Gastro-oesophageal reflux disease and *Helicobacter pylori*: an intricate relation

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Summary

Heartburn is a common symptom affecting 21–44% of the adult population on a monthly basis. Oesophagitis is less common, affecting 2% of individuals.

Epidemiological studies have shown that patients with gastro-oesophageal reflux disease (GORD) have similar incidence rates of *Helicobacter pylori* infection as do controls. Some groups have reported that there is a lower incidence, deducing that infection does not cause, and in some way confers protection against GORD. Additional supportive evidence is available from reports of GORD development following successful *H pylori* eradication. The mechanisms involved are complicated. Individuals with *H pylori* induced pangastritis and subsequent hypochlorhydria may be protected whereas those with an antral predominant gastritis, as in duodenal ulcer disease, with an increased acid output may be prone to development of GORD.

Recent evidence has linked *H pylori* infection with the development of inflammation of the gastric cardia—carditis. Reports are available which show that carditis is a frequent finding in patients with GORD. The incidence of both cardia and oesophageal carcinoma is increasing. The relation between GORD, carditis, intestinal metaplasia, and cardia carcinoma is unclear. Intestinal metaplasia may result from multifocal atrophic gastritis, linked to *H pylori* infection or from GORD and the development of Barrett's oesophagus. Long term follow up studies will be required to assess the malignant potential of these histological entities and whether or not *H pylori* infection has an aetiological role.

Introduction

Gastro-oesophageal reflux disease refers to the abnormal exposure of the oesophageal mucosa to gastric contents, resulting in a spectrum of conditions. Symptoms of heartburn or acid regurgitation affect 21–44% of the adult population on a monthly basis.^{1–3} Oesophagitis is less prevalent, and is reported to occur in up to 2% of individuals.^{4–5} Symptoms have been shown to have a specificity of 85–95% and sensitivity of 6–39%.⁶ Patients with GORD frequently present with atypical symptoms; up to 50% of endoscopically diagnosed cases of oesophagitis present with symptoms other than heartburn or acid regurgitation.^{7–9} In addition GORD is the underlying diagnosis in 2–15% of subjects undergoing investigation for dyspepsia. Accurate diagnosis of GORD can be difficult with currently accepted criteria including symptoms of heartburn and/or acid regurgitation, improvement with proton pump inhibitor (PPI)

treatment, 24 hour oesophageal pH assessment, and/or histological evidence of oesophagitis. Long term sequelae include benign strictures, Barrett's oesophagus, and adenocarcinoma.

Pathophysiological mechanisms described include abnormal transient relaxation of the lower oesophageal sphincter (TLOSR),^{10–14} impaired oesophageal motility,¹⁵ delayed gastric emptying,^{16–17} impaired mucosal defences,^{18–19} toxic nature of refluxed material (acid, bile),^{20–24} and the presence of hiatus hernia. Although it would appear that GORD is a multifactorial condition predominantly related to abnormal upper gastrointestinal motility, recent interest has focused on the relation between *Helicobacter pylori* infection and GORD.

H pylori and the aetiology of GORD

H pylori is a common infection, responsible for a variety of gastroduodenal pathology, duodenal and gastric ulcer, mucosa associated lymphoid tissue (MALT) lymphoma, and gastric carcinoma. The effects of *H pylori* infection on the pathophysiological mechanisms involved in the aetiology of GORD have been examined. *H pylori* infection has been shown to produce an increase in basal and stimulated gastric acid output through a number of mechanisms, including gastrin, somatostatin, and inflammatory mediators, and this phenomenon of increased acid output has been shown to occur in asymptomatic cases as well as those with peptic ulcer disease and non-ulcer dyspepsia.^{25–32} Increased acid secretion as a result of *H pylori* infection is a plausible aetiological mechanism of GORD in a subset of cases, supported by the observation that patients with duodenal ulceration are more likely to suffer from reflux oesophagitis.³³ However, *H pylori* colonisation of the gastric mucosa may result in hypochlorhydria as seen in individuals with a diffuse gastritis and gastric atrophy.³⁴ Patients with this pattern of disease seem to be at less risk of developing GORD than controls.^{35–36} There is evidence to associate *H pylori* infection with both the development of hypochlorhydria and increased acid secretion, depending on the inflammatory response induced. As a result, the effect of *H pylori* infection on the development of GORD is similarly contradictory.

Abbreviations used in this paper: GORD, gastro-oesophageal reflux disease; TLOSR, transient relaxation of the lower oesophageal sphincter; MALT, mucosa associated lymphoid tissue; PPI, proton pump inhibitor.

