ΠΡΟΣΚΕΚΛΗΜΕΝΕΣ ΞΕΝΟΓΛΩΣΣΕΣ ΑΝΑΚΟΙΝΩΣΕΙΣ ΕΛΛΗΝΩΝ ΕΡΕΥΝΗΤΩΝ

● *HELICOBACTER PYLORI* SPECIFIC ANTIBODY RESPONSES IN PATIENTS WITH PRIMARY BILIARY CIRRHOSIS

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Introduction: *Helicobacter pylori* (*Hp*) has been postulated as a trigger of primary biliary cirrhosis, characterised by disease-specific antimitochondrial antibody (AMA) responses against members the 2- oxo-acid dehydrogenase complex (OADC) of enzymes and in particular pyruvate dehydrogenase complex E2 subunit (PDC-E2). We have previously identified a remarkable amino acid similarity between the major PDC-E2 epitope and urease B of *Hp* but we have failed to demonstrate crossreactive immunity amongst the respective antigenic epitopes (Scan J Gastroenterol 2004).

Aims & Methods: We have hypothesised that if *Hp* is instrumental for the development of PBC-specific AMA, *Hp* antigens unrelated to urease B may indeed initiate cross-reactive immune responses to PDC-E2 or other AMA specific OADCs. The study included 100 PBC patients (all AMA positive), 100 demographically matched pathological controls and 30 healthy controls (all AMA negative). Serum samples from PBC patients and controls were tested for reactivity to individual mitochondrial antigens by immunoblot using a mitochondrial subfraction from human liver extract and by ELISAs using the major OADC recombinant antigens, namely PDC-E2, BCOADC-E2 and OGDC-E2. The fine specificity to *Hp* antigens was investigated by immunoblot using *Hp* extracts.

Results: Reactivity to at least one *Hp* antigen was present in 84 (84%) PBC patients, 87 (87%) pathological controls and 27 (90%) healthy controls. There was no correlation between individual mitochondrial bands immunofixed by PBC sera and specific reactivity to *Hp* antigens. Patterns of reactivity to individual *Hp* antigens did not differ between PBC patients, pathological and healthy controls. Absorption studies using individual mitochondrial antigens as solid phase inhibitors have failed to absorb out antibody reactivity to *Hp* antigens. Pre-incubation of PBC sera with *Hp* extract abolish reactivity to individual *Hp* antigens but did not have any effect on reactivities to PBC-specific anti-mitochondria antibody responses.

Conclusion: Anti-*helicobacter* antibody responses in patients with PBC do not possess a distinct pattern to those found in other pathological conditions. While present in PBC patients, anti-*Hp* antibody responses do not cross-react with PBC-specific anti-mitochondrial antibodies indicating that molecular mimicry and immunological cross-reactivity is most unlikely involved in the pathogenesis of the disease.

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● RELATIONSHIP BETWEEN *H. PYLORI* INFECTION AND DIABETES MELLITUS: A META-ANALYSIS

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Background: Diabetes mellitus (DM) has a multifactorial etiology, with both host genetic elements and environmental factors playing a role in its development.

Aims: The aim of this study was to examine the role of *Helicobacter pylori* infection in diabetes mellitus by meta-analyzing all relevant studies.

Methods: Extensive English language medical literature searches for human studies were performed up to the end of April 2008, using suitable keywords. Pooled estimates [odds ratio (OR) with 95% confidence intervals (CI)] were obtained using the random effects model. Heterogeneity between studies was evaluated with the Cochran Q test, whereas the likelihood of publication bias was assessed by constructing funnel plots. Their symmetry was estimated by the adjusted rank correlation test.

Results: Eighteen studies, from various countries (9 studies for DM type I and 9 studies for DM type II) examined *H. pylori* infection in patients and controls. For DM type I, the pooled OR with 95% CI was 1.246 (0.815–1.905) and the test for overall effect Z was 1.016 and $p=.31$. The respective values for DM type II were 1.876 (1.316–2.675), $Z=3.476$, $p=.001$.

