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PP1

DIETARY AND LIFESTYLE RISK FACTORS IN THE ETIOLOGY OF GASTROESOPHAGEAL REFLUX DISEASE, BARRETT ESOPHAGUS AND ESOPHAGEAL ADENOCARCINOMA

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Over the past three decades, incidence rates for esophageal adenocarcinoma (EADC) have increased steadily in North America. We conducted a 2-year prospective case-control study to test the hypothesis that dietary and lifestyle factors contribute to susceptibility for progression to EADC. We also studied patients with the precursor lesion, Barrett's esophagus (BE), and with clinically symptomatic gastroesophageal reflux disease (GERD), a well recognized risk factor associated with BE and EADC. Between 02/2001 and 02/2003, a total of 431 individuals were enrolled, with informed consent, in a hospital-based case-control study. Cases comprised patients with GERD (n=142), BE (n=130), and EADC (n=57), defined according to stringent clinicopathologic criteria. Controls comprised 102 healthy, strictly defined asymptomatic individuals from the same geographic region. For each participant, a 102-point structured questionnaire was administered, including sociodemographic information, family and medical history, body mass index (BMI), and lifestyle risk factors including tobacco and alcohol consumption, dietary intake and physical activity. The importance of dietary and lifestyle risk factors in GERD, BE and EADC was calculated using multivariate logistic regression. Obesity was independently associated with a significant increased risk for EADC (OR, 4.67; 95% CI, 1.27-17.19). Diets with high vitamin C content decreased the risk for GERD (OR, 0.40; 95% CI, 0.19-0.87), BE (OR, 0.44; 95% CI, 0.20-0.98), and EADC (OR, 0.21; 95% CI, 0.06-0.77). Multivitamin supplementation additionally reduced the risk of EADC (OR, 0.17; 95% CI, 0.03-0.90). For the more established risk factors, we confirmed that smoking was associated with increased risk for EADC (OR, 3.86, 95% CI, 1.23-12.10), and that increased alcohol (liquor) consumption was a risk factor for GERD (OR, 2.69; 95% CI, 1.05-6.92) and BE (OR, 3.06; 95% CI, 1.23-7.62). We conclude 1) that obesity, cigarette smoking and increased consumption of liquor are significant predictors of risk for progression of GERD and BE to EADC, and 2) that increased dietary vitamin C and multivitamin supplementation may be protective and reduce the risk for progression to EADC in this patient population.

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PP2

TARGETED BIOPSIES AFTER MAGNIFYING ENDOSCOPY ARE SUPERIOR TO RANDOM BIOPSIES FOR DIAGNOSING BARRETT'S ESOPHAGUS: A PROSPECTIVE RANDOMIZED STUDY WITH CROSS OVER DESIGN

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INTRODUCTION: Specialized columnar epithelium (SCE) is considered as pathognomonic for Barrett's esophagus. In contrast to standard video endoscopy, magnifying endoscopy after local acetic acid application enables recognition of the mucosal surface architecture. Thus, the aim of the current prospective study was to investigate the diagnostic yield of magnifying endoscopy with targeted biopsies as compared to 4-quadrant biopsies.

METHOD: Patients with visible columnar lined lower esophagus (CLE) or known Barrett's esophagus were included. After standardized PPI therapy (10 days; standard dosage) patients were randomized at a 1:1 ratio to undergo either magnifying endoscopy in conjunction with acetic acid application (10-15 mL; 1.5%) or standard video endoscopy with 4-quadrant biopsies. Surface structure within CLE was graduated according to Guelrud's classification (type I-II: endoscopic prediction: gastric epithelium; type III-IV: Barrett's epithelium). Biopsies were taken in a targeted fashion. 14 days after the initial endoscopy, all patients were re-examined in a cross over design. Primary outcome analysis was the histological diagnosis of Barrett's epithelium (per biopsy).

