GASTRIC JUICE IL-8 AND IL-8 IgA AUTOANTIBODIES: RELATIONSHIP TO GASTRIC PH.

J.E. Crabtree, G.R. Davies, S. Perry, J.J. Wyatt, F. Pechl, I.J.D. Lindley. Departments of Clinical Medicine and Pathology, St. James’s Hospital, Leeds, U.K. and Sandoz Research Institute, Vienna, Austria.

Purpose: The gastric mucosal production of IL-8, a neutrophil activating and chemotactic cytokine, and IgA autoantibodies to IL-8 is increased in Helicobacter pylori (HP) infection. IL-8 is acid stable but should be subject to proteolytic degradation if secreted luminally. The aims of this study were to determine if free IL-8 and IL-8/IgA immune complexes are present in gastric juice, their relation to H. pylori infection and gastric juice pH.

Methods: At endoscopy, gastric juice samples from 11 dyspeptic patients were collected into protease inhibitors and immediately frozen. Gastric juice pH was measured; following neutralisation to pH 7, free IL-8 and IL-8/IgA immune complexes were measured by ELISA. HP status was determined histologically on antral and corpus biopsies.

Results: In patients with gastric juice pH < 4, free IL-8 concentrations in HP+ and HP- patients were not significantly different, median (interquartile range (IQR)) being respectively 0.02 ng/ml (IQR 0 - 0.14) (n = 41) and 0.023 (IQR 0 - 0.21) (n = 37). In patients with gastric juice pH > 4, free IL-8 in HP+ (0.40 (IQR 0.12 - 1.49, n = 18) and HP- (0.48 (IQR 0.12 - 2.80, n = 15) was significantly greater (p < 0.002) than concentrations in patients with pH < 4. In patients with pH > 4, 10/15 HP+ (68%) and 7/18 (38%) of HP- were on acid suppressant drugs. IL-8/IgA immune complexes were detected significantly more frequently in both HP+ (70%) and HP- (71%) patients with gastric juice pH > 4 than those with pH < 4 (HP+, 15%; HP-,18%).

Conclusions: In hypochlorhydric states, either atrophy-associated or pharmaceutically induced, concentrations of free IL-8 in gastric juice are increased. This may reflect reduced proteolytic degradation of IL-8 at high pH or a reduction in gastric juice volume. The presence of complexes of IL-8/IgA in gastric juice suggests local IgA IL-8 autoantibodies may limit free bioactive IL-8.

ADOPTIVE TRANSFER OF HELICOBACTER-SPECIFIC LYMPHOCYTES ENHANCES INFLAMMATION IN MICE.

M. Mohammadi, R. Redline, S. Czin, J. Nedrud, Institute of Pathology and Department of Pediatrics, Case Western Reserve University, Cleveland, OH U.S.A.

We have previously shown that Helicobacter felis infection and or immunization induces a systemic cellular immune response in mice. This response was concordant with the inflammation observed in the gastric mucosal surfaces. In order to further characterize the role of Helicobacter-specific cellular immune responses, these lymphocytes were adoptively transferred to naive recipients which were subsequently challenged with H. felis.

Results: Groups of mice which received lymphocytes from H. felis infected or H. felis immunized/challenged mice demonstrated enhanced gastric inflammation as compared to the recipients of naive lymphocytes.

Conclusion: Helicobacter-specific lymphocytes induced by infection or immunization may contribute to disease pathogenesis but not to prevention of infection upon transfer.

GASTRIC JUICE NITRATE AND HELICOBACTER PYLORI INFECTION.

B. Melichar, R. Karlicek, J. Bures, O. Komarkova, S. Rejchrt and B. Fixa. Second Department of Internal Medicine, School of Medicine, and Department of Analytical Chemistry, School of Pharmacy, Charles University, Hradec Kralove, Czech Republic.

While the concentration of nitrate in gastric juice has been studied extensively, the reported results showed considerable variation. Nitrate was long thought of solely as an environmental carcinogen, and only recently it was demonstrated that nitrate is synthesized in important quantities by mammalian cells. Nitrate represents a metabolite of nitrite, a molecule associated with numerous functions in cell regulation and defence, and an elevation in nitrate levels in body fluids was linked to some pathological conditions. We have investigated nitrate concentrations in gastric juice obtained during endoscopic examinations of 49 patients referred for dyspeptic complaints. Nitrate was measured by an injection analysis using the Oiris reaction after reduction of nitrate to nitrite by cadmium. The presence of H. pylori was determined in all patients by urease test.

Nitrate concentrations were significantly higher in patients with biliary reflux (96.9 ± 89.8 vs 50.0 ± 53 μmol/l, Mann-Whitney test, p < 0.005). While same levels of nitrate were observed in H. pylori positive and negative patients in the whole group (70.9 ± 58.6 vs 77.2 ± 112.9 μmol/l), nitrate was significantly higher in infected patients with biliary reflux (96.1 ± 52.4 vs 0 μmol/l, p < 0.001). In fact, nitrate levels were bellow detectability limit (16.1 μmol/l) in all 4 H. pylori negative patients without bile contamination.

The present data indicate that biliary reflux could account for the divergence of the results of studies on gastric juice nitrate levels. When bile contamination is excluded, high nitrate levels appear to be linked to H. pylori presence, reflecting probably increased nitrite oxidation produced by inflammatory cells in this infectious disorder. Elevated gastric juice nitrate represent one possible explanation of the carcinogenic effects of H. pylori infection and biliary reflux.

ANTIGASTRIC AUTOANTIBODIES IN HELICOBACTER PYLORI GASTRITIS. PREVALENCE, IN SITU BINDING SITES AND POSITIVE CORRELATION WITH GASTRIC ATROPHY AND HYPERGASTRINEMIA.

