### Long-term Clinical Course of Ulcer Disease and Incidence of Reflux Esophagitis in a Large Cohort of Duodenal Ulcer Patients Followed After Eradication of Helicobacter pylori. L. Labenz, B. Tillenburg, U. Peitz, M. Sollbohmer, M. Stolte, G. Bissel. Department of Internal Medicine and Gastroenterology, Elisabeth Hospital Essen, Germany

**Aim:** The aim of the present study was to evaluate the long-term clinical course of formerly relapsing duodenal ulcer disease after cure of H. pylori infection.

**Methods:** 203 patients with endoscopically proven relapsing duodenal ulcer disease and without endoscopically visible signs of reflux esophagitis at the time of H. pylori eradication were prospectively followed for 1 to 5 years. During the follow-up without any antulcer drugs, patients were reinvestigated clinically and endoscopically in one-year intervals and when dyspeptic symptoms recurred. During each endoscopy, the H. pylori status was assessed by means of an urease test, culture, and histology.

**Results:** During follow-up of 346 patient years, 6 ulcers recurred (1.7% per patient year: 95%-CI: 1%-4%), which were associated either with H. pylori recurrence (n=1), intake of Aspirin or NSAIDs (n=4), or cryptogenic liver cirrhosis (n=1). A total of 4 patients had H. pylori recrudescence or reinfection, respectively, during the first year after treatment and none relapsed later (rate: 1.2% per patient year: 95%-CI: 0%-3%). Twenty patients (rate: 9.9%; 95%-CI: 6%-15%) developed an endoscopically proven reflux esophagitis, which was mild in grade I or II in 19 patients and severe in one female patient with stenosis of the duodenal bulb.

**Conclusion:** H. pylori eradication cures duodenal ulcer disease in the long-term. In addition, eradication of H. pylori is a stable phenomenon at least during the first five years after treatment. In patients with recurring dyspeptic symptoms, reflux disease should be considered.

### Long-term Effect of Anti-Helicobacter pylori Therapy on Gastric MALT Lymphoma. Histological and Molecular Evaluation of 15 Cases. A. Savino, G. Franzini, A. C. Wolferspoor, G. Zamboni, R. Neigrini, M. Graffeio, T. C. Dias, L. Pan, P. G. Issacson. Ospedale S. Orsola, Brescia Italy and University College London Medical School, London UK

Histological regression of gastric low-grade MALT lymphoma (ML) after eradication of Helicobacter pylori (H. pylori) infection has been reported. To assess the long-term efficacy of the antibiotic therapy, fifteen patients (7 females, age 34-78) with a diagnosis of gastric ML stage IE associated with H. pylori infection and biologic follow up for 11-44 months (mean follow up 23 months). At each sampling, histological evaluation and PCR of a nucleomoglobin heavy chain gene rearrangement were performed.

H. pylori was eradicated in 14 cases and histological remission was found in 13 cases 2 to 4 months after the eradication therapy. All the 13 cases with histological regression of lymphomas are free of disease and relapse after 8-30 months after eradication of H. pylori (mean 18 months). Monoclonality was demonstrated in 10 of the 13 cases with histological remission. Disappearance of PCR detected amplification bands following eradication of H. pylori was demonstrated in 6 cases and was synchronous to histologic remission in 4 of them whereas monoclonality persisted for 9 and 24 months in absence of histological evidence of lymphomas in the remaining 2. Monoclonality persists 13-27 months after eradication and histological remission in 4 cases.

The eradication of H. pylori induced a quick and persistent histological remission in 93% of cases. The molecular regression of ML seems to be much slower than the histological one.
GASTRIC B-CELL LYMPHOMAS INDUCED IN A SINGLE MOUSE STRAIN BY VARIOUS ISOLATES OF HELICOBACTER HEILMANNII: SIMILARITIES AND DIFFERENCES.