Conclusion: The results of this meta-analysis showed different relationships of *H. pylori* infection to DM type I and DM type II, stressing possible pathogenetic diversity between these two types of DM.

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● COULD THE ADDITION OF NARROW BAND IMAGING TO HIGH RESOLUTION MAGNIFICATION ENDOSCOPY BE OF ADDITIONAL VALUE IN THE IDENTIFICATION OF NORMAL GASTRIC MUCOSA, *H. PYLORI* INFECTION AND GASTRIC ATROPHY?

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Introduction: We have recently shown that high resolution magnification endoscopy [HRME] can reliably identify normal gastric mucosa, gastric atrophy and *H. pylori* associated gastritis based on the recognition of a honeycomb-type subepithelial capillary netwotk [HTSECN] in gastric body with regular arrangement of collecting venules [Cvs]. Narrow Band Imaging [NBI] is a new technique which by narrowing the light wave length, enhances the microvascular and microstructural architecture in gastrointestinal mucosa.

Aims & Methods: The aim of the study was to examine if the addition of NBI to HRME can also be an endoscopic tool in diagnosing the above mentioned conditions. A total of 100 consecutive dyspeptic patients [53 men, mean age 53.2 years] underwent gastroscopy with the Olympus GIF Q160Z magnifying endoscope with NBI. The gastric body was examined first with conventional endoscopy followed by HRME with and without NBI. With both techniques the magnified endoscopic findings were categorized into 3 types: type 1, HTSECN with regular arrangement of CVs; type 2, HTSECN but loss of CVs; and type 3, loss of HTSECN with irregular arrangement of CVs. The quality of the magnified images based on the ability to distinguish the CVs/SECN was classified during the endoscopy as 1. moderate 2. good and 3. excellent. 4 biopsy samples were obtained for histological analysis and 2 for CLO test. Targeted biopsies were taken from areas with type 3 pattern. Patients with *H. pylori* seen at histological examination or who were CLO+ were considered to be *H. pylori*+.

Results: The sensitivity, specificity, positive and negative predictive values of type 1 [for predicting the normal gastric mucosa]; type 2 [for predicting the *H. pylori* positive stomach] and type 3 [for predicting gastric atrophy] with and without NBI [p = ns] are shown on the table. There were 2 cases where HRME showed a type 2 mucosa, but NBI visualised Cvs [type 1], and a case where HRME showed only *H. pylori* infection but NBI visualised areas of gastric atrophy. The quality of the images were better when HRME was combined with NBI [2.95 vs. 2.37 p <0.01].

TABLE 1:

		Sensitivity	Specificity	PPV	NPV
Type 1, normal mucosa	HRME	94.3	96.5	98.5	87.5
	HRME+NBI	97.1	96.4	98.5	93.3
Type 2, *HP*	HRME	96.5	94.3	87.5	98.5
	HRME+NBI	100	97.2	97.2	93.3
Type 3, atrophy	HRME	93.3	100	100	98.8
	HRME+NBI	100	100	100	100

Conclusion: The combination of HRME with NBI seems to be superior to HRME in the identification of the normal gastric mucosa, *H. pylori* associated gastritis, and gastric atrophy. Further larger studies are needed in order to confirm this finding.

Reference: Anagnostopoulos GK, Yao K, Kaye P, et al. Endoscopy 2007;39:202-7.

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● HIGH-RESOLUTION MAGNIFICATION ENDOSCOPY WITH NARROW BAND IMAGING RELIABLY IDENTIFIES NORMAL GASTRIC MUCOSA, *HELICOBACTER PYLORI*-ASSOCIATED GASTRITIS AND GASTRIC ATROPHY

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Introduction: Although histology is considered to be the gold standard for detecting *H. pylori* infection and gastric atrophy, the reliability of histological detecting *H. pylori* depends on several factors and the Sydney system identifies only half of the cases with confirmed gastric atrophy.