G. Fallier, H. Steininger, Th. Kirchner. Institute of Pathology, University of Erlangen-Nürnberg, Germany.

A special feature of Helicobacter pylori (HP) gastritis is the chronic bacterial antigen persistence in an acquired MALT, which might meet some of the requirements for an initiation of antigastric autoimmune reactions.

Patients and Methods: Gastric biopsy samples of 60 patients were examined histologically. Sera of all patients were screened for IgG-antibodies to HP using an ELISA and for autoantibodies to human gastric mucosa by immunohistochemistry. Gastrin levels were measured using a radioimmunoassay kit (GASK-FR³). Results: HP-colonization and serological evidence for HP-infection could be found in 38% and 53% of patients respectively. The prevalence of antigastric autoantibodies in microscopically confirmed HP-colonization and in sera with positive HP-ELISA reached 54% and 56% respectively. One binding site was localized in the cytoplasm and at the luminal membrane of foveolar and glandular epithelial cells. This staining pattern was found in 14 cases, 10 of which were also positive for antibodies against HP. A second binding site was detected at the canaliculi within parietal cells. The canalicular autoantibodies showed advanced or atrophic changes in the corpus, four of them suffered from type B gastritis and three from type A gastritis. Only three of the 43 patients (7%) without these antibodies showed equivalent alterations. Furthermore, 10 patients showed high gastrinemia, which could be explained by type A gastritis in three patients and by pretreatment with omeprazole in further three patients. All of the four remaining cases with hypergastrinemia had anti-canalicular autoantibodies associated with HP-gastritis.

Conclusion: Antigastric autoantibodies occur in about 55% of cases with HP gastritis. Autoantibodies to canaliculi within parietal cells are correlated with antibodies to HP as well as with atrophic changes and hypergastrinemia. Thus antigastric autoimmune reactions might contribute to the pathogenesis and clinical complications of HP-gastritis.
IMMUNOREACTIVE MOLECULES ON GASTRIC MUCOSA. DOES H. pylori, AND SPECIFICALLY CagA+ STRAINS INFLUENCE ITS EXPRESSION?
Department of Gastroenterology, Hospital la Princesa, U.M. Madrid, Spain.
*Department of Medicine, Vanderbilt University, Nashville, Tennessee U.S.A.

The adhesion interactions of cells with other cells and with the extracellular matrix play a central role in the function of the immune system. The aim of our study was to analyze the expression of a variety of cell-surface adhesion receptors in the gastric mucosa and their H. pylori interaction. H. pylori infection, specifically by CagA(+)/CagA(-) strains, induces up or down-regulation in the expression of some of these molecules, affecting in this way the development of an immune response in the gastric mucosa. Material and methods: Fifty four patients were included in the study. HP was found in 64.8% of them (19 chronic gastritis(CG), 6 duodenal ulcers (DU) and 10 gastric ulcers (GU)), and HP negative in 35.2% of them (3 healthy individuals, 12 CG, 1 DU and 3 GU). HP infection was defined when at least two of the following tests were positive: histological examination, rapid urea test, and C13-urea breath test. ELISA to detect antibodies to CagA protein in the serum was performed in 29 of the 35 HP positive patients (14 CG, 6 DU and 13 GU). ELISA was performed by using a fragment of the recombinant CagA protein of HP expressed on E. coli as antigen. Gastric antrum crypt sections were processed by immunoperoxidase staining. Monoclonal antibodies used were: anti-VLA-4, -Integrins, anti-ICAM-1, -anti-ELAM-1, and anti-VCAM-1.

Results: VLA-4 was expressed by macrophages and lymphocytes in all 54 samples independently of HP status. However, lamina propria lymphocytes (LPL) differentiated from macrophages by morphological criteria, showed a strong expression of this molecule in 72% of cases when HP was present but only 20% of cases in HP negative individuals (p=0.001). Within HP+ group, VLA-4 expression by LPL is slightly higher in those patients CA+ (78%) than in those patients CA- (57%). ICAM-1 was constitutively expressed by endothelial cells and lymphocytes from follicles. Expression of this molecule appeared in a 24% of cases, most of which (64%) are infected by HP. ELAM-1 is expressed by activated endothelial cells, has been detected in a 45% of individuals CA+, while just a 15% of patients CA- show endothelial staining. Spread ELAM-1+ lymphocytes by the whole lamina propria appear in all the cases. VCAM-1 is expressed by no structure in healthy mucosa, but staining can be detected on follicles sometimes in lamina propria macrophages.

In conclusion, there is an enhancement of immunological molecule expression molecule in gastric mcosa of patients with HP infection, specifically by CagA+ strains. This suggests that the CagA+ strains are highly immunogenic and can induce more release of cytokines that up-regulates the expression of immunological adhesion molecules.

PLASMA LEVEL OF POLYMORPHONUCLEAR LEUKOCYTE ELASTASE IS RELATED TO THE DEGREE OF HELICOBACTER PYLORI-ASSOCIATED GASTRITIS. L. Escalante, S. Snider, G. Barbl, P. Safran, L. Perez-Perez-INTERNATIONAL GASTROENTEROLOGY SERVICE, S. Anna Hosp., Como, Italy; *ECONUM, VILLeneuve d’Aqosc, France.

