Long-term sequelae of *Helicobacter pylori* gastritis

**Summary**

Chronic *Helicobacter pylori* gastritis has been put forward as a risk factor for development of gastric mucosal atrophy and gastric cancer. The purpose of our study was to investigate the long-term effects of *H pylori* gastritis on the gastric mucosa. We prospectively studied 49 subjects negative for *H pylori* and 58 positive subjects for a mean follow-up of 11·5 years (range 10–13 years). Serum samples were obtained at the initial and follow-up visits for determination of *H pylori* IgG antibodies. Gastroscopies with biopsy sampling were done in all patients at both visits. Biopsy specimens were used for assessment of *H pylori* infection and histology.

Development of atrophic gastritis and intestinal metaplasia occurred in 2 (4%) uninfected and 16 (28%) infected subjects. Regression of atrophy was noted in 4 (7%) infected subjects. Development of atrophic gastritis and intestinal metaplasia was significantly associated with *H pylori* infection (p=0·0014; odds ratio 9·0, 95% CI 1·9-41·3). The proportion of atrophic gastritis in the study population showed an annual increase of 1·15% (0·5-1·8%).

We conclude that *H pylori* infection is a significant risk factor for development of atrophic gastritis and intestinal metaplasia. Our findings support strongly the causative role of this infection in gastric carcinogenesis.

**Introduction**

In 1982 flagellated bacteria were isolated for the first time by culture from endoscopic biopsy specimens of patients with gastritis and peptic ulceration. Since then, *Helicobacter pylori* has been recognised as the most important cause of chronic active gastritis. Ingestion of *H pylori* leads to acute gastritis, as reported in a few case studies. *H pylori* colonisation of the stomach is virtually always accompanied by histological signs of chronic inflammation. Bacterial infection can be diagnosed in nearly all subjects with gastritis, and this inflammation disappears completely within 6–12 months after eradication of the infection. Most infections are probably acquired in childhood and adolescence. Infection results in persistent chronic gastritis lasting for many years, possibly life-long.

Such chronic gastritis has been put forward as an important risk factor for the development of gastric mucosal atrophy, intestinal metaplasia, and eventually, gastric cancer. This hypothesis was based mainly on the results of a few prospective histological studies with repeated blind (without the aid of an endoscope) or endoscopically taken gastric mucosal biopsy specimens. More recently, three serological follow-up studies have confirmed a higher risk for development of gastric cancer many years after the first serological signs of *H pylori* infection. Combined analysis of these three studies revealed a significant trend towards an increased odds ratio with longer intervals between collection of serum and observation of gastric cancer. This finding may reflect development of atrophic gastritis and intestinal metaplasia with loss of *H pylori* colonisation in the years before development of cancer. The purpose of our study was to investigate the long-term effects of gastritis associated with *H pylori* on the gastric mucosa by repeated endoscopic biopsy sampling.

**Subjects and methods**

Between 1979 and 1983, 230 randomly selected patients referred for upper gastrointestinal endoscopy were studied with emphasis on investigation of gastric pepsinogen A and C. Gastric biopsy specimens were taken and serum samples obtained. In 1992 and 1993, follow-up data were obtained from 219 subjects. 40 had died by 1992, none from gastric cancer or peptic ulcer disease. Of the remaining 179, 15 were not available for follow-up because of serious illness or because they lived abroad. A request for participation in a follow-up study was sent to the 164 subjects who were alive and well according to their general practitioners. Informed consent for participation was given by 133 individuals (71 men). Initially, a history was obtained and blood samples taken for determination of *H pylori* serology. The results of that initial study have been published. 115 of the 133 subjects consented to follow-up gastroscopy with biopsy sampling. These 115 subjects were included in the histological follow-up protocol described here. Their mean (SD) age at the first visit was 49·0 (14·6) years (range 15–80 years). Mean follow-up was 11·5 years.
Second visit | First visit | N/NAG | AG | AG+IM | AG+IM+D
--- | --- | --- | --- | --- | ---
**H pylori negative**
N/NAG | 40 | 0 | 0 | 0 | 0
AG | 1 | 1 | 4 | 1 | 1
AG+IM | 0 | 0 | 0 | 1 | 1
AG+IM+D | 27 | 4 | 0 | 0 | 0
--- | --- | --- | --- | --- | ---
**H pylori positive**
N/NAG | 10 | 4 | 0 | 0 | 0
AG | 5 | 0 | 5 | 0 | 0
AG+IM | 1 | 1 | 0 | 0 | 2
AG+IM+D | *Including 1 individual with slight atrophy but moderate metaplasia at both visits.*

Presence of intestinal metaplasia (IM) and dysplasia were confined to subjects with atrophic gastritis. N=normal, NAG=nonatrophic gastritis, AG=atrophic gastritis, D=dysplasia. Table: Histological findings in 49 subjects negative for H pylori and 58 subjects positive for H pylori before and after follow-up (range 10–13 years). The study was approved by the ethics committee of the Free University Hospital.