Aim: In humans, the manifestation of Helicobacter-associated disease may be related to the host’s response to different Helicobacter isolates. We have recently shown that prolonged infection with a single strain of H. felis in Specific Pathogen Free (SPF) BALB/c mice results in the development of gastric carcinoma occurring in lymphoepithelial lesions (MALTS) and lymphoepithelial lesions consistent with MALT lymphoma. This study describes the colonization and pathological changes seen after long term infection with H. heilumannii and H. heilmannii-like organisms isolated from the bobcat, humans and other primates (red fronted lemur, mandrill monkey and crab-eating macaque).

Method: Gastric biopsies from different sources were inoculated per os into SPF BALB/c mice. The stomachs of animals sacrificed at 15, 19 and 24 months after infection were examined for histopathology.

Results: The organisms preferentially colonized the antrum and cardia areas of the stomach. Within these areas there were reactive changes in the epithelium with numerous mitotic cells. When compared to H. felis infected animals, there were similar pathological changes observed after infection with H. heilumannii, but the response was more aggressive. In the corpus and cardia regions the lymphocytic infiltrate was extensive, in some cases resulting in the severe destruction of the gastric epithelium. Lymphoid follicles appeared as early as 6 months and lymphoepithelial lesions at 15 months post infection. Some isolates were characterised by infolding of the gastric epithelium and a marked eosinophilic infiltrate. Of particular interest the most dramatic pathology was observed with the bobcat and one of the three human isolates.

Conclusions: Significant differences were seen in the pathology induced by various Helicobacter isolates in mice from the same animal colony including the development of low grade gastric B-cell lymphomas. Study of these differences may provide interesting insights in the pathogenesis of gastric MALT lymphoma.


Gastric carcinoma remains one of the most frequently diagnosed malignant diseases worldwide, particularly in Japan. Recent studies showed a significant association between H. pylori infection and gastric carcinoma. H. pylori infection is considered to be a risk factor for gastric carcinoma. However, the mechanism by which H. pylori infection predisposes to gastric carcinoma remains unclear.

We have recently demonstrated that H. pylori infection, and most persons infected with H. pylori will never have gastric carcinoma. Therefore, other factors that increase the risk of gastric carcinoma among persons infected with H. pylori need to be identified. Investigation of host factors with respect to the pathogenesis of H. pylori has been recommended. We previously reported a contribution of HLA-DQA1 gene to the host's disease response to H. pylori.

In addition, blood group A was found to be associated with gastric carcinoma especially diffuse type. We examined here the host's genetic factors in patients with atrophic gastritis or gastric carcinoma harboring H. pylori.

Methods: Sixty four H. pylori-positive patients with atrophic gastritis and 85 patients with gastric carcinoma (62 were H. pylori-positive, 23 were negative) were examined for HLA-DQA1 genotypes, and ABO blood groups. H. pylori infection was determined by the enzyme-linked immunosorbent assay (ELISA). HLA-DQA1 typing was done by the polymerase-chain reaction restriction fragment length polymorphism (PCR-RFLP) method.

Results: There was no significant difference in the distribution of ABO blood types among the subject groups. By contrast, the allele frequency of DQA1*0102 was significantly higher in H. pylori-negative gastric carcinoma patients and H. pylori-negative normal controls than in H. pylori-negative gastric carcinoma patients. In addition, the genotypes which possess the DQA1*0102 allele were significantly higher in gastric carcinoma patients and H. pylori-negative normal controls than in H. pylori-positive atrophic gastritis patients and H. pylori-positive gastric carcinoma patients.

Conclusions: Our findings suggest the presence of a genetic difference in the host between H. pylori-positive and H. pylori-negative gastric carcinoma. DQA1*0102 allele may contribute to the resistance against H. pylori infection and the lack of DQA1*0102 allele may be the host's genetic risk factor for H. pylori infection.