The aim of the present study was to attempt to establish a relationship between plasma polymorphpohuclear leukocyte elastase (PMN-E) and gastric mucosal inflammation associated with Helicobacter pylori (HP). Plasma PMN-E complex with a 1 proteinase inhibitor was assessed by Elisa method (K. Merck AG, Germany) in 28 patients with non-ulcer dyspepsia (18 HP +ve and 10 HP -ve) and in 10 HP-negative healthy controls. Six antral biopsies were taken in each patients. Three of them were used for determination of mucosal hexosamine content and expressed as the amount of hexosamine over the mucosal tissue dry weight. The remaining three were sent for histological grading of gastritis. As compared to healthy control, plasma PMN-E complex level was significantly higher in gastritis group (p<0.001). Further, a direct relationship appeared between PMN-E level and gastritis score (r: 0.78, p<0.01). Within gastritis group, PMN-E level was significantly higher when CagA+ strain was present by AgNOR-analysis (1.41 ± 1.29 vs 0.209.212.7, p<0.01). Accordingly, hexosamine level was significantly lower in HP +ve than in HP -ve and in controls (p<0.05). When plotting PMN-E on AgNOR-staining of biopsies, the patients showed a significantly higher ratio as compared to HP -ve (p<0.05).

These results suggest that HP-related infiltration of neutrophils of gastric mucosa brings about a significant PMN-E release with hexosamidagnegation.

TIME-COURSE OF BISTOLATING CHANGES IN HELICOBACTER PYLORI (H.p.) ASSOCIATED GASTRITIS DURING THE EARLY PHASE OF CURE THERAPY WITH OMEPRAZOLE (OM) AND AMOXYCILLIN (AMOX) IN DUodenal ULCER PATIENTS (DU)
J. Heiz, 'K. Plein, M. Stolze, ' Clinic of Gastroenterology, General Hospital Gelle, Institute of Pathology, Klinika Bayreuth, Germany

Gastritis (formerly eradication) of H. pylori was studied by appearance of both H.p. and activity (granulocyte infiltration) and decrease in the degree of gastritis when estimated at the endpoint of 4 - 6 weeks after cure therapy. However, the dynamic of these mucosal changes is not known. We therefore investigated the time course of histological mucosal changes in short intervals during and after H.p. cure therapy.

Methods: 12 pat.(9 male,mean age 38 ± 9) with acute duodenal ulcer were treated with IM (40 mg twice daily ± AMO 1,5 mg twice daily. Multiple arterial, fundic and duodenal biopsies were taken at the first endoscopy (day 0) as well as subsequent endoscopies on d 3,7,14,28 and 42, resp. in which the density of H.p. colonization, the level of activity and the extent of gastritis were graded on a scale of 0-4 (Gastroenterology 1992 10:1-12). In addition, urea breath and the diameter of ulcers until complete healing were assessed. + ( file test, urea)

Results: In the 12 pat. all ulcers were healed after 14 days. The initially positive urea test was negative in 11 pat. on d 3 and in 1 on d 7 and was again positive in 2 pat. on d 28 and d 42. resp.(4,p<0.01, cure rate of 83%). In the H.p cured pat. (n=10) the density of H.p. fell to zero in 7 pat. on d 3 and in 3 pat. on d 7. Mean score of activity of gastritis in the antrum was reduced by 56% on d 3 and 92% on d 7, while there were only slighter reduction rates in the body of gastritis (table 1). Similar changes were seen in the fundic and duodenal biopsies.

Mean Score
<table>
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<th></th>
<th>d0</th>
<th>d3</th>
<th>d7</th>
<th>d14</th>
<th>d28</th>
<th>d42</th>
</tr>
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<tr>
<td>Gastritis activity</td>
<td>2.70</td>
<td>1.20</td>
<td>0.22</td>
<td>0.23</td>
<td>0.22</td>
<td>0.13</td>
</tr>
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</table>

Conclusions: In HP-positive gastritis in DU pat. cure therapy with OM plus AMOX leads to a rapid fall in both HP density and activity of gastritis in the antrum and body within the first 3 to 7 days under therapy while the reduction in the degree of inflammation is more delayed and of a lesser extent.

(Density of inflammation with lymphocytes and plasma cells)

EVALUATIONS OF INFLAMMATORY, METAPLASTIC, PRENEOPLASTIC AND NEOPLASTIC CHANGES IN THE GASTRIC SURFACE EPITHELIUM BY THE AGNOR-METHOD
H. Steininger, G. Fallier, U. v. Streltzb, Th. Kirchner
Institute of pathology, University of Erlangen-Nürnberg, Germany

Recent reports indicate that intestinal metastasis type (IM) II might be interpreted as a reactive process to inflammation whereas intestinal metastasis type III (IM III) should rather be classified as dysplasia. We looked into this question by means of the AgNOR-technique.

Materials and Method: The study was based on 90 antral biopsies and included specimens from normal mucosa, different degrees of active chronic Helicobacter pylori (H.p.)-gastritis (gastriis-I), H.p.-colonized ulcer border, IM I and IM III (colonic type), dysplastic lesions (mild, moderate, severe, dysplasia II-II) and gastric carcinomas (intestinal and diffuse type after Laurin). Sections were AgNOR-stained and AgNOR-values were determined by a Texture-Analysis-System; average AgNOR number per cell, average size of the individual AgNOR-dot, entire AgNOR area per cell and the AgNOR quotient (AgNOR number divided by the average size of the individual AgNOR-dots). Mann-Whitney U-Test was applied to identify independence of individual groups. Mean values of the groups were used for cluster analysis according to Ward.

Results: Average AgNOR number per cell and AgNOR quotient increased stepwise from normal mucosa to carcinoma revealing significant differences between normal mucosa and gastritis II, as well as within the subsequent inflammatory changes. Ulcer border and IM I showed about the same values and differed distinctly from the relatively homogeneous dysplasia group which included IM III. Carcinoma II-II is characterized by the highest AgNOR-values and can be significantly different from the dysplasias. The average size of the individual AgNOR-dots decreased from normal mucosa to carcinoma, the entire AgNOR area increased slightly. Cluster analysis basing on the mean values of all parameters resulted in four clusters: 1) normal mucosa, of H.p.-gastritis II-II and ulcer border and IM I-3) IM III and dysplasia II-II -4) carcinomas of the intestinal and diffuse type.