RESULTS: 31 patients completed the study protocol (mean length CLE: 3.9 cm; mean age 64.3 years; 20 males). In total it was possible to evaluate 615 biopsies. 335 targeted biopsies after acetic acid application under magnifying endoscopy and 280 biopsies from the random 4-quadrant biopsies. In 188 biopsies, the magnifying endoscopy provided proof of specialized epithelium. 188 Barrett epithelium cases corresponded to a type III and type IV pattern in accordance with Guelrud's classification. In contrast, the pattern I-II confirm in 100% gastral and/or junctional epithelium. By using histology as the main outcome, the sensitivity and specificity if enhanced magniyfing endoscopy for patterns III and IV for detecting Barrett's epithelium were 100% and 64% (accuracy 83%). In 23 of 56 biopsies, pattern III showed Barrett's epithelium. If only the villous and cerebriform type IV is biopsied, the histological diagnosis of the intestinal metaplasia (165/188 biopsies) can be predicted with a sensitivity of 88%

and a specifity of 86% with an accuracy of 87%. With magnification endoscopy and targeted biopsies towards type III-IV lesions, a significant higher percentage of biopsies contained SCE (78%; 188/241) as compared to random biopsies (57%; 159/280) (P<0.001), the significance was even higher comparing only type IV to random biopsies (88% vs. 57%) (P<0.001). Furthermore, using magnifying endoscopy a maximum number of 5 biopsies was necessary to confirm Barrett's epithelium, which was significantly lower as compared to conventional endoscopy (10 biopsies) (P=0.032).

DISCUSSION: Magnifying endoscopy with targeted biopsies is superior to standard video endoscopy with random biopsies in the diagnosis of Barrett's esophagus. The diagnostic yield is significantly better and the number of biopsies needed to definitely confirm Barrett's epithelium is half as much as compared to random biopsies. Furthermore, targeted biopsies did not miss any relevant lesion from endoluminal abnormalities within CLE.

PP3
THE EXPRESSION OF VEGF ON INTESTINAL METAPLASIA AND GASTRIC CANCER IN *HELICOBACTER PYLORI* INFECTION

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Helicobacter pylori (*H. pylori*) infection is one of the causes of gastric cancer. A human gastric carcinogenesis model was proposed in which superficial gastritis is followed by chronic gastritis, intestinal metaplasia, and finally gastric carcinoma. Interleukin-16 (IL-16) is a pleiotrophic cytokine. The properties of IL-16 suggest that it may be involved in pathophysiological process of chronic inflammatory diseases. Vascular endothelial growth factor (VEGF) has been implicated in the growth and metastasis of human cancers.

AIM: The aim of this study is to investigate the expression of VEGF on *H. pylori* infected intestinal metaplasia (IM) and gastric cancer (GC), as well as the effect of *H. pylori* and IL-16 on cell proliferation and VEGF expression in gastric cells in vitro.

METHODS: Gastric biopsies were classified by histological findings as normal, IM, GC with *H. pylori* infection and uninfected normal gastric mucosa. AGS cells were incubated with the combination of IL-16 and *H. pylori*. Gastric epithelial cell proliferation was studied by BrdU uptake. The expression of VEGF was studied by ABC, ELISA and RT-PCR.

RESULTS: There was no significant difference in the expression of VEGF between *H. pylori* infected and uninfected normal mucosa (3.56±2.55% vs 2.48±1.70%, P=0.20). In *H. pylori*-infected mucosa, the expression of VEGF was increased in IM (6.17±1.79%, P<0.001), and GC (4.78±2.70%, P=0.009) than normal mucosa. Co-incubation with IL-16 increased BrdU uptake of AGS cells, which had been decreased by *H. pylori* infection. The administration of IL-16 decreased the expression of VEGF mRNA, which had been increased by *H. pylori*, but administration of IL-16 increased the levels of VEGF protein, which had been decreased by *H. pylori*.

CONCLUSIONS: In the early phase of *H. pylori* infection, IL-16 decreased VEGF expression, but long-term infection with *H. pylori* increased VEGF expression. This VEGF expression may be one of the important factors for gastric cancer induction by *H. pylori* infection, and the expression of VEGF can be a marker for gastric carcinogenesis.