HELCOBACTER PYLORI GASTRITIS IS ASSOCIATED WITH EXPRESSION OF VARIANT FORMS OF CD44 ON GASTRIC EPITHELIAL CELLS: IMPLICATIONS FOR GASTRIC CARCINOMA. K. Fan, A. H. Wind, A. M. Goggins X.G. Fan, PWN Keeling, D. Kelleher. Depts. of Clinical Medicine and Gastroenterology, St. James's Hospital, Trinity College Dublin, Ireland

CD44 is a cell adhesion molecule which is involved in adhesion of cells to extracellular matrix ligands such as hyaluronic acid. Numerous variants of CD44 are known to exist as a result of alternative splicing and post-translational modifications of the CD44 gene. Expression of CD44 variants has been noted in gastric, colorectal and breast cancers and lymphomas. It has been suggested that expression of CD44 variants (CD44v6 and CD44v9) by cancers could facilitate growth and metastasis of cancer cells. This is supported by evidence that expression of CD44 variants is associated with a poor prognosis in gastric cancer. The mechanism responsible for the expression of CD44v6 and CD44v9 in gastric epithelial cells is uncertain. We investigated the role of Helicobacter pylori (HP) infection on the expression of CD44 variants on gastric epithelial cells. Of the 18 dyspeptic patients used in this study 10 were HP positive and 8 were HP negative with normal gastric mucosa. HP infection was confirmed by the CLO test and histology. CD44 expression was present at low levels on normal gastric EC. CD44, CD44v9 and D.1.1 but not CD44v6 expression was observed. GC in HP chronic gastritis (HP+), CD44 expression in HP+ v normal antrum (HP-)(mean ± s.e.m.); 154±48 vs 29±10 MFI (mean fluorescence intensity), p<0.02. D.1.1 expression in HP+ vs HP- antrum; 216±50 vs 178±26 MFI, p<0.02. CD44v9 in HP+ vs HP- antrum; 2757 ± 142 MFI, p<0.05. There was no significant difference in CD44 expression on gastric IE in HP+ compared HP- normal antrum. Class II expression (DR, DP but not DQ) was increased on gastric EC and ILE of HP+ antrum compared to normal gastric mucosa.

In conclusion, increased expression of CD44 and MHC class II molecules on epithelial cells could reflect increased local production of cytokines involved in regulation of these molecules. These data suggest that HP either directly or through a local inflammatory response is responsible for increased expression CD44 and its variants (CD44v9). These data are of potential significance in relationship to increased expression of CD44 and CD44v9 on gastric carcinoma.

PREVALENCE OF GASTRIC ATROPHY, THE PRECURSOR LESION OF GASTRIC CARCINOMA IS INDEPENDENT OF THE PREVALENCE OF HP INFECTION: EVIDENCE THAT WHILE HP INFECTION MAY BE THE MAJOR DETERMINANT OF GASTRIC CARCINOMA IT IS NOT FOR GASTRIC ATROPHY. D. Y. Graham, H. M. Malaty, G. Globor, G. Polos, M. Ichinose, K. Miki, M. Asaka. Depts. of Medicine, VA Medical Center and Baylor College of Medicine, Corpus Christi Cancer Study, U.T. M.D. Anderson Cancer Center, Houston, TX, USA, the First Dept. Internal Medicine, University of Tokyo, Tokyo, and Hokkaido University School of Medicine, Sapporo, Japan.

Hp prevalence (ELISA) and the frequency of severe atrophic gastritis/gastric atrophy (PGE2/PGE2 ratio ≤2.0 & PGE2 ≥70 ng/ml) were investigated in 3 groups: 119 asymptomatic Hispanic and 111 Anglo women between the ages of 20 and 78 participating in Colorectal Cancer screening program in South Texas and 300 asymptomatic Japanese of either sex. The prevalence of Hp infection increased with age and was different for the 3 ethnic groups (e.g., ages 30-39; 72% in Hispanics, 41% in Japanese, and 13% in Anglo women). The age-adjusted gastric cancer mortality for Hispanic women and Japanese is 2 to 4 times that of Anglos and although the prevalence of gastric atrophy, the postulated precursor lesion of gastric cancer, was increased with age in all three groups, within birth cohorts (e.g. 20 to 29 yrs), no difference was observed between groups.

These results suggest that the difference in cancer risk between ethnic groups is more closely related to Hp infection rather than a gastric atrophy. In those Hp-infected ethnic groups with Hp infection were associated with other factors modifying factors such as diet or the higher prevalence of Hp “cancer strains” may be required to promote the transformation of gastric atrophy to gastric cancer.
ASSOCIATION BETWEEN GASTRIC CANCER AND H. PYLORI WITH REFERENCE TO AGE.