Conclusions: A stepwise process from normal mucosa through inflammatory, metaplastic, dysplastic to neoplastic changes can be well demonstrated by AgNOR-analysis. This analysis reveals IM III to be a dysplastic lesion.
GLYCOPROTEIN SYNTHESIS IN H. PYLORI GASTRITIS

A. Hackelberger *, D. Tiana *, K. Baczaiko *, M. Nilius *, P. Maletzker *, * Dept. of Gastroenterology, University of Magdeburg, Germany, # Institute of Pathology, University of Ulm, Germany.

Glycopen synthesis and secretion of gastric epithelial surface mucous cells (SMC) is altered in chronic gastritis depending on activity of inflammation and grade of gastritis.

Aim of this study: To investigate glycopen synthesis of SMC in relation to Helicobacter pylori (HP) infection and activity of gastritis.

Material and methods: Antral mucosal biopsies of 16 patients with HP positive gastritis and of 10 patients without infection were examined. Three biopsy specimens were processed for histology (HE + Whartin-Starrry) with grading of activity and rapid urease test; four additional biopsies were incubated for 0, 2, 4 and 6 hours at 37°C, 9% CO2, in Trowell’s T8 culture medium, supplemented with FCS and D(+)-glucosamine (0.185 mg/mL). The incorporation of D(+)-glucosamine as a precursor in mucus glycoprotein synthesis was investigated in histological sections by autoradiography. Labelled glycoproteins were quantified by counting grains per 100 SMC. The time dependent AsC was calculated by subtracting the background (0 hours).

Results: The D(+)-glucosamine incorporation rate in HP infected versus non-infected mucosal biopsies was different (p < 0.05). There was no further increase in D(+)-glucosamine incorporation with a higher degree of gastritis activity (tab.).

Conclusion: H. pylori infected active antral gastritis is characterised by an increased glycopen synthesis of surface mucous cells. This may be due to either the release of reactive, inflammatory mediators, or to bacterial virulence factors.

LYMPHOCYTIC GASTRITIS IN A 10-YEAR FOLLOW-UP.

S. Niemiä, T. Karttunen, T. Kerola & R. Karttunen. Dept. of Internal Medicine, University Hospital of Oulu and Dept of Pathology and Medical Microbiology, University of Oulu, Finland.

Lymphocytic gastritis (LG) is an inflammatory process of the gastric mucosa of unknown etiology and significance. We examined the course of LG and its relations to H. pylori infection in a 10-year follow-up. Gastroscopies with stepwise biopsies were performed on 96 patients initially in 1981 and after an interval of 10 years. 9 % of the patients (9/96) had features of LG in their gastric biopsies at the first examination and 12.5 % (12/96) at the second examination. 7 out of 9 patients (78%) had persistent LG during the follow-up. 5 patients had a new diagnosis of LG at the second examination. 9 out of 12 LG patients (75 %) at the second examination were H. pylori-positive histologically, while all had specific antibodies to H. pylori. The LG patients had significantly higher grade of corpus gastritis (p = 0.009) than the non-LG H. pylori-positive patients. The appearance of LG during the 10-year interval was associated with a significant increase in the grade of corpus gastritis (p = 0.043). During the follow-up, the LG patients, but not the non-LG H. pylori-positive patients, appeared to have a significant increase in the grade of intestinal metaplasia in the corpus mucosa (p = 0.043). The results suggest that H. pylori causes in some patients a gastritis that predominates in the corpus and is associated with an increase in the intraepithelial lymphocyte count. This particular form of gastritis may promote the progression of intestinal metaplasia.

GASTRIC AND INTESTINAL MOTILITY IN RATS EXPERIMENTALLY INFECTED WITH "GASTROSPIRILILUM SUIS".

I. Duval-Aturu*, H. P. Sebela*, A. Sgouros*, A. P. Barros*, Laboratory of Research in Bacteriology and Dept. of Surgery*, Facultade de Medicina/UFMG, Belo Horizonte, Brazil.

It was demonstrated that the antral somatostatin contents are decreased in patients. Taking into account that this hormone is involved in the gastric motility, we evaluated the gastrointestinal motor response in animals infected with "Gastrospirillum suis", a bacterium recently included in Helicobacter genus. We studied gastric body, duodenal and jejunal segments obtained from 22 rats divided into five groups: without infection (A), and 4 (B), 8 (C), 16 (D) and 56 days after inoculation per os of gastric mucus obtained from a "G. suis"-positive pig. The motor response of gastric, duodenal and jejunal segments to acetylcholine was evaluated in an organ bath by a dose-response curve to acetylcholine. The parameters available in dose-response curve were threshold dose, maximum contraction, and affinity (pD2). They were compared by multivariate analysis (Newman-Keuls) and paired t test.

There was a decrease in threshold dose in gastric body in groups D (p = 0.001) and E (p = 0.027) when compared to the control group. The maximum contraction was also different in group D (p = 0.048). The affinity of the muscle receptor to agonist was increased in only group E (p = 0.036) in duodenum. In duodenum there was a difference in threshold dose in all infected animals when compared to the control group (group B, p = 0.008; C, p = 0.024; D, p = 0.024; E, p = 0.024). The multivariate analysis of maximum contraction showed differences between the groups (p = 0.04), but in respect to affinity, there was no difference between the groups in duodenum. The jejenum, the threshold dose decreased in groups C (p = 0.0001), D (p = 0.0001) and E (p = 0.002) but other parameters were not different among the groups.