Aims & Methods: The aims of the study were to describe the magnified endoscopic findings with Narrow Band Imaging [NBI] in the gastric body, correlate these with histology, and evaluate their reproducibility. A total of 100 consecutive dyspeptic patients [53 men, mean age 53.2 years] underwent gastroscopy with the Olympus GIF Q160Z magnifying endoscope with NBI. The findings were categorized into 3 types: type 1, honeycomb-type subepithelial capillary network (HTSECN) with regular arrangement of collecting venules [CVs]; type 2, HTSECN but loss of CVs; and type 3, loss of HTSECN with irregular arrangement of CVs. The quality of the magnified images based on the ability to distinguish the CVs/SECN was classified during the endoscopy as 1. moderate, 2. good and 3. excellent. 4 biopsy samples were obtained for histological analysis and 2 for CLO test. Targeted biopsies were taken from areas with type 3 pattern. Patients with *H. pylori* seen at histological examination or who were CLO+ were considered to be *H. pylori* +. In the second part of the study, 120 images were shown [twice with 1 week interval] to 3 endoscopists in order to examine inter- and intraobserver variability in image assessment.

Results: 69/70 patients with type 1 pattern corresponded to an *H. pylori*-negative, nonatrophic stomach (type 1 vs. types 2/3, $P < 0.001$). All 15 patients with type 3 findings had gastric atrophy on targeted biopsies (atrophic vs. nonatrophic mucosa $P < 0.001$). 28/30 cases with type 2 findings corresponded to an *H. pylori* + stomach. Of the 2 patients with type 2 findings and an *H. pylori*-negative stomach, all had areas with gastric atrophy, possibly indicating missed infection. The sensitivity, specificity, and positive and negative predictive values of: (A) type 1 for predicting normal gastric mucosa were 97.1% (89.2-99.5), 96.5% (80.3-99.8), 98.5% (91.2-99.9), and 93.3% (76.4-98.8), (B) type 2 for predicting a *H. pylori*-infected stomach were 100% (84.9-100), 97.2% (89.4-99.5), 93.3% (76.4-98.8%), and 100% (93.5-100) and (C) type 3 for predicting gastric atrophy were all 100%. The quality of the images was almost excellent [2.95/3]. The kappa values for inter- and intraobserver agreement in predicting histology were 0.89 and 0.94 respectively.

Conclusion: High-resolution magnification endoscopy with NBI can reliably identify the normal gastric mucosa, *H. pylori* associated gastritis, and gastric atrophy.

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● CagA PROTEIN PHOSPHORYLATION IN *H. PYLORI* INFECTED GASTRIC EPITHELIAL CELLS MAY BE RELATED WITH REDUCED FAK ACTIVATION AND INCREASED PYK2 ACTIVITY

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Introduction: Src-dependent phosphorylation of *Helicobacter pylori* CagA protein on repeating EPIYA motifs may be contributing to perturbation of focal adhesions of gastric epithelial cells. We describe herein, the effect of CagA phosphorylation on focal adhesion kinase (FAK) and proline-rich tyrosine kinase (Pyk2) activation in gastric epithelial cells following infection with *H. pylori* clinical strains isolated from gastric biopsies.

Methods: CagA, FAK, Pyk2 expression was detected in total lysates of AGS cells infected over 36 hours with pairs of isogenic *H. pylori* strains expressing CagA protein with variable numbers of EPIYA motifs (2 or 3, 3 or 4, and 3 or 5). Tyrosine phosphorylated proteins were detected by Western blotting following immunoprecipitation with antiphosphotyrosine antibody. Levels of activated phospho-Tyr-397FAK were assessed by a specific antibody against Tyr-397 autophosphorylation site.

Results: Following *H. pylori* infection of AGS cells in vitro, CagA species harboring more EPIYA phosphorylation motifs exhibited higher levels and rates of tyrosine phosphorylation, accompanied by a time-dependent decrease in Tyr-397FAK phosphorylation in three of four isogenic pairs. Total tyrosine-phosphorylated levels of FAK were also marginally reduced as a result of *H. pylori* infection. A concomitant time-dependent increase in tyrosinephosphorylated Pyk2 levels as well as increased Pyk2 degradation was observed.