In order to assess the influence of age on association between gastric cancer and H. pylori, we conducted a large case-control study in Kanto area of Japan. Serology was collected between 1988 and 1994 from gastric cancer patients aged 20-69 years, who were diagnosed at 10 hospitals, and from screen-positive (control) general health check programs in the same area. 100 healthy volunteers from the area were also examined. 418 gastric cancer patients and 358 controls (50.9% males) were included.

The seropositive percentage and odds ratio for association were presented in the Table, divided into five ten-year age groups. Odds ratios in all age groups were significantly elevated except the oldest. The magnitude of odds ratio was negatively related to age (p<0.01). The decrease in odds ratio with age was mainly due to an increase in the seropositive percentage in controls.

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>No. of subjects</th>
<th>Seropositive%</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>20 (90.0%)</td>
<td>20 (90.0%)</td>
<td>23.1 (5.2, 103.0)</td>
</tr>
<tr>
<td>30-39</td>
<td>121 (91.9%)</td>
<td>121 (91.9%)</td>
<td>11.0 (5.8, 20.8)</td>
</tr>
<tr>
<td>40-49</td>
<td>124 (91.9%)</td>
<td>124 (91.9%)</td>
<td>9.6 (4.8, 19.4)</td>
</tr>
<tr>
<td>50-59</td>
<td>216 (88.8%)</td>
<td>216 (88.8%)</td>
<td>3.3 (1.9, 5.5)</td>
</tr>
<tr>
<td>60-69</td>
<td>216 (88.8%)</td>
<td>216 (88.8%)</td>
<td>1.6 (0.9, 2.6)</td>
</tr>
<tr>
<td>Total</td>
<td>750 (93.7%)</td>
<td>750 (93.7%)</td>
<td>4.7 (3.8, 6.1)</td>
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</tbody>
</table>

ERADICATION OF DUODENAL ULCER AFTER HELICOBACTER PYLORI ERADICATION IS RELATED TO HIGH HISTAMINE OUTPUT.

AW Harris, PA Gummett, PS Philp, MR Jayson, JH Baron. Parkside Helicobacter Study Group, Central Middlesex and St Mary's Hospitals, London and Gastroenterology Unit, Northwick Park Hospital, Harrow, England.

Eradication of H. pylori (Hp) reduces recurrence of duodenal ulcer (DU) to <2% per annum. It is not clear why DU recurs rarely in the absence of Hp reinfestation or NSAID. Basal (BAO), gastric releasing peptide (GRP) and gastrin (PG)-stimulated peak acid outputs (PAO) are increased in Hp-ve DU and return to the range of Hp+ve controls after eradication. Does acid output in patients with recurrent DU after Hp eradication also return to the control values?

We studied 6 patients (5 men, mean age 41, range 28-53) with symptomatic and endoscopic recurrence of DU: six months (mean 18 months) after Hp eradication, and compared them with 10 Hp+ve controls with normal endoscopy (4 men, mean age 33, range 24-40), and with Hp+ve non-recurrent DU before (n=10, 7 men, mean age 37, range 22-56) and six months after (n=8, 6 men, mean age 39, range 24-58) Hp eradication. None had taken NSAID. Hp status was determined by antral and body histology and by the 13C urea breath test, and classified as Hp+ve on any +ve result and Hp-ve on all three tests. After an overnight fast, a NG tube was passed, the stomach emptied, and 30 min basal aspirate collected. GRP (40 pmol/kg) was then infused for 45 min. After a 30 min washout, Pg (6pg/kg) was injected i.m. Thirteen 15 min aspirates were collected after each stimulus.

Acid outputs are expressed as mmol/h and normalised to 70kg body weight. BAO, PAO+PAO, and PAO, were significantly (p<0.05) higher in Hp+ve DU than Hp+ve controls, with median (range) BAO 7 (2-17) vs 2 (0.3-6), PAO 20 (0.3-64) vs 10 (1-25) and PAO 44 (20-79) vs 25 (12-40). Six months after Hp eradication, median (range) BAO, PAO, and PAO, in DU were 3 (1-11), 14 (1-45) and 29 (6-40), respectively, all significantly (p<0.05, Wilcoxon signed rank test) lower than before Hp eradication and within the range of controls. In Hp+ve recurrent DU median (range) BAO, PAO, and PAO, were 5.5 (0-15), 18.5 (2-8) and 38 (27-60), respectively, PAO was significantly (p<0.05) higher than Hp-ve controls within the Hp-ve DU range.