IgG antibodies against H pylori were measured by ELISA. 9 Upper gastrointestinal endoscopies were done with Olympus endoscopes (K, Q, and 1T series). Biopsy specimens were obtained with standard biopsy forceps. During the first endoscopy, specimens (n=3) were taken from the gastric corpus in all cases, and from additional sites in case of endoscopic abnormalities. During the second endoscopy, biopsy samples were taken from the gastric corpus (n=5 for histology) and antrum (n=3, 2 for histology, 1 for H pylori culture).

Haematoxylin-eosin-stained and modified-Giemsa-stained 4 μm histological slides were obtained from the original paraffin blocks of the first visit and from the follow-up biopsy specimens. All slides were assessed by one pathologist according to the Sydney classification. 19 The pathologist was unaware of clinical and endoscopic data and first study results. The following items were separately evaluated: H pylori colonisation, presence of an acute inflammatory component (ie, the amount of neutrophilic infiltration), presence of a chronic inflammatory component (ie, the amount of mononuclear-cell infiltration), presence of mucosal atrophy, presence of intestinal metaplasia, and presence of mucosal dysplastic changes. All these items were separately scored both in the antrum and in the corpus on a grading scale from 0 to 3, representing absent (0), slight (1), moderate (2), or severe (3). Comparison between initial and follow-up histology scores of the corpus allowed determination of histological changes during follow-up. Progression and regression of abnormalities were defined as a change of at least two steps on the four-point scale. To diminish any sampling effects, a one-step change during follow-up was not considered significant.

Presence of H pylori infection at the first visit was assessed by serology and histology. In the case of a discrepant result, the result of histology was considered predominant over serology, unless bacteria were not observed on an atrophic mucosa with positive serology because this finding was regarded as a sign of past infection. The presence of infection at follow-up was assessed by culture, histology, and serology. A patient was regarded as positive for H pylori if culture was positive, or if both histology and serology were positive.

Statistical analysis was done by Fisher’s exact test, McNemar’s test, Wilcoxon signed rank test, Mann-Whitney test, one-way analysis of variance by paired t test, or by multiple regression analysis. Statistical significance was set at p less than 0.05.

**Results**

The first upper gastrointestinal endoscopy showed that 4 subjects had a duodenal ulcer or duodenitis, 4 a gastric ulcer, 5 a reflux oesophagitis, 2 had a Barrett oesophagus; no specific endoscopic abnormalities were observed in the remaining 100.

The follow-up endoscopy showed that 3 subjects had a duodenal ulcer or duodenitis, 1 had scarring of the pylorus without ulceration at the time of endoscopy, 1 had a submucosal tumour of the stomach with echoendoscopic signs consistent with a leiomyoma, and 3 had undergone a distal stomach resection for complicated peptic ulcer disease. In addition, 5 subjects had reflux oesophagitis and 5 had a Barrett oesophagus, 1 of whom had a small symptomless Barrett ulcer that was due to adenocarcinoma. A distal oesophagus resection was done. 1 subject had a flat gastric ulcer of the smaller curvature with histological appearance of adenocarcinoma; a subtotal stomach resection was done (see below). The remaining 96 subjects had no specific endoscopic abnormalities. Diagnosis of gastritis, atrophy, and metaplasia was based solely on histology and not on endoscopic appearance.

115 patients were studied twice by endoscopy. 4 patients were excluded from analysis because no histological material was available from the first visit. 1 subject had successfully been treated with H pylori eradication therapy, and for this reason he was excluded from histological follow-up analysis. 3 patients had been treated with antral resection for complicated peptic ulcer disease within 1 year of the first endoscopy; they were excluded from histological follow-up analysis because of the confounding possibility of postoperative chronic biliary reflux gastritis. Thus, 107 subjects were included in the final analysis of histological follow-up.