Conclusions: CagA time-dependent EPIYA-phosphorylation may be accompanied by reduced levels of FAK autophosphorylation at Tyr-397 and total phospho-FAK. A concomitant increase in Pyk2 activation may reflect functional compensation for the loss of FAK activity. *H. pylori* infection during its initial stages may be related with cagA-dependent deregulation of FAK activity in focal adhesions.

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● CagA PROTEIN DIVERSITY WITH RESPECT TO EPIYA PHOSPHORYLATION MOTIFS IN *H. PYLORI* INFECTED CHILDREN – RELATION TO HISTOPATHOLOGY

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EPIYA tyrosine phosphorylation motifs (TPMs) *A*:EPIYAKVNK, *B*:EPIYAQVAKK and *C*:EPIYATIDDLG in CagA protein of *Helicobacter pylori*, and in particular the presence of increasing numbers of repeating C-motifs has been linked to heavier cagA dependent pathogenicity in adults. Our aim was to assess whether EPIYA diversity was related to the severity of histopathology in a pediatric population. Clinical isolates from children (n=94, mean age 10.7 years old ± 0.3) were analyzed by amplification and sequencing of the 3' variable region of cagA gene. Empty-site-cagA PCR was used for the detection of cagA-negative strains. Clonal relatedness was analyzed by RAPD PCR and MLST analysis. *H. pylori* colonization and associated gastritis was evaluated by the modified Sydney system.

Eighty-one cases (86.2%) were found to be single-strain infections, with 39.5% being attributed to *cagA*-negative strains. CagA-positive strains harbored one or two EPIYA-C repeats (46.9% and 13.6%, respectively,) whereas no strains with more than two repeats were detected. In 13 cases, mixed isolate infections were observed with simultaneous presence of *cagA*-negative and -positive clones with one and two EPIYA repeats, derived from microevolution of the initial infecting *H. pylori* strains. Histological analysis revealed marked chronic inflammatory infiltration in 39 cases (42.9%) and marked chronic active gastritis (n = 7, 7.7%) in the antrum. No significant positive association was observed between EPIYA diversity, levels of *H. pylori* colonization, or the grade and severity of associated gastritis in the antrum. Thus, EPIYA diversity in CagA protein is not related to histopathological parameters in infected children. However, no strains with more than two EPIYA-C repeats were observed.

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● IS *HP* ERADICATION NECESSARY IN MORBID OBESE PATIENTS PRIOR TO LAPAROSCOPIC ADJUSTABLE GASTRIC BANDING (LAGB)?

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Background: Laparoscopic adjustable gastric banding (LAGB) is considered as a safe and efficient restrictive bariatric procedure. However, the necessity of prior *HP* eradication in these patients in relation to the short and long-term tolerance of the operation to be undertaken remains unclear.

Aim of the study: To investigate if the *HP* status affects the short and long-term tolerability of LAGB in morbid obese patients.

Patients-Methods: Thirty morbid obese patients (median BMI 45, range 35–55), 25 female, 5 male, age range 20–61 year were studied. All had failed in various, previous methods and attempts of weight loss. In all patients upper GI endoscopy was performed during the preoperative assessment and the *HP* status was evaluated with a rapid urease test. All patients were postoperatively followed-up daily in the first 7 days after LAGB placement and monthly thereafter for a median of six months.

Results: Endoscopy revealed hiatal hernia (12 pts, 40%), gastritis (9 pts, 30%), oesophagitis (6 pts, 20%), small gastric erosions (1 pt, 3.3%) and was unremarkable in 7 patients (23.3%). Nine patients were tested *HP* positive (30%) whereas twenty-one negative (70%). All patients (100%), independently to their *HP* status, experienced only mild upper gastrointestinal symptoms postoperatively, necessitating no further treatment. During the follow up period (median 6 months, range 1–24 months), 6 patients (20%) developed severe gastroesophageal reflux symptoms with 2 patients being *HP* positive.

Conclusion: *H. pylori* status does not seem to significantly affect tolerability of LAGB and, therefore, prior eradication is probably not justified.

