The significance of \textit{cagA}\textsuperscript{+} \textit{Helicobacter pylori} in reflux oesophagitis

V J Warburton-Timms, A Charlett, R M Valori, J S Uff, N A Shepherd, H Barr, C A M McNulty

Abstract

Background—\textit{Helicobacter pylori} is a gastroduodenal pathogen associated with ulceration, dyspepsia, and adenocarcinoma. Recent preliminary studies have suggested that \textit{H pylori} may be protective for oesophageal adenocarcinoma. In addition, strains of \textit{H pylori} identified by the presence of the cytotoxin associated gene \textit{A} (\textit{cagA}) are shown to have a significant inverse association with oesophageal adenocarcinoma. Given that \textit{cagA} \textit{H pylori} may protect against oesophageal carcinoma, these strains may be protective for oesophagitis, a precursor of oesophageal carcinoma.

Aims—The aim of this study was to investigate the association between \textit{cagA} \textit{H pylori} and endoscopically proved oesophagitis.

Patients—The study group included 1486 patients attending for routine upper gastrointestinal tract endoscopy.

Methods—At endoscopy the oesophagus was assessed for evidence of reflux disease and graded according to standard protocols. Culture and histology of gastric biopsy specimens determined \textit{H pylori} status. The prevalence of \textit{cagA} was identified by an antibody specific ELISA (Viva Diagnostika, Germany).

Results—\textit{H pylori} was present in 663/1485 (45\%) patients and in 120/312 (38\%) patients with oesophagitis. Anti-CagA antibody was found in 499/640 (78\%) \textit{H pylori} positive patients. Similarly, anti-CagA antibody was found in 422/521 (81\%) patients with a normal oesophagus and in 42/60 (70\%) with mild, 24/35 (69\%) with moderate, and 11/24 (46\%) with severe oesophagitis. The risk of severe oesophagitis was significantly decreased for patients infected with \textit{cagA} \textit{H pylori} after correction for confounding variables (odds ratio 0.57, 95\% confidence interval 0.41–0.80; \( p = 0.001 \)).

Conclusions—These results suggest that infection by \textit{cagA} \textit{H pylori} may be protective for oesophageal disease.

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Keywords: \textit{Helicobacter pylori}; \textit{cagA}; gastro-oesophageal reflux disease; oesophagitis; oesophageal adenocarcinoma; hiatus hernia

\textit{Helicobacter pylori} is an important and prevalent gastroduodenal pathogen associated with ulceration, dyspepsia, and adenocarcinoma. \textsuperscript{1, 2} Circumstances that promote the development of \textit{H pylori} associated diseases include host and environmental influences and features of the infecting strain.\textsuperscript{1}

Significant gastroduodenal disease is particularly associated with infection by evidently virulent \textit{H pylori} strains that possess the cytotoxin associated gene (cag) pathogenicity island (PAI).\textsuperscript{4} The cag PAI is a segment of DNA with a distinct nucleotide composition compared with the rest of the chromosome, containing genes thought to have an association with pathogenesis. With \textit{H pylori} the guanosine and cytosine content is 38–45\% for other chromosomal sequences and 35\% for the cag PAI.\textsuperscript{5} The cag PAI contains, among others, the cytotoxin associated gene \textit{A} (\textit{cagA}).\textsuperscript{6}

\textit{cagA} is present in about 70\% of UK strains.\textsuperscript{7} Patients infected by \textit{cagA} \textit{H pylori} have a greater risk of developing duodenal ulcer disease and gastric adenocarcinoma.\textsuperscript{8} \textit{H pylori} expressing \textit{cagA} are also known to contribute to significant gastric inflammation and cytokine production.\textsuperscript{8} Anti-CagA antibodies predict infection by a \textit{cagA} strain. The CagA protein is possibly a surface expression protein or part of the export machinery necessary for stimulating the enhanced local inflammatory response seen with \textit{cagA} infections.\textsuperscript{9}

