Effect of *Helicobacter pylori* eradication on development of dyspeptic and reflux disease in healthy asymptomatic subjects

D Vaira, N Vakil, M Rugge, L Gatta, C Ricci, M Menegatti, G Leandro, J Holton, V M Russo, M Miglioli

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Background and aim: There are few data on the course of *Helicobacter pylori* infection in asymptomatic subjects. The aim of this study was to assess the effect of eradication therapy on the development of dyspeptic and gastro-oesophageal reflux disease in a cohort of asymptomatic individuals observed over a prolonged period.

Methods: A total of 169 blood donors infected with *H pylori* who had volunteered for studies on eradication in 1990 formed the cohort. To be included in this cohort subjects had to have no symptoms, as determined by a validated symptom questionnaire at the baseline visit. Eighty eight subjects were infected with *H pylori* while 81 had successfully undergone eradication therapy. Subjects were followed up (annually) using the same symptom questionnaire and in 2000 they underwent repeat endoscopy.

Results: Thirteen subjects developed symptoms during follow up. The incidence of symptoms in *H pylori* positive subjects was 1.893/100 person-years of follow up and in *H pylori* negative individuals 0.163/100 person-years of follow up. *H pylori* infected subjects were significantly more likely to develop symptoms (log rank test, p = 0.003) as well as those infected with CagA positive strains (log rank test, \( p = 0.017 \)). The development of symptomatic gastro-oesophageal reflux disease was no different in individuals with and without eradication (odds ratio 0.57 (95% confidence interval 0.26–1.24); \( p = 0.163 \)).

Conclusions: *H pylori* eradication prevents the development of dyspeptic symptoms and peptic ulcer disease in healthy asymptomatic blood donors and is not associated with an increase in the incidence of symptomatic gastro-oesophageal reflux disease.
on selective blood agar), and one sample was obtained from the antrum for the rapid urease test. The endoscopic examinations were performed by an investigator blinded to the H pylori status of the patient. Rapid urease tests were performed by nursing staff and results were not communicated to the endoscopist.

Subjects were classified as being infected with H pylori at baseline if the rapid urease test and histology were positive and/or if culture of gastric biopsy specimens was positive. All other patients were classified as negative.

At inclusion in this study, 88 subjects were infected with H pylori while 81 were H pylori negative.

Baseline visit
At the baseline visit, subjects completed a symptom questionnaire that has been validated in Italian subjects by the Italian Dyspepsia Study Group and measures a number of dyspeptic and GORD related symptoms. Serum samples were obtained and analysed later for the anti-CagA antibody by western blot. The characteristics of the cohort are shown in Table 1.

Annual follow up examinations
Subjects returned annually to complete the same validated symptom questionnaire used at baseline. They underwent a physical examination and a review of any medications taken for dyspeptic symptoms in the previous year (NSAIDs, proton pump inhibitors, H2 receptor antagonists, antibiotics). Subjects developing dyspeptic or GORD symptoms during the year were considered to be CagA positive by Drs Covacci, Telford, and Burroni (IRIS-Biocine, Siena, Biotech, UK). As controls, the following sera kindly provided by Drs Covacci, Telford, and Burroni (IRIS-Biocine, Siena, Italy) were used: antirecombinant CagA, antirecombinant VacA, antipurified urease, and heat shock protein. Subjects were considered to be CagA+ if more than four bands of reaction were evident in the blots.

Statistical analysis
The principal end point of the study was the development of symptoms, and subjects developing symptoms left the study as they had reached the predefined end point. Statistical tests used were Fisher’s exact test (two tailed) for frequencies and the Mann-Whitney rank sum test or the Kruskal-Wallis test as they had reached the predefined end point. Statistical tests used were Fisher’s exact test (two tailed) for frequencies and the Mann-Whitney rank sum test or the Kruskal-Wallis test as they had reached the predefined end point.