TABLE

%AGS only	*H.pylori* 10^5cfu/mL	*H.pylori*+ IL-16 10^{-9}M	*H.pylori*+ IL-16 10^{-10}M
BrdU uptake	85.19±13.57*	102.80±14.67**	97.82±15.24**
VEGF protein	83.55±11.71*	100.29±22.58**	103.90±25.67**
VEGF mRNA	173.33±18.18*	153.11±15.14**	91.41±19.15**

**significant difference from AGS only; **significant difference between with and without IL-16. P<0.01 was taken as statistically significant*

PP4
EARLY *HELICOBACTER PYLORI* INFECTION IS RELATED TO GASTRIC CANCER RISK IN CHILE, A HIGH-RISK AREA: A POPULATION-BASED STUDY

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Relationship between gastric cancer (GC) and *H. pylori* (HP) infection is controversial. Chile has a high HP infection rate and a high but heterogeneous GC mortality rate, increasing steadily from North to South, and higher for men than for women (Relative risk [RR]: 2.6). Genetics and environmental factors could be involved in these differences.

AIM: To determine if regional variation in HP infection rate helps to explain the geographical differences in GC mortality rate.

METHODS: GC mortality rate (1985-2002) was obtained for all Chilean counties. Adjusted RRs of GC were calculated using a hierarchical Poisson regression model. The RR varied from 0.28 to 2.25. Counties were categorized into two statistically different groups: Counties with higher GC mortality risk (HGC), with a mean (range) RR of 1.25 (1.01-2.25) and counties with lower GC risk (LGC) with a mean (range) RR of 0.85 (0.28-0.99). We studied a population-based random sample of 2609 subjects, older than 17 years, 1302 from HGC and 1307 from LGC. Serum IgG anti-HP antibodies (arbitrary units/mL) and % of seropositivity for HP infection were determined by a previously validated ELISA.

RESULTS: HP infection rate for the whole sample was 73% (95%CI: 70%-76%). Mean (95%CI) anti-HP IgG titers (arbitrary units/mL) was 198.6 (182.4-214.7) and 174.3 (159.2-189.5) in HGC and LGC, respectively (P<0.05). HP infection rate (95%CI) was 79.5% (73.5-82.4) and 68.1% (65.5-74.0) in HGC and LGC, respectively (P<0.05). A significant interaction was observed between age and gender for HP infection rate. HP infection rate in subjects 17 to 24 years old was significantly higher in HGC than in LGC (79.7% vs 46.1%, respectively; P<0.05). The difference was more evident for men (82.8% vs. 43.9%, respectively) than for women (76.5% vs. 48.2%, respectively). HP infection rate was not significantly different comparing HGC and LGC among people above 25 years old. In both HGC and LGC, HP infection rate declined in people over 65 years old. This was more evident in HGC than in LGC, although without statistical significance.

CONCLUSIONS: In Chile, HP infection rate is high in general population. Crude HP infection rate is slightly higher in counties with higher than in counties with lower GC mortality risk. HP infection seems to occur early in life in HGC, especially for men, perhaps increasing the chance to develop premalignant lesions. The age at infection could be as important as the HP infection by itself to determine the risk of GC.

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PP5
PREDICTIVE VALUE OF THE 13-C-UREA BREATH TEST IN THE CHOICE OF SECOND- AND THIRD-LINE ERADICATION OF *HELICOBACTER PYLORI* INFECTION

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BACKGROUND: Urea breath test (UBT) has proved to be one of the most accurate methods for assessing *Helicobacter pylori* (Hp) status. Little is known, however, about the predictive value of this test in the choice of eradication regimens.

AIM: A retrospective follow-up of the change over time of UBT values after successive treatments in patients with eradication failures.

METHODS: One-hundred thirty-four patients with duodenal ulcer whose Hp infection persisted (confirmed by UBT) after first-line therapy were enrolled in a cross-over study to receive either 2×40 mg pantoprazole + 2×1000 mg amoxicillin + 2×500 mg clarithromycin or 2×400 mg ranitidine bismuth citrate + 2×500 mg metronidazole + 2×500 mg clarithromycin for 7 days. Forty-one patients with failed second-line treatment were randomized to receive third-line quadruple therapies with pantoprazole, amoxicillin (in the doses given above) and 4×500 mg tetracycline and either 3×100 mg nitrofurantoin or 4×120 mg bismuth subsalicylate. In all groups, UBT was performed 6 weeks after the end of the eradication. The UBT values were arranged in series according to the first, second and third-line therapy, and succes of failure of the given therapy. Differences were assessed by the ANOVA test. The correlation between the pre-treatment UBT values and rate of Hp eradication was assessed by the Spearman's rank order test. UBTs were performed by using il all caes the same isotope-selective infrared spectrometer. Values >4 delta over baseline (%0 DOB) were considered as positive and no pre-defined grey-zone was used.