The role of \textit{H pylori} in gastro-oesophageal reflux disease (GORD) has only recently received attention largely because the prevalence of \textit{H pylori} in patients suffering from GORD is similar to the normal population.\textsuperscript{10} However, eradication of \textit{H pylori} from those suffering from duodenal ulcer may promote reflux oesophagitis with a consequent increased risk of oesophageal/gastric cardia adenocarcinoma.\textsuperscript{11} \textit{H pylori} with the \textit{cagA} gene are significantly less prevalent in subjects with oesophageal adenocarcinoma.\textsuperscript{12} Diminution of peptic ulcer disease and adenocarcinoma of the distal stomach have paralleled the decreasing prevalence of \textit{H pylori} infections in the developed world.\textsuperscript{13} At the same time, there has been an increase in GORD, Barrett’s oesophagus, and adenocarcinoma of the distal oesophagus and proximal stomach of epidemic proportions,\textsuperscript{14} suggesting that \textit{H pylori} may protect against these oesophageal diseases, including those that predispose to carcinoma, such as Barrett’s oesophagus. Indeed, in a

Abbreviations used in this paper: \textit{cag}, cytotoxin associated gene; \textit{cagA}, cytotoxin associated gene \textit{A}; PAI, pathogenicity island; GORD, gastro-oesophageal reflux disease; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; LOS, lower oesophageal sphincter.
nested case control study, Barrett’s oesophagus and oesophageal adenocarcinoma were less common in *H pylori* infected patients. This study was specifically aimed at assessing the association between *cagA* and *H pylori* infection and endoscopically proved oesophagitis in a large cohort of unselected patients being investigated for upper gastrointestinal symptoms. The information was collected before the widespread use of proton pump inhibitors (PPIs).

**Methods**

**PATIENTS**

Gloucestershire Royal Hospital has had an open access endoscopy service for 20 years. In 1986 a study of the role of *H pylori* in upper gastrointestinal tract disease in an unselected cohort of 1486 upper gastrointestinal endoscopy patients was undertaken and therefore forms an ideal cohort to examine the role of *H pylori* in GORD. Endoscopies were performed by consultant gastroenterologists, surgeons, trainee gastroenterologists, GP gastroenterologists, and clinical assistants. A detailed endoscopy report form was completed by all endoscopists immediately after the examination. This had been in routine use in the department for some years and all endoscopists were trained and familiar with the grading. The endoscopist recorded the oesophageal appearance on a proforma as normal, mild oesophagitis (definite mild erythematous inflammation on the ridges of the oesophagus), severe oesophagitis (confluent inflammation with superficial ulceration), or moderate oesophagitis (moderate or confluent inflammation without ulceration). This grading was based on the system described by Blackstone. Hiatus hernia, varices, achalasia, monilia, or a motility problem were graded as normal. Oesophageal ulcer, stricture, and long segment Barrett’s oesophagus (2 cm of concentric columnar epithelium above the oesophageal sphincter) were deemed as evidence of severe oesophagitis. The presence of short segment Barrett’s, an entity not well recognised in 1986, was not recorded. Gastric biopsy specimens were taken from all patients within 5 cm of the pylorus and the presence of *H pylori* infection was assessed by histology, microaerobic culture, and the biopsy urease test.

**HISTOPATHOLOGICAL EXAMINATION**

Two gastric biopsy specimens were placed in 10% formal saline and processed for histopathological evaluation. Sections were stained by haematoxylin and eosin, periodic-acid Schiff, and the half Gram method. Biopsy specimens were assessed by a histopathologist without knowledge of the patient’s clinical details. Sections were graded for neutrophil (polymorphonuclear) infiltration, mononuclear cells, mucus depletion, *H pylori*, intestinal metaplasia, and lymphoid aggregates on a 0–3 scale with 3 being severe. The severity of chronic active gastritis was graded as mild, moderate, or severe according to standard protocols, or the biopsies were deemed normal.

