development of eczema but not for infections of the respiratory tract. The role of infectious agents in atopic diseases needs further investigations [80].

8. Conclusion

\textit{H. pylori} is the key pathogen in gastroduodenal diseases. All infected individuals develop chronic gastritis, and in a subset of patients a progression to severe complications occurs. The cure of \textit{H. pylori} represents a change in the paradigm of peptic ulcer disease treatment. The challenge now is to prevent \textit{H. pylori} infection and in particular to prevent gastric cancer by \textit{H. pylori} eradication.

\begin{itemize}
  \item In chronic NSAID users \textit{H. pylori} eradication alone is not sufficient to prevent peptic ulcer and complications.
  \item \textit{H. pylori} is the most proven risk factor for human gastric adenocarcinoma.
  \item \textit{H. pylori} eradication prevents the development of pre-neoplastic lesions.
  \item \textit{H. pylori} eradication before the development of pre-neoplastic conditions (atrophy, intestinal metaplasia) has the best potential to prevent from gastric cancer.
  \item Unexplained iron deficiency anaemia or idiopathic thrombocytopenic purpura are recommended indications for \textit{H. pylori} eradication therapy.
\end{itemize}

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\textbf{Practice points} \\
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- \textit{H. pylori} eradication is recommended in infected patients with different gastroduodenal pathologies. \\
- In uninvestigated dyspepsia a test-and-treat strategy is recommended in young patients without alarm symptoms. \\
- \textit{H. pylori} eradication does not cause GERD. \\
- In patients receiving long-term maintenance PPI therapy \textit{H. pylori} eradication is recommended. \\
- In naive NSAID users \textit{H. pylori} eradication may prevent peptic ulcer and peptic ulcer bleeding. \\
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\textbf{Research agenda} \\
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- Further elucidate mechanisms how \textit{H. pylori} infection triggers the development of gastric cancer. \\
- Develop screening and new treatment strategies for gastric cancer development. \\
- Study the role of \textit{H. pylori} in extragastroduodenal diseases. \\
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