RESULTS: In patients with successful second-line eradication, UBT values decreased from 12.4 DOB (confidence interval 95%. CI: 9.7-15.7) to l.8 (CI: 0.9-2.5) (P=0.00l); in those with persistent infection, they increased from 13.2 (CI: 7.3-19.1) to 19.2 (CI: 13.4-25.00) (P=0.03). After quadruple regimens, UBT decreased in successfully cases from 16.2 (CI: 13.4-19.6) to l.3 (CI 0.8-1.8) (P=0.00l) and increased from 19.3 (16.3-22.4) to 25.8 (19.8-31.8) in failures (P=0.04). There was a negative correlation either in case of the second- and third line regimens between the pre-treatment UBT values and rates of eradication (r=0.23 and r=0.26, respectively).

CONCLUSIONS: Serial assessment of the UBT values after successive eradication regimens showed a progressivwe increase over tike in failed cases. The significance of this phenomenon must be further studied (ongoing antimicrobial resistance? increased colonosation? other?). Pretreatment UBT values would predict the success/failure of the subsequent therapy: UBT values over 15%0 DOB were associated with unacceptably low rates of eradication, regardless of the regimens used and these patients need more effective therapeutic schedules, not yet included in the current recommendations.

PP6
GASTRIC ULCER: INFLUENCE OF ENDOSCOPIST EXPERTISE IN SECOND-LOOK GASTROSCOPY COST/BENEFIT ANALYSIS

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AIM: Once a gastric ulcer is diagnosed as benign, we routinely perform a second gastroscopy to definetively discharge malignance. Data concerning cost/benefit of this second endoscopy are scant. The aim of this study is to determine the obtained clinical benefit and the cost of the second look endoscopy performance, analyzing the possible influence of endoscopist expertise.

MATERIAL AND METHODS: Gastric ulcers diagnosed in our Unit in a three year period (2001-2003) were reviewed. Ulcerated tumors were not included in the study. We determined diagnostic accuracy for malignancy of the first and second gastroscopies, including endoscopic biopsies. We calculated the number of necessary second look endoscopies (NNE) to diagnose a new case of malignant gastric ulcer, and the influence of endoscopist expertise (staff vs. resident). The cost of diagnosing a new case of malignant gastric ulcer was also calculated considering the cost of a gastroscopy in our environment (public medicine=138.8 $; private medicine=252.1 $) and the influence of the endoscopist expertise.

RESULTS: 125 consecutive gastric ulcers were analized. Diagnosis was achieved by a staff endoscopist in 98 cases and by a resident endoscopist in the remaining 27. 22 malignant ulcers and 103 benign ulcers were diagnosed in the first gastroscopy. Diagnostic accuracy of this initial endoscopy was: global=98.4%; staff=98.98%; resident=96.16% (P=n.s.). One case of early gastric cancer and another of low grade MALT lymphoma were diagnosed in the second look endoscopy, reaching 100% of diagnostic accuracy. NNE was: global=62.5; staff=98.04; resident=26.04, and so the cost of a new malignant ulcer was: global in public medicine=8676 $ and in private medicine 15754 $; staff in public medicine=13613 $ and in private medicine=24713 $; resident in public medicine=3616 $ and in private medicine=6564 $.

CONCLUSIONS: 1. In our series, routine second-look gastroscopy in gastric ulcers achieves a diagnostic accuracy of 100% concerning the nature of the ulcer. 2. Second-look gastroscopy only adds 1.02-3.84% to diagnostic accuracy, depending on first endoscopist expertise. 3. NNE and the cost of diagnosing a new malignant ulcer in second-look gastroscopy are influenced by endoscopist expertise. So, concerning cost/benefit, the indication of a second-look gastroscopy is controversial if the initial endoscopy has been performed by an experienced endoscopist.