Table 1: Characteristics of asymptomatic subjects forming the cohort

<table>
<thead>
<tr>
<th></th>
<th>H pylori positive (n=88)</th>
<th>H pylori eradicated (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>57/31</td>
<td>56/25</td>
</tr>
<tr>
<td>Age (y) (mean (SD))</td>
<td>47 (11)</td>
<td>47 (12)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Smokers</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Chronic NSAID intake</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Race</td>
<td>All Caucasian</td>
<td>All Caucasian</td>
</tr>
</tbody>
</table>

NSAID, non-steroidal anti-inflammatory drug.

Figure 1: Flow chart of the study.

Anti-CagA antibody determination
CagA status was determined by western blot using the serum sample obtained at baseline. A whole cell suspension of H pylori CCUG 17874 (CagA positive type strain) was denaturised in Laemml’s solution at 100°C for 10 minutes, and run electrophoretically in a 10% sodium dodecyl sulphate-polyacrylamide gel. Separated proteins were transferred to nitrocellulose which was saturated for 30 minutes with a 3% defatted milk solution in phosphate saline buffer, pH 7.5, containing 0.1% Triton X (MTB). Nitrocellulose strips were incubated with serum samples diluted 1:1000 in MTB at room temperature overnight. After washing with MTB, strips were incubated with antihuman immunoglobulin G conjugated with peroxidase at room temperature for 90 minutes. The strips were washed and the reaction was visualised by an enhanced chemiluminescence assay (Amersham, Pharmacia Biotech, UK). As controls, the following sera kindly provided by Drs Covacci, Telford, and Burroni (IRIS-Biocine, Siena, Italy) were used: antirecombinant CagA, antirecombinant VacA, antipurified urease, and heat shock protein. Subjects were considered to be CagA+ if more than four bands of reaction were evident in the blots.

Flow chart of the study.
Endoscopic findings are reported in table 2. (11) years), as assessed by the gold standard endoscopy. and 73 were not (47 men and 26 women; mean (SD) age 46 (40 men and 34 women; mean (SD) age 49 (10) years). H pylori throughout the study. Of the latter, 74 were infected with H pylori (7.7) years) had duodenal ulcers but there were no endoscopic ulcers in the H pylori negative group. Fourteen subjects infected with H pylori (eight male and six female; mean (SD) age 50 (7.4) years) had oesophagitis at endoscopy. All 14 patients had Los Angeles grade A oesophagitis. Five of 14 subjects were CagA positive (four male and one female; mean (SD) age 50 (7.4) years) had oesophagitis at endoscopy. Five of 14 patients had Los Angeles grade A oesophagitis. Five of 14 patients had Los Angeles grade A oesophagitis. Five of 14 patients had Los Angeles grade A oesophagitis. Five of 14 patients had Los Angeles grade A oesophagitis. Five of 14 patients had Los Angeles grade A oesophagitis. Five of 14 patients had Los Angeles grade A oesophagitis. Five of 14 patients had Los Angeles grade A oesophagitis. Five of 14 patients had Los Angeles grade A oesophagitis. Five of 14 patients had Los Angeles grade A oesophagitis. Five of 14 patients had Los Angeles grade A oesophagitis. Five of 14 patients had Los Angeles grade A oesophagitis.

**RESULTS**

A flow chart of the study is shown in fig 1. One hundred and thirteen (66.9% (95% confidence interval (CI) 59.5–73.5)) subjects were infected with CagA positive strains of H pylori while 56 (33.1% (95% CI 26.5–40.5)) harbouring CagA negative strains of H pylori. Of the 169 subjects, nine did not complete the follow up and were not included in the final analysis. Two died of colon cancer after six and eight years of follow up, respectively (one was infected with H pylori in 1990). Seven refused to continue the annual follow up (one was infected with H pylori in 1990). However, all of these subjects were still asymptomatic at their last follow up visit before they left the study. Of the 160 subjects who completed the study, 13 developed symptoms (12 H pylori positive and one H pylori negative) while 147 remained asymptomatic throughout the study. Of the latter, 74 were infected with H pylori (40 men and 34 women; mean (SD) age 49 (10) years) and 73 were not (47 men and 26 women; mean (SD) age 46 (11) years), as assessed by the gold standard endoscopy. Endoscopic findings are reported in table 2.