In conclusion, the gastric infection of rats with "G. suis" changes the gastric motor pattern in response to acetylcholine. These alterations may be related to alterations in hormonal secretion induced by bacteria in the stomach.

Financial support: CNPq - Brazil.

COMPARISON OF IMMUNOHISTOCHEMISTRY AND HISTOLOGY FOR THE DIAGNOSIS OF HELICOBACTER PYLORI INFECTION AFTER TREATMENT.


There is no consensus on the best method to diagnose Helicobacter pylori (H pylori) infection after treatment.

The aim of this study was to compare the value of immunohistochemistry (IHC) and histology for the diagnosis of H pylori infection after treatment.

Material and methods: 86 H pylori infected patients (positive urease test and histology) were studied during four weeks (Lansoprazole D1-D4) + one or two antibiotics D1-D4). At day 56, all patients were evaluated for the presence of H pylori: they had two antral and two fundic biopsies for histology (using HE and cresyl violet stains) and for IHC (using a polyclonal antibody, DAKO). 40471), one antral biopsy for culture, one antral biopsy for polymerase chain reaction (PCR) and a C13 urea breath test.

Results:

- IHC was positive in 27 cases and negative in 59 cases.
- Histology was positive in 28 cases and negative in 58 cases.
- In 83 cases, IHC and histology gave concordant results.
- Two patients had positive histology and negative IHC, and one patient had negative histology and positive IHC. In these three cases, culture, PCR and C13 urea breath test were positive.

Conclusion: Histological examination is specific (100%) and sensitive (96%) for the diagnosis of persistent H pylori infection after treatment. IHC allows to arise the sensitivity level to 100%. IHC could be useful after treatment to assert H pylori eradication, when histology is negative.
FREQUENCY OF ANTRAL INTESTINAL METAPLASIA AFTER H. PYLORI ERADICATION IN DUODENAL ULCER PATIENTS. J I Wyatt, C W Warren, Histopathology Dept. St. James’s Hospital, Leeds, L9 7TF.

Eradication of H. pylori results in improvement of histological gastritis, but it is unclear whether intestinal metaplasia is reversible in these circumstances.

301 patients with duodenal ulcer who were enrolled into two trials of Omeprazole 20mg qid (4 weeks) and clarithromycin 500mg tid (2 weeks) vs. Omeprazole 20mg qid (4 weeks) and clarithromycin placebo (2 weeks) had repeat endoscopy by biopsy 4-6 weeks post treatment; 227 were re-biopsied at 6 months post treatment and 64 at 12 months. H. pylori status was assessed by urea breath test, histology and bacteriology. The gastritis in paired antral biopsies from each of these endoscopies was graded by the Sydney System.

Intestinal metaplasia (IM) occurred usually as small isolated foci in 100/602 biopsies from 73/301 (24%) patients at initial endoscopy; its detection is very dependent on sampling error. The number of biopsies showing IM at follow-up is shown in the table.

<table>
<thead>
<tr>
<th>4 wks</th>
<th>6 mins</th>
<th>12 mins</th>
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<tr>
<td>HP +ve</td>
<td>IM no IM</td>
<td>IM no IM</td>
</tr>
<tr>
<td>HP -ve</td>
<td>38 202</td>
<td>27 179</td>
</tr>
<tr>
<td>p*</td>
<td>0.46</td>
<td>0.07</td>
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There was no trend for the grade of IM in decrease in patients rendered Hp negative. The relative proportions of complete and incomplete IM did not alter.

We conclude that focal IM is relatively common in the antrum of DU patients; this large study showed a trend towards reduction in IM following Hp eradication, but this was not statistically significant.

THE SPECTRUM OF GASTRITIS IN ZAMBIAN PATIENTS WITH AIDS. R.M. Genta, H. El-Zimaity, H.M. Malaty, H.B. DuPont, A. Steephana, I.L. Reijman, C. Chintu, VAMC, Baylor College of Medicine, University of Texas School of Medicine, Houston, Texas, and University of Zambia, Lusaka, Zambia.

Background: Several reports from different parts of the world have indicated that AIDS patients may have a lower prevalence of H. pylori seropositivity than the general population. Few histopathologic studies have been performed and have yielded conflicting results.

Objectives: To compare the prevalence of H. pylori infection and the histological features of gastritis in two Zambian populations of similar socio-economic condition but differing for HIV-positive status.

Methods: Patients presented at the Lusaka University Hospital with diarrhea or other gastrointestinal complaints. 68 HIV (+) and 48 HIV (-) patients underwent upper endoscopy. Two antral biopsy specimens were sent to Houston, where they were processed, and stained with the Genta stain. Activity, chronic inflammation, atrophy, intestinal metaplasia, and the density of Hp were assessed using a previously described 6-point visual analog scale.

Results: H. pylori was detected in 40 of 48 HIV-negative subjects (83%) and in 19 of 68 AIDS patients (29%) (p<0.0001). The features of Hp-gastritis were different in AIDS patients and in HIV-negative subjects: AIDS patients had greater mononuclear cell responses (p<0.06), fewer lymphoid follicles (p<0.01), and a greater prevalence of intestinal metaplasia (32% vs. 10%; p<0.05). Neutrophilic infiltration was similar in the two groups of patients. Among Hp-negative subjects, the prevalence of intestinal metaplasia was 8% in AIDS patients and 25% in HIV-negative patients.

Conclusions: These results indicate that Hp-gastritis has different histopathologic features in AIDS patients and that it is likely that AIDS, rather than antibiotic usage, makes the gastric environment inhospitable for Hp. Furthermore, in light of the low and inconsistent relationship between Hp and intestinal metaplasia in these and other groups of patients, the causal relationship between Hp and the development of intestinal metaplasia should be re-evaluated.