PP7
CLINICAL RESEARCH ON THE TREATMENT OF CHRONIC HEPATITIS B WITH THYMOSIN-α1 AND LAMIVUDINE VERSUS INTERFERON-α AND LAMIVUDINE

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It has recently been shown that thymosin-α1, a synthetic polypeptide of thymic origin, an immune modifier, is able to promote disease remission and inhibition of hepatitis B virus replication. We evaluated the efficacy and safety of thymosin-α1 and lamivudine treatment compared with interferon-α and lamivudine treatment on the patients with chronic hepatitis B who were difficult to be treated well, failed to lamivudine treatment alone. Eighty-three patients (Age: 18-60) with confirmed chronic hepatitis B and positive for HBV DNA with an elevated ALT of at least two times normal who failed to lamivudine treatment alone were entered into this study. Eighty three patients were randomly assigned to receive either thymosin-α1 1.6 mg SC twice weekly and lamivudine 100 mg p.o daily (group I, N=43) or 5MU of interferon-α three times weekly and lamivudine 100 mg po daily (group II , N=40) for 6 months. At the end of treatment, complete response (defined as ALT normalization and HBV DNA loss) occurred in 11 of 43 (25.58%) in group I and in 22 of 40 (55%) in group II (P<0.01). After a follow up period of 6 months, a complete response was observed in 18 of 43 (41.86%) in group I and 19 of 40 (47.50%) in group II (P>0.05). After a follow up period of 12 months, a complete response was observed in 25 of 43 (58.14 %) in group I and 12 of 40 (30%) in group II (P<0.05) . So thymosin-α1 with lamivudine may be more effective than interferon-α and lamivudine by immunomodulatory effect. Compared with interferon-α and lamivudine, thymosin-α1 and lamivudine are better tolerated and seem to induce a gradual and more sustained ALT normalization and HBV DNA loss. Unlike interferon-α, thymosin-α1 was well tolerated by all patients. The side effect of thymosin-α1 group was rare. The better response was in HBeAg-negative and HBV DNA-positive patients. However such results need to be confirmed with a randomized double-blind study with larger number of patients in the future.

TUESDAY, SEPTEMBER 13

PP8
IMMUNOSUPPRESSIVES AND SURGERY REDUCE RISK OF GI CANCERS IN PATIENTS WITH CROHN'S DISEASE: A CASE CONTROL STUDY

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BACKGROUND AND AIM: An increased risk of colon and other cancers has been reported in patients with inflammatory bowel disease (IBD). Risk factors are considered to be either related to or independent of IBD. We performed a case-control study to investigate several potential risk factors for gastrointestinal (GI) and non-GI cancers in patients with Crohn's disease (CD).

METHODS: Hospital discharge databases at St Michael's Hospital, Sunnybrook and Women's Health Sciences Centre and Mount Sinai Hospital in Toronto, Ontario were searched from January 1993 to May 2003 to identify cases with both CD and any non skin cancer. For each case, two CD controls without cancer were matched for age, gender, site and duration of disease. Medical records of cases and controls were reviewed (by ELS) and data assessing risk factors and describing malignancy were abstracted using a standardized data collection sheet. Binary logistic regression was performed and odds ratios (OR) with 95% confidence intervals (CI) were calculated to identify factors significantly associated with increased or decreased risk of neoplasm.

RESULTS: A total of 1351 CD patients were hospitalized during the 11 year period. Sixty-five patients (4.81%) had one or more malignancies. For 6 cases (9%) only one non-cancer control was available. 37 cancers were of GI origin, with colorectal cancer comprising 41% (N=26) and small bowel cancer 14% (N=9) of malignancies. The most prevalent non-GI malignancies were lung (N=4; 6%), breast (N=4; 6%) and central nervous system (N=4; 6%). Factors associated with a decreased risk of all malignancies included surgical intervention (OR 0.432, 95% CI 0.226-0.826) and azathioprine use (OR 0.386, 95% CI 0.173-0.864). A history of fistula was associated with an increased risk of both GI and non-GI malignancies (OR 1.742, 95% CI 0.831-3.651). When the analysis was restricted to only GI cancers, these relationships became even more robust; fistula, azathioprine and surgery had OR 2.386, 95% CI 0.986-5.772, OR 0.275, 95% CI 0.095-0.796 and OR 0.518, 95% CI 0.222-1.209, respectively. Other risk factors such as smoking, stricture, 5-ASA use and family history of cancer had no significant correlation with malignancy.