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Table 1 Epidemiological studies investigating the role of *Helicobacter pylori* infection in gastro-oesophageal reflux disease (GORD)

Prevalence of <i>H pylori</i> in GORD	
Similar to controls	O'Connor and Cunnane ⁴⁵
	Borkent and Beker ⁴⁶
	Walker and colleagues ⁴⁷
	Cheng and colleagues ⁴⁸
	Newton and colleagues ⁴⁹
	Befrits and colleagues ⁵⁰
	Liston and colleagues ⁵¹
Decreased	Werdmuller and Loffeld ⁵²
	Vicari and colleagues ⁵³
	Ohara and colleagues ⁵⁵
	Haruma and colleagues ⁵⁴
Severity of GORD and <i>H pylori</i>	
Similar to controls	O'Connor and Cunnane ⁴⁵
	Newton and colleagues ⁴⁹
	Werdmuller and Loffeld ⁵²
Increased	Cargill and colleagues ⁵⁷
Decreased	Grebenev ⁵⁶
	Sehiguchi and colleagues ⁵⁵

Delayed gastric emptying has been reported in association with GORD development. Results of studies exploring the effect of *H pylori* on gastric emptying are variable. Several groups have reported no difference between *H pylori* positive and negative subjects.^{37–39} Other groups have shown abnormal antroduodenal motility in patients with GORD and *H pylori* and delayed gastric emptying in patients with antral predominant gastritis, with or without *H pylori* infection.^{40–42} There is no clear evidence to associate *H pylori* infection with a definite dysfunction of gastric emptying and it is unlikely to be a major aetiological factor linking *H pylori* and GORD.

It has been postulated that *H pylori* colonisation of the gastric cardia may result, through inflammatory mediators and vagal stimulation, in increased TLOS episodes, hence increasing the likelihood of GORD development.^{42–44} Several groups are investigating the role of carditis with respect to GORD but as yet there is no clear evidence to support this hypothesis.

Epidemiology

Epidemiological studies have in general found little or no association between *H pylori* infection and GORD (table 1), similar infection rates being reported in patients with GORD and in controls.^{45–51} Some groups have reported a lower incidence of *H pylori* infection in individuals with GORD and have surmised that infection in some way reduces an individual's risk of reflux oesophagitis.^{35 52–54} The observation that *H pylori* infection was negatively associated with the severity of oesophagitis has added weight to the theory of a protective role for *H pylori* in GORD.^{55 56} However, there is evidence to the contrary.⁵⁷

More recently the nature of the infecting organism has been examined. To date three groups have shown that *cagA* positive infecting strains reduce the risk of both GORD and its complications, including Barrett's oesophagus and oesophageal and cardia carcinoma.^{53 58 59} Infection with *cagA* positive strains of *H pylori* is associated with a more severe mucosal

inflammation in the corpus and antrum, potentiating the risk of developing gastric atrophy and achlorhydria.^{60–62}

Such mechanisms have been suggested to explain the negative association between *cagA* positive strains and GORD. In addition an increased density of infection, associated with virulent infecting strains, may result in an increased production of ammonia, thus potentiating the effects of PPIs.⁶³ The fact that virulent strains are responsible for 80–100% of duodenal ulcers and are associated with an increase in acid production seems contradictory.⁶⁴ Yet it is known that a history of peptic ulcer is associated with a reduced risk of proximal and distal gastric cancers.⁶⁵ With regard to Barrett's oesophagus the majority of studies have again found no association with *H pylori*.^{66 67} Henihan *et al* have shown a positive correlation between the severity of chronic inflammation in Barrett's oesophagus and *H pylori*. The possible mechanisms underlying this observation are unknown.⁶⁸

Carditis, *H pylori*, and GORD

The gastric cardia is the most proximal portion of the stomach, occupying a small zone just distal to the oesophagogastric junction. Under normal circumstances, it comprises tightly packed mucus secreting cells and is devoid of inflammatory cells. Recent interest has focused on carditis, as a possible marker or consequence of GORD or as a possible extension of *H pylori* induced pangastritis.

Carditis has been reported to be a sensitive marker of GORD. Oberg *et al* have revealed a positive association between carditis and GORD, as determined by a 24 hour ambulatory pH oesophageal probe assessment.⁶⁹ This study did not examine the role of *H pylori* infection. Others disagree, and have reported that carditis is a manifestation of extensive *H pylori* colonisation and is independent of oesophagitis.^{70–72}

The incidence of proximal gastric cancers like that of oesophageal adenocarcinoma is increasing,⁷³ whereas that of *H pylori* infection and distal gastric cancer is falling. Barrett's oesophagus, a consequence of GORD, is a risk factor for the development of oesophageal adenocarcinoma with known premalignant histological markers including intestinal metaplasia and dysplasia. Intestinal metaplasia of the cardia may similarly be a marker of malignant potential though it is not known whether it arises as a long term consequence of GORD or as a result of *H pylori* infection and associated pangastritis. Consideration of the malignant potential of intestinal metaplasia at the cardia is warranted as it has been identified in proximity to adenocarcinomas of this region.^{74 75} Surprisingly intestinal metaplasia of the cardia has been reported in 5–23% of subjects undergoing routine endoscopy and was found more frequently in controls than in those with either oesophagitis or Barrett's oesophagus.^{73 76–78} Correlation with *H pylori* status and intestinal metaplasia in other regions of the stomach is lacking; however, two studies reported to date have found a positive