49 patients were negative for H pylori at the first visit (table). In 5 (10%) subjects, histological signs of gastritis were observed. In 7 (14%) of the 49 subjects, including the 5 with chronic gastritis, moderate to severe atrophy was found on histological screening (table). All these 7 subjects were seronegative. 6 of the 7 also had intestinal metaplasia and 2 of them showed signs of dysplasia. During follow-up, only 2 of 49 subjects became infected with H pylori, leading to development of chronic non-atrophic pangastritis in both. Both these subjects showed seroconversion. 1 uninfected subject developed moderate atrophic gastritis of the corpus for unknown reasons. Another subject had no specific abnormalities at the first visit, but developed severe mucosal atrophy of the corpus and pernicious anaemia during follow-up. This was also
the only subject in the uninfected subgroup who developed intestinal metaplasia. The remaining 45 (92%) patients negative for *H pylori* showed no histological changes. At follow-up, none of the uninfected individuals showed evidence of development of dysplasia, and dysplasia regressed in 1 subject. The proportion of atrophic corpus gastritis among the 49 initially uninfected subjects increased from 14 to 18% (p=0.048; McNemar’s test), with an annual increase of 0.3% (95% CI 0.04-1.2%) (figure). The proportion of intestinal metaplasia in the corpus increased from 12 to 14%, corresponding to an annual increase of 0.2% (0-0-9%). The rate of dysplasia decreased from 4 to 2%.

58 patients were infected with *H pylori* at the initial visit (table). Infection was accompanied by chronic gastritis in all these subjects (table). In 14 (24%) of the initially infected subjects, moderate to severe atrophy was found on histological screening at the first visit. In 6 of these 14, and in 1 subject with minimal atrophy, histological signs of moderate to severe intestinal metaplasia were observed. 2 patients showed signs of dysplasia. After a mean 11-5 years, 4 subjects showed regression of atrophy in the corpus from moderate to absent. However, in 16 (28%) of the 58 individuals who were initially infected, substantial progression of atrophy was noted, and was accompanied by development of moderate to severe intestinal metaplasia in 6 (figures 1 and 2). We did not see regression of intestinal metaplasia in any subject. In 6 subjects who developed atrophic gastritis, a concomitant decrease or disappearance of *H pylori* colonisation was noted. Nevertheless, these 6 subjects were still serologically positive at the end of follow-up. 1 positive individual developed early gastric cancer at the age of 55, 8 years after the initial endoscopy. Both her father and brother had had stomach cancer. She was treated with a subtotal gastrectomy. No signs of recurrent cancer have been noted in the subsequent 5 years. The frequency of atrophic corpus gastritis among the 58 initially infected patients increased from 24 to 45% (p=0.014, McNemar’s test), with an annual increase of 1.8% (1.0-2.9%) (figure). The rate of intestinal metaplasia in this group increased from 12 to 22%, corresponding to an annual increase of 0.9% (0.3-1.8%), and the rate of dysplasia increased from 3 to 5%.

Development and progression of atrophy during follow-up was noted in 2 (1 male) of the 49 uninfected subjects and 16 (9 male) of the 58 infected subjects (p=0.0014, Fisher’s exact test; odds ratio 9-0, 95% CI 1.9-41.3). Comparison after exclusion of the pernicious anaemia patient in the uninfected subgroup gave a p value of 0.0003 (odds ratio 17.9, 2.3-141). Logistic regression analysis yielded an adjusted odds ratio for *H pylori* infection of 7.7 (1.2-13.9), whereas the odds ratios adjusted for other multivariate factors including age, sex, and gastric mucosal inflammatory scores did not reach statistical significance. In the total study population, the annual increase in atrophic corpus gastritis was 1.15% (0-6-1.8%). At the first visit, atrophic gastritis was noted in 7 of 49 uninfected subjects and 14 of 58 infected subjects (p=0.23, Fisher’s exact test). At the second visit, atrophic gastritis was present in 9 of 47 at that time uninfected individuals and 26 of 60 infected subjects (p=0.012, Fisher’s exact test) (figure). There were no significant differences in age between the uninfected (mean [SD] age 48 [14.5] years) and infected (50 [12-4] years) patients that might have accounted for differences in development of atrophy (p=0.19, Mann-Whitney test). In infected individuals, development of atrophy and metaplasia was not significantly related to activity of gastritis at the first visit (p>0.1, Wilcoxon signed-rank test), nor to the level of the serology absorbance index (p>0.1, Mann-Whitney test).