**CULTURE OF *H pylori***

Two biopsy specimens for culture were sent in normal saline to the laboratory. The biopsies were smeared across chocolate agar medium and *Campylobacter* selective medium. *H pylori* type strain NCTC11637 was incubated with the isolates to control for changes in atmospheric conditions. Plates were then incubated in a microaerobic atmosphere for 5–7 days. Plates were examined at five and seven days. *H pylori* was confirmed by Gram film and the rapid urease test. *H pylori* infection was considered present when *H pylori* was confirmed by either culture or histology.

**CagA SEROLOGY**

Venous blood (10 ml) was stored as serum at −70°C in duplicate. Anti-CagA antibody titres were determined without prior knowledge of *H pylori* or oesophagitis status by use of the p120 CagA ELISA kit (Viva Diagnostika, Germany). This is a semiquantitative kit with a calibration calculation for each plate. Plates were read at 450 nm on a Titerdek Multiscan (mcc/340 MK11) ELISA plate reader. Results were judged positive or negative according to the manufacturer’s instructions and by cut off values validated by a select group of samples assessed blindly by western blot (Helicoblot 2.0; Biorad, UK).

**DATA COLLECTION**

Patient consent for the study and data on age, sex, past medical history, drug history, tobacco use, alcohol consumption (none, mild <15 units/week, moderate 15–30 units/week, severe >30 units/week), and family history of upper gastrointestinal disease (peptic ulcer, malignancy, hiatus hernia, dyspepsia in spouse, parent, sibling, or child) were obtained by standard questionnaire administered by nurses before the endoscopy. Full details of the questionnaire can be obtained from the authors. Ethics approval was obtained from the Gloucestershire Royal Hospital ethics committee and patients gave informed signed consent for biopsy specimens to be taken.

**STATISTICS**

Initially the association between oesophagitis and *H pylori* and *cagA* status was assessed using χ² tests of associations and trend. The association between oesophagitis and other factors was also assessed. Any factor having some evidence of association (p<0.2) was used in a multivariable logistic regression analysis.

The dependent variable in this analysis was whether or not the patient had endoscopically confirmed oesophagitis. The candidate predictor variables came from several areas. Demographic factors were: age group (<40, 40–49, 50–59, 60–69, ≥70), sex (male or female), smoking (none, ex, or current), alcohol consumption (none, mild, moderate, or heavy), and past medical history of, or current, hiatus hernia. Family history factors were: other gastrointestinal disease and parent with a gastrointestinal disease. Drug history factors were: antacids more than twice a week, non-steroidal anti-inflammatory drug (NSAID), aspirin, and...
Table 1  Prevalence of Helicobacter pylori infection in subjects with and without oesophagitis

<table>
<thead>
<tr>
<th>Oesophagitis</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>H pylori positive</td>
<td>543 (46%)</td>
<td>61 (38%)</td>
<td>35 (41%)</td>
<td>24 (37%)</td>
<td>663</td>
</tr>
<tr>
<td>H pylori negative</td>
<td>629 (54%)</td>
<td>101 (62%)</td>
<td>50 (39%)</td>
<td>41 (63%)</td>
<td>821</td>
</tr>
<tr>
<td>Total</td>
<td>1172</td>
<td>162</td>
<td>85</td>
<td>65</td>
<td>1484</td>
</tr>
</tbody>
</table>

*H pylori status for one patient unknown.

Table 2  Proportion of patients cagA positive by category of oesophagitis

<table>
<thead>
<tr>
<th>Oesophagitis</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>cagA positive</td>
<td>422 (81%)</td>
<td>42 (70%)</td>
<td>24 (69%)</td>
<td>11 (46%)</td>
<td>499</td>
</tr>
<tr>
<td>cagA negative</td>
<td>96 (19%)</td>
<td>18 (30%)</td>
<td>11 (31%)</td>
<td>13 (54%)</td>
<td>141</td>
</tr>
<tr>
<td>Total</td>
<td>518</td>
<td>60</td>
<td>35</td>
<td>24</td>
<td>640</td>
</tr>
</tbody>
</table>

*One patient gave borderline results consistently.