Table 2 Carditis, associations, and prevalence of intestinal metaplasia

Study	Patients with intestinal metaplasia (%)	Association with <i>H pylori</i>	Association with GORD
Goldblum and colleagues ⁷²	9	Yes	No
Morales and colleagues ⁷⁶	23	Yes	N/A
Hirota and colleagues ⁷⁷	5.3	Yes	N/A
Trudgill and colleagues ⁷⁹	18	No	No
Spechler and colleagues ⁷⁵	18	No	N/A

GORD, gastro-oesophageal reflux disease; N/A, information not given.

relation between cardia intestinal metaplasia, *H pylori* infection, and diffuse multifocal intestinal metaplasia. Current available evidence suggests that the risk of developing intestinal metaplasia of the cardia is related to age^{79 80} and *H pylori* status but not to GORD (table 2). Whether or not individuals on long term PPIs are at an increased risk, as reported for distal intestinal metaplasia, and whether this is a confounding factor is unknown. Assessment of the malignant potential of intestinal metaplasia of the cardia will require further study and its association with *H pylori* infection confirmed as the results may change current management strategies.

H pylori eradication and GORD

The indications for *H pylori* eradication treatment have been broadened in recent years to include several conditions, not only peptic ulceration but also MALT lymphoma, early gastric cancer, and non-ulcer dyspepsia.^{81 82} The European consensus guidelines considered the role of eradication treatment in patients with GORD on long term treatment with PPIs. Recent publications have implicated concomitant PPI treatment and *H pylori* infection with the accelerated development of atrophic gastritis and increased epithelial cell proliferation.⁸³⁻⁸⁶ Kuipers and colleagues⁸³ studied 59 *H pylori* positive subjects treated with either omeprazole or fundoplication for a mean follow up of five years. Thirty one per cent treated with a PPI versus only 5% treated surgically developed atrophic gastritis. Atrophic gastritis is considered a risk factor for the subsequent development of gastric carcinoma. The situation is not clear cut as a recent study by Lundell *et al*, involving a randomised trial with a three year follow up, showed no increased risk of atrophic gastritis in *H pylori* positive subjects taking PPIs compared with controls.⁸⁶ The observation that PPIs are more effective in *H pylori* positive individuals has also brought the policy of prescribing eradication treatment in this setting into question.^{87 88} Most reports do suggest that *H pylori* infection and PPI treatment increases an individual's risk of developing gastric atrophy and as such the benefits of eradication treatment probably outweigh the possible drawbacks.

The successful eradication of *H pylori* infection in cases of duodenal ulcer has been recently reported to be associated with the subsequent development of GORD.⁸⁹ There are two possible explanations: either *H pylori* infection is protective and eradication induces GORD, or successful treatment with possible alterations in lifestyle, unmasks pre-existing or a propensity for GORD.⁹⁰ GORD has been

reported to develop in 9–63% of patients following successful *H pylori* treatment.^{91 92}

However, up to 20% of patients with duodenal ulcer have pre-existing GORD on initial presentation.⁹³ With such a high incidence of concomitant disease and an associated increased risk of GORD development with age, it is unlikely that GORD arises de novo in patients with peptic ulcer simply as a result of *H pylori* eradication and healing of corpus gastritis with an associated return to normal acid secretion.^{94 95} More prospective long term follow up studies are again required to clarify this issue.

Conclusion

H pylori infection does not seem to play a causal role in GORD, based on available epidemiological data. Despite this the effect of *H pylori* infection on the efficacy of acid suppressants, the gold standard treatment for GORD, as well as the possible long term effects of both infection and GORD require practitioners to address the issue of whether or not to test for *H pylori* in patients with GORD and if present whether eradication treatment should be prescribed. The Maastricht consensus report considered this issue and advised, on the basis of supportive evidence, that *H pylori* treatment should be given to patients with GORD requiring long term acid suppression. The Canadian consensus report does not currently support this management strategy, as there is a need for additional supportive evidence to link *H pylori* infection and the long term use of PPIs with the development of gastric atrophy.

Reports of de novo GORD development in patients after successful treatment of *H pylori* associated duodenal ulceration also raise management issues. The possible development of GORD is unlikely to alter the strong indication for *H pylori* eradication in patients with duodenal ulceration but may enable clinicians to inform patients prior to treatment or select an at risk group.

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