In DU recurrent after Hp eradication, PAO remains within the Hp+ve DU range. By contrast in non-recurrent DU PAO fell to the control range after Hp eradication. Our findings suggest that there may be a subset of DU that return an abnormally high response to gastrin. AWH is supported by a grant from Lederle Laboratories, UK.

PARAETAL CELL SENSITIVITY TO GASTRIN DISTINGUISHES H. PYLORI INFECTED DU PATIENTS FROM INFECTED HEALTHY VOLUNTEERS.

D. Gillespie, E. El-Omar, K.E.L. McColl. University Department of Medicine, London, United Kingdom.

It is unclear why Hp produces duodenal ulceration in only a minority of infected subjects. In all subjects it increases gastric output and the magnitude of this is similar in those with and without DU. We have investigated whether those who develop DU are more sensitive to the acid mimetic effects of gastrin.

Patients and Methods: Fifteen Hp positive healthy volunteers and six Hp positive duodenal ulcer patients were examined. Each group was matched for age, sex and body weight. After a 30 minute basal period, Gastrin-17 was infused i.v. in doses of 3.0, 20.0 and 70.0 pmol/kg/h over consecutive 30 minute periods. Gastric juice was collected in 15 minute aliquots and acid output determined. Dose-response curves were plotted and the G17 dose required to produce half maximal acid response (D50) calculated.

Results: None of the groups showed a statistically significant difference in maximal acid output to G-17. However, the Hp positive DU patients were significantly less sensitive to gastrin than the Hp negative healthy volunteers (p<0.03). In addition, the Hp positive DU patients were more than twice as sensitive to gastrin compared to the Hp positive healthy volunteers (p<0.004).

<table>
<thead>
<tr>
<th>Median MAO to G17 (mmol/h)</th>
<th>Healthy Volunteers</th>
<th>Healthy DU Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAOP, (range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>38.5 (21.8-60.2)</td>
<td>20.8 (18.6-54.8)</td>
</tr>
<tr>
<td>DU</td>
<td>53.7 (27.7-61.3)</td>
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HELCOBACTER PYLORI AUGMENTS THE PH-RAISING EFFECT OF OMEPRAZOLE IN DUODENAL ULCER PATIENTS.


Aim: The effect of eradicating H. pylori (HP) on baseline gastric pH and on intragastric acidity when combining omeprazole therapy in duodenal ulcer (DU) patients was investigated.

Methods: HP infection and eradication were assessed by urease test. pH, histology and urea breath test. Before eradication and 4 to 6 weeks after stopping eradication therapy, intragastric acidity (ingold glass electrode 5 cm below the cardia) was measured after a one-week treatment with omeprazole (OME) 20 mg (group I; 17 DU patients) or without treatment (group II; baseline pH, DU patients). Results: Cure of bacterial infection resulted in a decrease of the gastric pH during treatment with omeprazole 20 mg od, while the baseline pH remained unchanged (Table).

<table>
<thead>
<tr>
<th>Group</th>
<th>Median pH Before After Erad</th>
<th>Erad</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>OME 20 mg od</td>
<td>5.5</td>
<td>3.0</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Baseline</td>
<td>5.7</td>
<td>3.3</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Postprandial</td>
<td>5.2</td>
<td>4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nighttime</td>
<td>6.4</td>
<td>2.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusion: Intragastric pH during OME treatment decreases markedly after HP eradication in DU patients, while baseline pH remained unchanged after eradication. The acid-reducing effect of omeprazole and the loss of efficacy of omeprazole in DU patients after HP eradication will have to be studied in the future. As a consequence of our studies, previous studies relating gastric pathology and healing of peptic lesions must be repeated separately for HP positive and negative subjects.