Table 3  Multivariable logistic regression analysis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Estimated odds ratio</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (y)</td>
<td>&lt;40</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40–49</td>
<td>1.01</td>
<td>0.61–1.68</td>
</tr>
<tr>
<td></td>
<td>50–59</td>
<td>1.55</td>
<td>0.98–2.45</td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>1.71</td>
<td>1.09–2.69</td>
</tr>
<tr>
<td></td>
<td>&gt;70</td>
<td>1.72</td>
<td>1.06–2.78</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.61</td>
<td>0.44–0.83</td>
</tr>
<tr>
<td>Smoking</td>
<td>Non</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ex</td>
<td>1.13</td>
<td>0.62–1.34</td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>0.91</td>
<td>0.75–1.45</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>None</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild</td>
<td>1.04</td>
<td>0.75–1.45</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>1.45</td>
<td>0.91–2.32</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>1.82</td>
<td>0.77–4.31</td>
</tr>
<tr>
<td>H pylori –ve</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H pylori ++ve</td>
<td>1.05</td>
<td>0.67–1.66</td>
<td></td>
</tr>
<tr>
<td>Drug history, NSAID</td>
<td>None</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1.54</td>
<td>0.76–3.15</td>
</tr>
<tr>
<td>Drug history, antacids</td>
<td>No</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1.58</td>
<td>1.19 to 2.11</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>0</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1–100</td>
<td>0.83</td>
<td>0.57–1.21</td>
</tr>
<tr>
<td>Hiatus hernia</td>
<td>No</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>4.86</td>
<td>3.59–6.57</td>
</tr>
</tbody>
</table>

H2 blocker as either treatment or maintenance. Histological factors were: intestinal metaplasia (absent, present), mucosal type, and mononuclear and polymorphonuclear infiltration. The final factor was the status of the endoscopist. The variable giving H pylori status was classified as H pylori negative, H pylori positive, and cagA +, or H pylori positive and cagA +.

Logistic regression analysis results in some loss of information as the ordinal classification of oesophagitis was dichotomised into present or absent. The likelihood ratio test was used to assess the significance of the predictor variables.

**Results**

Oesophageal grading was available for 1485/1486 (97% male, 53% non-duplicate patients. In the multivariable analysis, no specific grade of endoscopist was more or less likely to report oesophagitis. H pylori infection was detected in 663/1484 (45%) patients and in 120/312 (38%) patients with oesophagitis (table 1). Anti-CagA antibody was detected in 499/640 (78%) H pylori positive patients. The cagA status of the 663 H pylori positive patients and its association with oesophagitis is presented in table 2. cagA + H pylori were found in 422/521 (81%) patients with a normal oesophagus, in 42/60 (70%) with mild oesophagitis, in 24/35 (69%) with moderate oesophagitis, and in 11/24 (46%) with severe oesophagitis. The inverse association with a cagA strain remained, even after correction for other confounding factors in a multivariable logistic regression analysis (table 3). For those patients who were H pylori positive with a cagA + strain the estimated odds of oesophagitis were nearly half those in the H pylori negative group (odds ratio 0.57, 95% confidence interval (CI) 0.41–0.80; p=0.0001). Those patients that were H pylori positive but with a cagA – strain were at a slightly increased odds of oesophagitis (odds ratio 1.05, 95% CI 0.67–1.66); however, this was not statistically significant.

The results of the multivariable logistic regression model are presented in table 3. Considering age as a risk factor, the odds of oesophagitis was not significantly higher in the 40–49 year category compared with the 40–49 year old category. For the other three age groups, the odds of oesophagitis compared with those <40 years increased by over 50% (odds ratios 1.55, 1.71, and 1.82 in the 50–59 years, 60–69 years, and 70 years or over age categories, respectively). The pattern of the odd ratios indicates that there was not a steady increasing frequency of oesophagitis with age but rather a large step up in the frequency around the age of 50 years.