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● A LYOPHILIZED FORM OF S. BOULARDI ENHANCES THE EFFECT OF PPI-TRIPLE THERAPY IN PATIENTS WITH ORGANIC OR FUNCTIONAL DYSPEPSIA

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Aim: To assess whether the addition of a probiotic enhances the efficacy of classic omeprazole-triple therapy.

Methods: Seventy patients were included in a prospective, randomized, controlled, investigator-blind trial. Eligible patients had *H. pylori* infection as evidenced by positive CLO-test and histology on gastric biopsies. Exclusion criteria were aspirin/NSAID use, GORD, and chronic liver disease. Patients were randomly assigned to treatment with Ultralevure® caps tid for 14 days (1 capsule contains 50 mg of live cells of Saccharomyces boulardii in lyophilized form) [stratum A, n = 36] or no treatment (stratum B). All patients received generic omeprazole (20 mg bid), klarithromycin (500 mg bid) and amoxicillin (1 g bid) for 14 days. Eradication of *H. pylori* was assessed by UBT 6 weeks later.

Results: At baseline there were no significant differences between strata in age, gender, BMI, smoking, underlying disease (peptic ulcer or non ulcer dyspepsia), and prior treatments. *H. pylori* was eradicated in 30/36 (83%) patients in stratum A versus 20/34 (59%) in stratum B ($p = .034$). Three patients in stratum A and 7 in stratum B stopped treatment for adverse effects; this was associated to diarrhoea in 4/7 patients in stratum B and one patient in stratum A. No systemic infection with S. boulardii was identified. Multi-factorial analysis did not reveal any patient or disease related parameter associated with favorable outcome of treatment except from use of probiotics.

Conclusion: S. boulardii enhanced the effect of a classic PPI triple therapy; this was at least in part the result of prevention of antibiotic- and PPIs-induced diarrhoea.

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● WHAT CUMULATIVE *H. PYLORI* ERADICATION RATES CAN BE ACHIEVED IN CLINICAL PRACTICE BY ADOPTING FIRST, SECOND AND THIRD LINE REGIMENS PROPOSED BY THE MAASTRICHT III CONSENSUS?

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Background: The European Helicobacter Study Group (EHSG) convened the third Maastricht Consensus conference, to review and to update guidelines on the management of *Helicobacter pylori* (The Maastricht III Consensus Report 2005). The guidelines cover indications for therapy, management and treatment strategies.

Aim: To examine the cumulative *H. pylori* eradication rates which can be achieved in clinical practice by adopting first, second and third line treatment regimens as proposed by the Maastricht III consensus.

Methods: *H. pylori* positive patients were treated initially with a first line eradication triple regimen consisting of Omeprazole, Amoxicillin, Clarithromycin (O+A+C) and subsequently with a second line quadruple regimen consisting of Omeprazole, Bismuth, Metronidazole and Tetracycline (O+B+M+T). Finally, after two previous *H. pylori* eradication failures, patients received Omeprazole, Ampicillin and Levofloxacin (O+A+L) as a third-line empirical strategy. The success rate was calculated by both intention to treat (ITT) and per protocol (PP) analyses.

Results: 540 consecutive *H. pylori* positive patients received the first line treatment (O+A+C). *H. pylori* was eradicated in 380 patients and 40 patients were withdrawn (ITT 70.3%, PP 76%). The remaining 120 *H. pylori* positive patients received the second line treatment (O+B+M+T). *H. pylori* was eradicated in 83 patients and 7 patients were withdrawn (ITT 69.1%, PP 73.45%). Finally the remaining 30 *H. pylori* positive patients received the third line treatment (O+A+L). *H. pylori* was eradicated in 21 patients and 0 patients were withdrawn (ITT 70%, PP 70%). Thus, out of 540 patients initially included in the study *H. pylori* was eradicated in 484 patients, 47 were withdrawn and only 9 remained positive. These results give 89.6 % ITT and 98.1 % PP cumulative *H. pylori* eradication rates.

Conclusion: By adopting first, second and third line regimens, as proposed by the Maastricht III consensus, high cumulative *H. pylori* eradication rates can be achieved. Thus a substantial number of cultures to determine sensitivity to antibiotics can be avoided with beneficial consequences concerning cost.

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