CONCLUSION: Patients with CD are at risk for colorectal and small bowel cancer. A history of fistula was positively associated with the development of gastrointestinal cancers. Importantly, the use of azathioprine or surgical intervention, were associated with a lower likelihood of developing GI malignancy. This supports aggressive control of chronic inflammation in IBD as a potential preventive measure for developing GI cancer.

PP9

OXIDATIVE DNA DAMAGE MIGHT BE A HIGH RISK FACTOR OF COLITIC CANCER IN PATIENT WITH ULCERATIVE COLITIS

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Patients with ulcerative colitis (UC) have high incidence of colon cancer, but the mechanism of carcinogenesis is unknown. We previously reported that the 8-hydroxydeoxyguanosine (8-OHdG), the marker of oxidative DNA damage, was high in colonic mucosa from patients with active UC and that the 8-OHdG was decreased by medical therapy. In oxidative DNA damage, 8-OHdG, which causes DNA mutation in vivo and in vitro, is suggested to be a good marker of carcinogenesis. We have followed up eleven patients with active UC for 8 years and found colitic cancer in two of the patients. To elucidate a possible role of oxidative DNA damage in carcinogenesis, we measured levels of 8-OHdG in these patients at present and before 8 years.

METHOD: We compared the amounts of 8-OHdG in the DNA of sigmoid colonic mucosa in eleven patients (9M: 2F) with active UC and a patient with colitic cancer at present and before 8 years. All patients have received mesalazine and prednisolone for 8 years. 8-OHdG in eleven healthy subjects were measured as controls. DNA extraction and digestion were carried out inside an anaerobic incubator EAN-140 (TABAI Espec, Japan) to prepare samples under oxygen-free condition. 8-OHdG levels were detected using high performance liquid chromatographic 8-OHd (HPLC)-electrochemical detection and expressed at the ratio of G/105 deoxyguanosine (dG) (Carcinogenesis 1996;17:787-791).

RESULTS:

TABLE

8-OHdG/10^5dG	
Active UC before 8 years 1.19±0.11	n=9
UC at present 0.79±0.09*	n=9
Colitic cancer before 8 years 1.48±0.06	n=2
Colitic cancer at present 1.36±0.06	n=2
Control subject 0.63±0.06	n=11
(mean±SE)	(*P<0.05 vs before 8 years)

The 8-OHdG levels in patients with active UC significantly decreases after the medical therapy. The 8-OHdG level remains high in the patients developing colitic cancer.

CONCLUSION: Oxidative DNA damage might be a high risk factor of colitic cancer in patient with UC.

PP10

INCREASED EXPRESSION OF THE CHEMOKINE FRACTALKINE IN CROHN'S DISEASE AND ASSOCIATION OF THE FRACTALKINE RECEPTOR T280M POLYMORPHISM WITH A FIBROSTENOSING DISEASE PHENOTYPE

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BACKGROUND: The fractalkine receptor CX3CR1 has been shown to be involved in inflammation and immune response. Recently, we and others (Science 2005;307:254-8) demonstrated that CX3CR1 controls the clearance of entero-invasive pathogens by intestinal dendritic cells particularly in the ileum. Moreover, two polymorphisms of CX3CR1 (V249I and T280M) were reported.

AIMS: Our aim was to analyze fractalkine expression and the role of CX3CR1 polymorphisms in Crohn's disease (CD).

METHODS: We determined fractalkine mRNA expression in the intestinal epithelial cell (IEC) line SW480 after stimulation with proinflammatory cytokines as well as in human biopsies taken from endoscopically inflamed (n=14) and non-inflamed (n=14) CD lesions by semi-quantitative and quantitative PCR, respectively. Using restriction fragment length polymorphism analysis, genomic DNA from 206 patients with CD and 211 unrelated controls was analyzed for the two single nucleotide polymorphisms in the CX3CR1 gene which result in the V249I and T280M substitutions.