The risk of oesophagitis was significantly lower in females, with an odds ratio of approximately two thirds that for males. There was no association between smoking status and oesophagitis. The estimated odds of oesophagitis increased with increasing alcohol consumption. A test of linear trend (p=0.11) indicated weak evidence. The precision with which the odds ratios were estimated could indicate that the increase observed was due entirely to chance.

Those patients taking NSAIDs were associated with an increased odds of oesophagitis (odds ratio 1.54, 95% CI 0.76–3.15). However, this increase failed to reach statistical significance possibly because of the small numbers; only 46 patients had taken NSAIDs. Those patients taking antacids more than twice a week were associated with an increased odds of oesophagitis (estimated odds ratios of 1.58, 95% CI 1.19–2.11). There was no association with aspirin or H2 blockers (p=0.89 and 0.92, respectively).

Several histology variables exhibited a weak association with oesophagitis grade. However, polymorphonuclear infiltration and intestinal metaplasia were the only variables significantly associated with oesophagitis. After allowing for other variables, there remained a weak association between intestinal metaplasia and oesophagitis; those patients with intestinal metaplasia had a reduced odds of oesophagitis (odds ratio 0.83, 95% CI 0.57–1.21).
Warburton-Timms, Charlett, Valori, et al.

Those patients with either a past history of hiatus hernia or who currently have this condition were associated with a significantly increased risk of oesophagitis (estimated odds ratio 4.86, 95% CI 3.59–6.57; p<0.0001).

Discussion

The aim of this study was to investigate the relationship between cagA+ H pylori and endoscopically proved oesophagitis. Our study was performed prospectively on 1486 unselected consecutive patients attending open access endoscopy for investigation of dyspepsia. The study was carried out before the widespread use of PPIs and therefore our results were not influenced by the effects of hypochlorhydria. Other preliminary studies have found similar results but were multicentre investigations, lacked serology in many cases, or were performed on fewer patients. Several studies have examined the relationship with H pylori but have not determined CagA status. We found that patients infected by cagA+ H pylori had half the likelihood of developing oesophagitis compared with those infected by cagA− H pylori and those not infected. Over 80% of H pylori isolated from patients with an endoscopically normal oesophagus were cagA−, this proportion decreasing to 70%, 69%, and 46% in mild, moderate, and severe oesophagitis, respectively. When other factors associated with the development of oesophagitis were taken into account in a multivariable logistic regression analysis, this association between cagA+ H pylori was still evident. The risk of oesophagitis in the cagA− H pylori positive patients was no different to that in the H pylori negative patients.

A possible shortcoming of our study is that grading oesophagitis by endoscopic appearance does not necessarily reflect the extent of gastro-oesophageal reflux. Ambulatory 24 hour pH monitoring is the gold standard test of reflux but it is cumbersome and would be difficult to justify in a study such as this. Given the few patients suffering from severe oesophagitis and the highly significant difference in the prevalence of cagA, we feel that our results are accurate. One criticism may be that we identified cagA positivity by serology. Although the cagA gene is a marker of the presence of the PAI, it may not be a completely reliable marker of virulence. Some cagA+ strains may have more virulent genes than others, depending on how much of the cag PAI is present. This problem could be overcome with a more reliable marker of a fully intact cag PAI which returns to normal when the organism is present in the stomach. Acid exposure of the oesophagus is higher, and lower oesophageal sphincter (LOS) pressure is lower in the presence of hiatus hernia. It seems likely that the relationship of hiatus hernia and reflux oesophagitis is causal, mediated by a reduction in protective mechanisms for oesophagitis in hiatus hernia.