Eight (10.8%) H pylori positive subjects who were asymptomatic (six male and two female; mean (SD) age 52 (7.7) years) had duodenal ulcers but there were no endoscopic ulcers in the H pylori negative group. Fourteen subjects infected with H pylori (eight male and six female; mean (SD) age 50 (7.4) years) had oesophagitis at endoscopy. All 14 patients had Los Angeles grade A oesophagitis. Five of 14 subjects were CagA positive (four male and one female; mean (SD) age 49.4 (7.4) years). Twenty one H pylori negative subjects (14 male and 7 female; mean (SD) age 47 (10) years) had oesophagitis; 19 subjects had grade A oesophagitis, one grade B, and one grade C oesophagitis. Persistent H pylori infection was not associated with a reduced risk of oesophagitis (odds ratio (OR) 0.57 (95% CI 0.26–1.24); p = 0.163). Among subjects with persistent H pylori infection, those harbouring CagA positive strains did not have an increased risk of oesophagitis (OR 1.68 (95% CI 0.5–5.62); p = 0.163). Moreover, the risk of oesophagitis in subjects infected with CagA strains compared with those not infected was not significant (OR 2.32 (95% CI 0.8–6.8); p = 0.15).

**Development of symptoms**

Symptoms developed in 12 subjects infected with H pylori and in one who had successful eradication of the infection (log rank test, p = 0.003) (fig 1). The symptoms that developed were: heartburn (n = 3), epigastric pain (n = 8), heartburn and epigastric pain (n = 1), and regurgitation (n = 1).

<table>
<thead>
<tr>
<th>Finding</th>
<th>H pylori positive (n = 12)</th>
<th>H pylori eradicated (n = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>4 (33.3%; 13.8–60.9)</td>
<td>0</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>1 (8.3%; 1.5–35.4)</td>
<td>0</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>1 (8.3%; 1.5–35.4)</td>
<td>0</td>
</tr>
<tr>
<td>Erosive duodenitis</td>
<td>1 (8.3%; 1.5–35.4)</td>
<td>0</td>
</tr>
<tr>
<td>Erosive gastritis</td>
<td>4 (33.3%; 13.8–60.9)</td>
<td>0</td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>1* (8.3%; 1.5–35.4)</td>
<td>1* (100%; 20.7–100)</td>
</tr>
</tbody>
</table>

Values are number [%; 95% confidence interval].

*Grade A according to Los Angeles classification.
Endoscopic findings in subjects developing symptoms are shown in table 3. The odds ratio for the development of symptoms in *H pylori* positive subjects was 5.68 (95% CI 1.84–17.6) compared with those who had successful eradication. The incidence of symptoms in *H pylori* positive subjects was 1.893/100 person-years of follow up and in *H pylori* negative individuals 0.163/100 person-years of follow up, respectively (fig 2). Subjects infected with CagA positive strains (n = 9) were also significantly more likely to develop symptoms compared with those who were CagA negative (n = 1) (log rank test, p = 0.017) (fig 3). The odds ratio for the development of symptoms in *H pylori* CagA positive subjects was 3.64 (95% CI 1.36–23.5) compared with those infected with CagA negative strains.

**DISCUSSION**

The association between chronic *H pylori* infection and dyspeptic symptoms is still not clear. Some population surveys report no relationship between *H pylori* infection and dyspepsia after controlling for confounding factors. However, a large population study has recently demonstrated that *H pylori* infection was significantly associated with dyspepsia and may be responsible for 5% of upper gastrointestinal symptoms in the community after controlling for confounding factors. The results of our study appear to confirm these data. We estimate that the incidence of symptoms in *H pylori* positive subjects was 1.893/100 person-years of follow up while in subjects with eradication of *H pylori* the incidence was 0.163/100 person-years of follow up. Furthermore, subjects infected with *H pylori* CagA positive strains were more likely to develop symptoms compared with those harboring *H pylori* CagA negative strains. However, neither *H pylori* infection nor CagA status was associated with any particular symptoms. Our data also provide an estimate of the risk of developing peptic ulcer disease. Eight of 147 subjects were found to have asymptomatic duodenal ulcers and all were still infected with *H pylori*. We found that peptic ulcer disease was equal or more common in asymptomatic *H pylori* infected subjects than in symptomatic *H pylori* infected subjects. Similar findings were reported by Buckley et al who found no significant difference between the *H pylori* positive asymptomatic group and *H pylori* positive dyspeptic patients with regard to duodenal ulceration or antral ulceration and/or duodenal erosions. Population based studies have also suggested that *H pylori* infection is a strong risk factor for ulcer disease.