BLOOD LEUKOCYTES IN H. PYLORI INFECTION. T. J. Karttunen, S. Niemelä, T. Kerola. Departments of Pathology and Internal Medicine, University of Oulu, Oulu, Finland

Systemic effects of Helicobacter pylori infection were characterized by quantitating different types of leukocytes in peripheral blood and relating their amount with mucosal inflammation.

Methods: Endoscopy with stepwise biopsies was performed on 96 dyspepsia patients (mean age 62 years, range 49-80) consisting of 40 males and 56 females. Occurrence of H. pylori was studied from sections stained with Warthin-Starry. Severity of inflammation including amounts of neutrophils, eosinophils and mononuclear cells in antral and body mucosa was estimated. Peripheral blood leukocyte count and differential count were determined with automatic flow cytometric method.

Results: Table shows the means and ranges of blood leukocyte counts in H. pylori positive and negative patients.

<table>
<thead>
<tr>
<th>Total leuk. (x10^3)</th>
<th>Neutrophils (3.3-16.6) ns</th>
<th>Lymphocytes (2.2-7.5) 0.008</th>
<th>Eosinophils (0.2-0.9) ns</th>
<th>Monocytes (0.4-2.0-8) ns</th>
<th>Basophils (0.06-0.6) 0.003</th>
</tr>
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<tbody>
<tr>
<td>Hp pos. (n=58)</td>
<td>6.5  (3.3-9.6) 0.02</td>
<td>5.7  (2.2-10.2)</td>
<td>3.2  (1.1-6.7)</td>
<td>1.8  (0.9-3.3)</td>
<td>0.3  (0.1-0.7)</td>
</tr>
<tr>
<td>Hp neg. (n=38)</td>
<td>7.0  (3.3-9.6) 0.02</td>
<td>7.2  (2.2-10.2)</td>
<td>3.2  (1.1-6.7)</td>
<td>1.8  (0.9-3.3)</td>
<td>0.3  (0.1-0.7)</td>
</tr>
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</table>

Among all subjects the total number of blood leukocytes showed a significant correlation with numbers of mucosal eosinophils (R=0.2) and mononuclear cells (R=0.2). Numbers of blood basophils correlated with those of mucosal neutrophils (R=0.2).

Conclusions: Results indicate that mucosal inflammation in H. pylori gastritis is reflected in the amount of peripheral blood leukocytes. Significant increase of blood basophilic leukocytes suggests involvement of allergic mechanisms in H. pylori gastritis.
ANTIBODIES TO CAG A PROTEIN IN PATIENTS WITH H. PYLORI INFECTION AND ATROPHIC GASTRITIS.

I. Beales, J.E. Crabtree*, A. Covacci**, J. Cailar. Departments of Medicine, Hammersmith Hospital, London & St. James's University Hospital, Leeds *. I.R.I.S., Siena, Italy **.

Introduction: Strains of H. pylori (Hp) which express the 128–140 kDa product of gene cagA appear to be more likely to cause duodenal ulcers (DUs). A recent report shows that such strains are also associated with gastric cancer. These findings are interesting but remain controversial. Atrophy and intestinal metaplasia (IM) are regarded as important precursor steps in gastric carcinogenesis. Therefore, we examined the prevalence of serum IgG antibodies to the CagA protein in our infected patients with (i) DUs, (ii) atrophy ± IM or (iii) neither of these.

Methods: Hp infection was diagnosed by at least two positive results from culture, histology, rapid urease or 13C-ulcer breath test. The presence of atrophy ± IM was assessed on 3 antral and 3 corpus biopsies. Serum IgG antibodies to CagA protein were measured by ELISA using a recombinant fragment of CagA. Results were expressed as ELISA units (0–100), the cut–off for positivity being 7.5 units.

Results: Antibodies to CagA were detected in 57/103 (56%) of patients with proven active Hp infection compared to 3/43 (6.9%) without infection. Antibodies to CagA were significantly more prevalent in the groups with active DUs (15/20: 75%) (p<0.05), and IM (34/39: 86.9%) (p<0.05) or gastric ulceration (5/5: 100%) (p<0.05) than in those with chronic gastritis without ulcer nor atrophy ± IM (13/40: 32.5%).

Conclusions: These findings indicate that an immunological response to CagA is associated with the development of atrophic gastritis as well as gastrointestinal ulceration. Testing for antibodies to CagA may identify individuals at high risk of developing ulcers or cancer, who particularly merit therapy.

HELICOBACTER PYLORI INFECTION INFLUENCES ON THE GASTRIC ACID SECRETIONS

R.Kodama, T.Fujisaka, M.Tokioka, T.Kubota, K.Murakami, M.Nasu, Second Department of internal Medicine, Oita Medical University, 1–1 Hasama–machi Oita, 879–35, Japan

It is widely accepted that H. pylori infection associated with atrophic gastritis that is thought to be the precursor of gastric carcinoma. However, it is unclear the relationship between H. pylori infection and gastric acid secretions. We investigated the persistence of H. pylori infected Japanese monkeys to clarify the relationship between H. pylori infection and gastric acid secretions. 13 Japanese monkeys (6 monkeys as infected group, 7 monkeys as control group) were used in this study. Endoscopic mucosal resection (EMR) in the pyloric area and fundic area were performed to all monkeys. The atrophic changes of pyloric area was evaluated from the proprial glandular height using EMR specimens. The function of gastric acid secretion were evaluated from the number of parietal cells in fundic gland using EMR specimens. Endoscopic Congo–Red test was performed to evaluate the changes in the area relating gastric acid secretions. Gastrin levels after meal–stimulation were compared with both group.