RESULTS: All proinflammatory stimuli (TNF-alpha, IL-1beta, LPS) significantly increased fractalkine mRNA expression in IEC between 65- and 150-fold compared to baseline expression levels. In CD patients, fractalkine mRNA levels were significantly increased between 1.3- and 7.9-fold (average 3.4-fold) in inflamed lesions when compared to non-inflamed colonic mucosa (P=0.02). Intestinal fractalkine mRNA levels correlated highly with the IL-8 mRNA expression in inflamed and non-inflamed tissue (r=0.931). IL-8 mRNA expression levels were on average 9.1-fold higher (range 1.4- to 31-fold) in inflamed tissue compared to non-inflamed colonic mucosa. However, no difference in the V249I and T280M genotype frequencies between CD patients and the control group was observed. In the CD group, 33.0% were heterozygous and 8.3% homozygous for the V249I polymorphism, while 23.3% were heterozygous and 4.4% homozygous for the T280M polymorphism. All T280M homozygotes were diagnosed of intestinal stenosis (P=0.03 vs. wildtype and heterozygous carriers) and had significantly more often ileocolonic involvement than patients with wildtype and heterozygous genotypes (P=0.01). Similar trends were found for homozygous carriers of the V249I genotype (P=0.06 for intestinal stenosis; P=0.07 for ileocolonic involvement).

CONCLUSIONS: The mRNA expression of the chemokine fractalkine is up-regulated by proinflammatory cytokines and increased in inflamed CD lesions. The CX3CR1 T280M polymorphism appears to influence CD phenotype and localization as all carriers of the homozygous T280M polymorphism developed intestinal stenoses and showed more frequently ileocolonic involvement.

PP11

ABSENCE OF CHRONIC NITRIC OXIDE PRODUCTION INCREASES THE PREVALENCE OF COLITIS-ASSOCIATED ADENOCARCINOMA AND IS ASSOCIATED WITH ENHANCED CYCLOOXYGENASE-2 EXPRESSION AND ACTIVITY IN INTERLEUKIN-10-DEFICIENT MICE

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INTRODUCTION: In this study, we used interleukin-10-deficient (IL-10$^{-/-}$) mice to examine the role of chronic nitric oxide (NO) produced from inducible nitric oxide synthase (iNOS), in the development of colitis-associated neoplasia and examined the relationship to cyclooxygenase (COX)-2 expression and activity.

METHODS: Wild type (WT; 129Sv/Ev, n=16), IL-10$^{-/-}$ (n=17) or IL-10$^{-/-}$ iNOS$^{-/-}$ (n=21) mice were studied between age of 7.5-9 months. Neoplastic changes were scored according the presence of epithelial hyperplasia, aberrant crypt foci, inflammation, abnormal crypt formation, submucosal invasion of crypts, neoplastic nuclei and adhesions. Real-time PCR was used determine relative expression of p53, β-catenin and COX-2 mRNA. Protein expression was determined by immunohistochemistry. PGE_2 levels were measured using a competitive ELISA in the presence and absence of COX inhibitors. Statistical analysis was performed using ANOVA t test.

RESULTS: Mucosal polyps were observed in 66% of IL-10$^{-/-}$ and involved an average of 5.9±3.1 mm of colon. In contrast, 100% of IL-10$^{-/-}$ iNOS$^{-/-}$ mice presented with polyps which extended 11.4±1.6 mm length of colon (P<0.05). Histological neoplastic scores were significantly higher in IL-10$^{-/-}$ iNOS$^{-/-}$ compared with IL-10$^{-/-}$ mice (P<0.05). 44% of IL-10$^{-/-}$ and 61% of double mutants showed signs of submucosal crypt invasion respectively. No polyps or adhesions were observed in WT mice. No significant increase in p53 and β-catenin mRNA levels was observed in IL-10$^{-/-}$ mice over WT however a two/four fold increase was noted in the double mutants (P=0.062 and P<0.05 respectively). Interestingly an impressive 6-fold increase (P<0.01) in COX-2 message was observed in IL-10$^{-/-}$ iNOS$^{-/-}$ over IL-10$^{-/-}$. A significant increase PGE_2 synthesis was observed in IL-10$^{-/-}$ and IL-10$^{-/-}$ iNOS$^{-/-}$ mice over wild type mice (P<0.05). Indomethacin significantly inhibited PGE_2 synthesis by 88%, 69% and 50% in wild type, IL-10$^{-/-}$ and IL-10$^{-/-}$ iNOS$^{-/-}$ mice respectively. A selective COX-2 inhibitor, NS-398, inhibited PGE_2 synthesis by 21%, 23% and 58% in wild type, IL-10$^{-/-}$ and IL-10$^{-/-}$ iNOS$^{-/-}$ mice respectively illustrating increased COX-2 activity in the absence of chronic NO production.