Some studies have suggested that eradication of *H pylori* may be associated with the development of reflux oesophagitis and it has been proposed that subjects infected with CagA positive strains of *H pylori* might be at decreased risk for GORD and its complications. Other studies have demonstrated that symptoms of heartburn improve after eradication of *H pylori* and that the incidence of reflux disease is not increased. However, this controversy has not been satisfactorily resolved and is important in clinical decision making because eradication therapy to prevent one disease (for example, gastric cancer) may increase the risk of another. The studies performed to date were either in patients with duodenal ulcer disease or in those with an established diagnosis of GORD. The results of our study do not support the notion that *H pylori* infection protects against reflux disease. The number of subjects developing symptoms was small and a type II error given the small numbers cannot be ruled out. Given the low incidence of oesophagitis in both groups, it would be difficult to argue that the disappearance of *H pylori* from Western populations is the major cause of the apparent increase in GORD in those populations. Therefore, the low incidence and apparent similarity between the *H pylori* positive and negative groups over such a long period may be of clinical significance. Similarly, infection with a CagA positive strain did not protect against GORD. The outcome with regard to GORD may be different in our study of asymptomatic subjects because they may have a lower prevalence of severe corpus gastritis or may lack the other pathophysiological abnormalities that lead to reflux disease (lower oesophageal sphincter dysfunction, hiatus hernia).

Treatment of asymptomatic *H pylori* infection is an area of interest for several reasons. Firstly, chronic *H pylori* infection may lead to gastric atrophy and intestinal metaplasia, which are significant risk factors for the development of gastric cancer. Treating the infection may arrest this harmful sequence, reducing the risk of gastric cancer. Gastric cancer is the second most common cause of death from malignancies in the world, and five year survival rates are less than 20% in most countries. Cost effectiveness studies have suggested that a screening and treatment strategy for *H pylori* infection would be cost effective if the risk of developing gastric cancer were reduced by more than 30%. However, concerns about testing healthy people, creating anxiety if eradication therapy fails, and the potential for the development of resistant strains due to widespread antibiotic use have prevented such a strategy from being adopted.

Secondly, the cost of the management of dyspeptic patients is quite high, costing a health maintenance organisation $4.4 million in the USA. Eradication treatment in subjects with asymptomatic infection could reduce downstream costs related to dyspepsia and peptic ulcer disease as well as the morbidity associated with these diseases. Although none of the patients in our study developed complicated ulcer disease, preventing complicated ulcer disease may be an additional advantage of eradication therapy in asymptomatic subjects.

The principal limitations of our study were that blinding was not performed and that it was not a randomised controlled trial of *H pylori* eradication (that is, patients were not randomly assigned to eradication and follow up). Instead, subjects were randomly assigned to treatments in the original study and therefore success or failure of eradication was determined by the regimen patients were assigned to. The groups were comparable with regard to demographic characteristics and all subjects were healthy and asymptomatic who volunteered for blood donation when they were recruited. They were all Italians, living in the same community, with similar diets, smoking habits, and NSAID use. Selection bias needs to be considered when interpreting our results. It could be argued that patients who failed to have eradication in the original trials were non-compliant and that this may be a marker of a different lifestyle and other undefined characteristics that could influence the outcome of our study. We believe that this is unlikely because all subjects had high compliance rates in the original trial. Persistence of *H pylori* infection was most likely due to the use of ineffective treatment combinations because proton pump inhibitors triple therapy was unknown at that time. Blinding of subjects to their *H pylori* status was not considered ethical at the time this study was begun because we had limited knowledge of the consequences of persistent *H pylori* infection.

In conclusion, *H pylori* eradication prevents the development of dyspeptic as well as peptic ulcer disease in healthy asymptomatic blood donors and is not associated with an increase in the incidence of symptomatic GORD.

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