Results:Proprial glandular height in the pyloric areas significantly decreased (p<0.05) in infected group over 1.5 years after inoculation with H. pylori. The average number of fundic cells in fundic area decreased (p<0.05) over 2 years after inoculation with H. pylori. Gastrin levels after meal–stimulation were significantly higher (p<0.05) in infected group than control group. The changes in the area of gastric acid secretions grossly was reduced over 3.5 years after inoculation with H. pylori.

Conclusions: These results suggest that the persistent colonization with H. pylori caused atrophic gastritis, and it reduced gastric acid secretions.

HELIcobacter pylori GASTRITIS WITH CYTOTOXIN ASSOCIATED PROTEIN ANTIBODIES (CagA) IN A POPULATION AT HIGH RISK FOR GASTRIC CANCER: A SEMIQUANTITATIVE AND COMPUTER AIDED MORPHOLOGICAL STUDY.

L.Baldini, F.Bonvicini, S.Pretolani, N.Figura, L.Cogliandro, G.Capiati, G.Epifanio, A.Armutzzi, C.Fasanello, P.Miglio G.Gazzarini, I Patolgie Medica, Universita di Bologna, I Patologia Medica, University of Siena, Dept. Int. Medicine, Catholic University, Rome, and Dept. Int. Medicine, Malpighi Hospital, Bologna, Italy

The cytotoxin-associated gene A (CagA) protein is required for the pathogenic activity of cytotoxin H. pylori strains. High titer of antibodies to CagA protein were reported in patients with peptic ulcer and gastric cancer. Gastritis is supposed to be a precursor step for the development of these lesions. Aims: to study the prevalence of atrophic gastritis in H.pylori CagA +ve patients with respect to CagA -ve ones and to evaluate other possible morphological differences as well. Methods: 107 subjects were randomly selected from a representative sample of a population at high risk for peptic disease and gastric cancer (San Marino Study I); 78 were H.pylori positive and 29 were negative. A blood sample was taken for anti-CagA detection. Mucosal biopsies were taken from gastric antrum and corpus and processed for the histopathological study. The following parameters were graded: 0–3: inflammation, activity, atrophy, intestinal metaplasia; mucosal associated lymphoid tissue (MALT) was also evaluated. A computerized image analysis system was used to evaluate the inflammatory infiltration of lamina propria in a selected number of patients (28). Statistical analysis was made with Mann–Whitney test and Chi-squared test, when appropriate. Results: Antibodies to CagA were found in 35/78 H.pylori positive patients (48%). Atrophic gastritis was found in 12/29 CagA +ve patients and in 64% of negative ones (n.s.). Inflammation and activity are significantly higher in CagA +ve gastritis vs CagA -ve ones (p<0.05 and p<0.005, respectively). Intestinal metaplasia was in 30% of CagA +ve patients and in 12% of CagA -ve ones (n.s.). No difference was found as far as MALT in concerned. The computerized image analysis confirms the semi-quantitative data. These data show that CagA+ve gastritis is associated with a higher grade of mucosal lesions with respect to CagA-ve gastritis. Further studies are needed to verify the role of cytotoxic strains in the development of atrophy.
GLANDULAR Proliferation and homeostasis of specific cells are differentially affected in gastric corpus and antrum in HELICOBACTER PYLORI (HP) induced gastritis.

T. Vorgólová, G. Hurlimann2, A. Zimmermann1, L. Varga1, R. Ulibo1, F. Hatarn1, Department of Immunology, University of Tartu, Estonia1, Gastrointestinal Unit and Institute of Pathology2, University Hospital, Bern, Switzerland.

Epidemiological studies have identified an association between HP and gastric carcinoma. Epithelial cell proliferation is an indicator of risk for adenocarcinoma. We aimed to assess the effect of HP on gastric epithelial cell proliferation and on homeostasis of specific cells. In addition we were interested in the expression of the apoptosis protector oncogen protein, bcl-2, which is in a major role of follicular lymphomas of the gastrointestinal tract and in a few MALT lymphomas, whereas the latter is associated with HP infection.

Methods: In 57 patients (28 HP+ve, 29 HP-ve) antrum and corpus biopsies were analysed for HP-density, inflammatory changes and immunostaining for PCNA, Ki-67, bcl-2 oncogene, beta-H2, K-ATPase, gastrin and somatostatin. In the antrum and corpus five gastric mucosal glands were divided for analysis into upper, middle and lower section. Results were expressed as gastritis score, mean values of labelling (LI) and density of the cells.

Results: In contrast to the antrum, there was a significant correlation between CNLI and Ki-67 LI and the gastritis score (r=0.25, p=0.0016) in the corpus. This also applied to the relation between Ki-67 LI and the HP-density in corpus glands (r=0.32; p=0.04). Bcl-2 positive epithelial cells were seen in antrum and corpus but predominantly in HP+ve cases. HP+, K-ATPase positive parietal cells were reduced in gastritis as a function of disease severity, antral G- and D-cells, in relation to degree of HP-density.

Conclusion: Our data suggest that HP-induced corpus, but not antral gastritis is in part associated with an increase of HP. Upregulated epithelial cells from programmed cell death in gastritis. Prolonged hyper proliferation and reduced apoptosis of the gastric epithelium exerted by HP infection could be a major contributing factor for human gastric carcinogenesis. Homeostasis of antral G- and D-cells appears to be directly governed by HP whereas loss of parietal cells mix is more of a degenerative process.

HELICOBACTER PYLORI AND GASTRIC CANCER: AN ENDOSCOPIC SURVEY OF HEALTHY CHILDREN IN HIGH AND LOW RISK AREAS FOR GASTRIC CANCER IN CHINA.