### Discussion

*H pylori* is the most important cause of chronic active gastritis. Such gastritis is thought to be involved in the possible sequence of gastric mucosal atrophy, intestinal metaplasia, and gastric cancer. A WHO working group concluded that there is sufficient evidence that *H pylori* has a causal role in the chain of events leading to gastric cancer. Development of atrophic gastritis is a central feature of the multistep process leading to gastric cancer. However, data on this feature are limited and mostly derived from cross-sectional or retrospective studies. Until now, only three cohort follow-up studies have been published. The Finnish study was the first and had the longest follow-up, extending up to 30 years. This study started with blindly sampled biopsy specimens. For historical reasons the *H pylori* status of the study subjects was not reported. The annual rate of development of atrophic gastritis in the cohort was about 1%. The second and largest study, which included 1422 subjects from an area of Colombia with a high gastric cancer risk, reported an annual increase of 1.7% in rate of corpus atrophy, 0.9% in intestinal metaplasia, and 0.7% in dysplasia during mean follow-up of 5-1 years. The third study, from Estonia, reported on 142 individuals with follow-up of 6 years. This was the only study in which the *H pylori* status of the included subjects was reported. The authors were, however, unable to study the strength of any association between atrophy and *H pylori* because almost all subjects were infected. The annual increase in rate of atrophic corpus gastritis in this population was 1.25%.

The results of our study are very much in agreement with the earlier three studies. The Colombian study reported a slightly faster rate of development of atrophic gastritis. However, that study was done in a population with a high gastric-cancer risk and most subjects were probably *H pylori* positive. The reported annual increase...
in atrophic gastritis did not differ much from the results in our subgroup of infected individuals despite large differences in genetic background and diet. The same holds true for the Estonian population. The _H pylori_ status of the subjects in the Finnish study is unknown, but the results are similar to those of our study.

Our most important finding is that development of atrophy is largely confined to the subgroup of individuals who are infected with _H pylori_. Development of atrophy in the gastric mucosa was strongly associated with _H pylori_ infection. Atrophic gastritis is thus not a direct and inevitable consequence of ageing, but the result of infection. This finding is in accordance with an earlier cross-sectional study. The investigators studied acid output and histology in relation to age. Atrophic gastritis was observed in 10 of 16 _H pylori_ positive men over the age of 65 years, whereas atrophy was present in only 1 of 12 uninfected men of the same age. In our cohort, prevalence of atrophic gastritis was rare in the uninfected group at the initial visit and changes were noted in about 28% of subjects leading to a significantly higher rate of atrophy at the end of follow-up by comparison with uninfected individuals. In the infected subgroup, however, atrophic gastritis was already more prevalent at the initial visit and changes were noted in about 28% of subjects leading to a significantly higher rate of atrophy at the end of follow-up by comparison with uninfected individuals. In the uninfected group, 7 subjects had atrophic gastritis at the first visit; 5 of these had chronic active inflammation of the gastric mucosa. The possibility that these subjects had once been infected with _H pylori_ and had become seronegative cannot be excluded. If this were the case, our current results might underestimate the strength of the association between _H pylori_ infection and atrophic gastritis.

In our study population, we could not identify specific factors such as histological severity of gastritis or level of systemic IgG antibody response that were predictive of development of atrophy. In a minority of infected individuals, regression of abnormalities was seen during follow-up. In 4 subjects this regression occurred despite continuing infection. Although a substantial number of biopsy specimens were taken and a strict definition of histological change was adopted requiring at least two steps difference on a four-point Sydney scale, a sampling effect cannot be excluded.

Regression of histological signs of atrophic gastritis during repeated biopsy sampling has been described before, with a relative frequency of regression compared with progression of between 0·29 and 0·36. With exclusion of 1 patient who had regression of atrophy after helicobacter eradication, we observed a ratio of regression to progression of 0·22. Most likely, this is largely due to sampling effects in a multifocal atrophic mucosa, although a real regression of abnormalities despite continuing infection cannot be excluded. It could be that development of atrophy is, to a certain extent, a balancing process with some replacement of lost glands.

In conclusion, the results of our study show that _H pylori_ is an important risk factor for development of atrophic gastritis and intestinal metaplasia. Therefore, this study strongly supports the concept of _H pylori_ as a major risk factor for gastric cancer.

The preliminary data of this study were presented at the annual meeting of the American Gastroenterology Association, May, 1994, in New Orleans. The study was made possible by financial support of the Netherlands Digestive Diseases Foundation.

References