It seems a contradiction that cagA+ H pylori are positively and negatively associated with two conditions, peptic ulcer and reflux oesophagitis, that both respond to control of acid secretion. This is probably explained by the severity and distribution of the gastritis associated with H pylori infection in a particular individual. Antral predominant gastritis is probably the most important predictor of duodenal ulcer disease in the presence of H pylori infection. Antral predominant gastritis leads to reduced antral D cell density and somatostatin concentrations. This in turn leads to high serum gastrin and, in the presence of a normal corpus, to increased gastric acid, leading to a higher duodenal acid load and duodenal ulceration. As acid is produced in the gastric glands of the corpus, the amount of acid secreted in any H pylori infected stomach is dependent largely on the severity of corpus gastritis. More severe corpus gastritis is associated with lower acid output, which returns to normal when H pylori is eradicated.

Compared with cagA− negative strains, cagA positive strains are associated with enhanced development of atrophic gastritis wherever the organism is present in the stomach. Atrophy of the corpus leads to the destruction of gastric glands and, in turn, hypochlorhydria. As this advances, the acid load presented to the duodenum and oesophagus diminishes, so protecting against GORD. This effect is lost when H pylori is treated, leading to an increased risk of developing oesophageal reflux. The possibility that corpus gastritis plays a crucial protective role is supported by a study showing that patients with reflux symptoms without oesophagitis more often had active corpus gastritis than those with GORD with erosive oesophagitis. Our data showed that patients with antral intestinal metaplasia were less likely to have severe oesophagitis. Corpus biopsies were not taken for histological analysis in 1986 and therefore we are unable to predict the pattern of gastritis. H pylori is found in the cardia in almost all patients in whom infection is detected in the gastric antrum and body. Thus patients who develop gastro-oesophageal reflux disease and atrophy may have an increased risk of gastric carcinoma but a decreased risk of GORD.
gastritis (so-called antral predominant gastritis) will have normal acid production and are therefore at increased risk of GORD and possibly oesophageal adenocarcinoma.

Gastro-oesophageal reflux arises from a weak LOS or one that relaxes inappropriately. 46, 47 LOS pressure can be affected by smoking 48 and it was interesting to find that the ex-smokers in our study had a higher, although not significantly increased, risk of oesophagitis than current smokers. This may suggest that the effect of smoking on the LOS is not reversible. It is more likely however that the continued risk may be due to persistent airways disease and chronic cough that might promote gastro-oesophageal reflux.

It has been suggested that LOS pressure may be increased by the raised serum gastrin concentrations present in H pylori infections. 49 Although initial animal studies demonstrated this association, 50 a recent study showed no association between increasing gastrin concentration and LOS pressure. 51

One mechanism that affects the pattern of gastritis and the likelihood of GORD is administration of PPIs. 52 Our data were collected before the widespread use of PPIs and general practitioners were asked to stop H2 antagonists before endoscopy. Those patients taking antacids more than twice a week had an increased risk of oesophagitis but it is difficult to interpret this association as causal as it could simply reflect use to relieve symptoms.

H pylori infection per se was not associated with a protective effect against oesophagitis. Some studies have found an inverse relation between H pylori and oesophagitis once H pylori has been eradicated 53 but most studies have found, like ours, that H pylori is not associated with oesophageal disease, positively or negatively. 54, 55

The debate on treatment of patients infected with H pylori continues. The WHO has classified H pylori as a grade 1 pathogen 56 and therefore it would be unwise to stop treating this infection or base management on CagA status alone. 57 However, our study has raised the possibility that eradication of CagA strains of H pylori may lead to exacerbation of oesophagitis. If this proves to be the case, eradication may lead to a significant increase in health care costs as treatment of reflux symptoms consumes nearly 1% of the NHS budget. 58 Perhaps more significantly, it may lead to an increase in oesophageal adenocarcinoma. Further well-controlled studies are required to resolve the intriguing relationship between H pylori and oesophageal disorders and to inform future eradication policies.

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