Y. Lu, P. Hu, D.J. Liu, H. Li, M. Chen, S.L. Hazi, H.M. Mitchell, A. Lee and the First Municipal People's Hospital of Guangzhou, P. R. China, Sun Yat-sen University of Medical Science, P. R. China, Military General Hospital of Beijing, P. R. China. University of New South Wales, Australia.

We have performed endoscopically an epidemiologic survey on 353 healthy children in a high risk area (Anmal County, Guangdong Province) and a low risk area (Chonghua County, Guangdong Province) for gastric cancer (GCA) to investigate the relation between Helicobacter pylori (HP) and GCA. Students in one school each were randomly selected. Each subject underwent interview, serum collection (HP IgG antibody) and endoscopy. Biopsy specimens were taken from the antrum and body for histology and urease testing. HP was considered positive by histology plus serology or urease test. Hp incidence was as follows:

GCA risk (death rate) 7-8 yrs 9-10 yrs 11-12 yrs Total
High risk (54/100,000) 35/79(44%) 26/66(39%) 38/104(37%) 99/212(52%)
Low risk (3/100,000) 10/39(26%) 13/38(34%) 39/104(38%) 62/181(34%)

Endoscopic findings in two areas were different. There were 2 cases of duodenal ulcer in each group, and 14 cases of chronic gastritis in high risk and 13 in low risk area. Histological features of HP associated gastritis were shown in following table:

<table>
<thead>
<tr>
<th>Hp (+) gastritis</th>
<th>High risk (n=89)</th>
<th>Low risk (n=62)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation: antrum</td>
<td>89/89 (100%)</td>
<td>62/62 (100%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>antrum + blymph</td>
<td>42/89 (47%)</td>
<td>48/62 (78%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Activity</td>
<td>71/89 (80%)</td>
<td>24/62 (39%)</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Atrophy</td>
<td>7/89 (8%)</td>
<td>0/62 (0%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lymphoid follicle</td>
<td>58/89 (65%)</td>
<td>24/62 (39%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

We conclude that: in high risk area for GCA, Hp incidence in children is significantly higher (p<0.05) and approaches adults' levels at 8-9 years of age with mucosal atrophy proceeding. Early acquisition of Hp may play important role in the development of GCA.

EVALUATION OF LARGE GASTRIC FOLDS IN PATIENTS WITH HELICOBACTER PYLORI INFECTION BY ENDOSCOPIC ULTRASOUND BEFORE AND AFTER ANTIBIOTIC THERAPY.

C. Avuduk, F. Navab, F. Hamp, B. Coughlin. Deps. of Radiology and Pathology, Baystate Medical Center, Springfield, MA

Large gastric folds may result from infectious, inflammatory, neoplastic, vascular, or infiltrative disorders involving a part or the entire gastric wall. Helicobacter pylori (HP) infection of the gastric mucosa is associated with an active gastritis characterized by mucosal edema and infiltration of the submucosa and submucosal with neutrophils, eosinophils, macrophages, and lymphocytes. The purpose of the study was 1) to study patients with large gastric folds noted on computed tomography (CT), upper gastrointestinal series (UGI), or endoscopy with endoscopic ultrasound (EUS) and biopsies to determine the prevalence of HP infection and the intrinsic location of the gastric wall thickening; 2) to re-examine HP infected patients with EUS and biopsies after antimicrobial therapy to determine if resolution of the wall thickening accompanied eradication of HP. Methods: 32 patients with HP positive gastric folds were studied. 18 patients were found to have HP infection and were treated with amoxicillin 1 gm BID and omeprazole 40 mg BID x5 days. One month after antimicrobial therapy patients were re-examined by EUS and gastric biopsies were obtained. Results: 1) 18/12 patients had HP infection and gastritis. 2) In the HP infected group EUS demonstrated diffuse thickening of the inner 3 layers (mucosa-luminal, muscularis, and submucosa) without thickening of the 4th and 5th layers of the gastric wall. 3) Following antimicrobial therapy EUS demonstrated concomitant resolution of this gastric wall thickening and normalization of layers 1-3. Conclusions: HP associated gastritis is a common cause of large gastric folds and 2) EUS allows measurement of the gastric wall thickening and documents the resolution of this wall thickening upon eradication of HP and resolution of gastritis.

HELICOBACTER HELLMANNII INFECYON AND PRIMARY GASTRIC LOW-GRADE MALIGNT Lymphoma: A Case Report


Background: Recent data have linked chronic Helicobacter pylori infection with the development of a primary gastric low-grade malignant lymphoma (Parsonnet et al., NEJM 1994; 330:1126 - 1130). Case report: We diagnosed a 79 year old female patient having a 2 cm large flat polypoid lesion of the right gastric wall, and the histological examination revealed a primary gastric low-grade MALT lymphoma and a chronic gastritis associated with Helicobacter hemllmannii colonization (Heilmann & Borchard, Gut 1991; 32:137-140). Aim of the study was to investigate whether elimination of the H. hemllmannii infection may lead to regression of the MALT lymphoma. Results: The diagnosis of MALT lymphoma was confirmed histologically by detection of typical lymphoepithelial lesions. Treatment with omeprazole 40 mg tid and aspirin 750 mg tid, both for 14 days lead to complete regression of HP gastric colonization and endoscopic regression of the tumor after 4 weeks at the first post-treatment endoscopic examination. Molecular DNA analysis using PCR detected monoclonal B-cells before treatment which disappeared at the time of complete histological tumor regression. Conclusion: The data suggest that there may exist a link between H. hemllmannii infection and development of primary gastric low-grade MALT lymphoma, and that the MALT lymphoma itself may completely regress after elimination of H. hemllmannii infection.