CONCLUSION: Our data suggest that the absence of chronic NO production increases the incidence of neoplastic changes in IL-10$^{-/-}$ mice possibly through regulation of COX-2 expression.

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PP12

COLORECTAL CANCER SCREENING TEST PREFERENCES: DO DESIRED TEST ATTRIBUTES MATCH REALITY?

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BACKGROUND: Colorectal cancer (CRC) screening rates in Canada remain low despite national evidence-based CRC screening guidelines recommending annual or biennial fecal occult blood testing (FOBT) for those over age fifty.

OBJECTIVES: To determine CRC screening preferences and whether preferred and actual test attributes are congruent.

METHODS: In-depth, in-person interviews were completed with 220 people recruited through an random digit dial survey on CRC screening experiences that included 1808 residents age 50-74 years of Alberta, Canada. For the interviews, subjects were selected to provide a range of previous FOBT screening experience. Subjects were asked which screening test they would prefer to undergo after an explanation of the test procedure but not the accuracy of the test. CRC screening test preferences were grouped into clinic-based test (colonoscopy, sigmoidoscopy, CT colonography) versus home FOBT. Those who did not give a specific test preference were excluded (n=13). Subjects rated test attributes that would increase the likelihood that they would undergo FOBT.

RESULTS: The study sample (n=207) consisted of 52% females and 56% urban residents. For screening, 65% preferred a home FOBT and 35% preferred a clinic-based test (12% colonoscopy, 5% sigmoidoscopy, 18% CT colonography). Gender, urban vs rural residence, marital status and age did not influence test preference (P>0.05). Overall, 47% of subjects had had a previous home FOBT and 43% had had a previous clinic test for either screening or clinical indications. Of those who previously had a clinic test, 60% indicated a preference for a home FOBT for future screening compared with 65% of those who had undergone a previous home FOBT. Among those who stated a preference for FOBT, attributes that would increase the likelihood of carrying through with FOBT screening are shown in the table.

CONCLUSION: Although FOBT appears to be the preferred test, among those stating a preference for FOBT there is a disconnect between the desire for a very accurate test and the true accuracy of FOBT. Providing clear information on test attributes may aid a person's choice of a screening test, but a primary care physician's recommendation may be the most important factor in determining screening test acceptance.

TABLE

I'd be more likely to be tested if the test was...	Agree/strongly agree
Recommended by my doctor	98.7%
Easy to do	81.4%
Recommended by cancer agency	78.7%
Based on the latest technology	73.8%
Very accurate	71.6%
Not a lot of preparation	39.6%

Funding: National Cancer Institute of Canada, MSI Foundation, Alberta Heritage Foundation for Medical Research

PP13

ROSIGLITAZONE HAS AN ANTI-INFLAMMATORY EFFECT BY DECREASING INFLAMMATORY CYTOKINES IN A RAT MODEL OF NON-ALCOHOLIC STEATOHEPATITIS

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OBJECTIVES: Rosiglitazone, an oral PPAR-γ agonist anti-diabetic agent significantly attenuated liver inflammation and ALT elevations in methionine and choline deficient diet (MCDD) model of non-alcoholic steatohepatitis (NASH) in our previous studies. It basically decreased interleukin (IL)-6 in 4 weeks of induction study. We also aimed to assess whether long term use of rosiglitazone could affect inflammatory cytokine levels in MCDD induced NASH model.

MATERIAL AND METHODS: Male Wistar rats were fed with MCDD for 4 weeks. After establishment of NASH, they were divided into 4 groups. Group 1: (n=6) and group 2: (n=6) rats were given MCDD supplemented with choline and methionine, whereas group 3: (n=7) and group 4: (n=7) rats continued to receive MCDD for an additional 8 weeks. Group 2 and 4 were treated with rosiglitazone maleate (10 micromol/bw/d, PO) while group 1 and 3 were given saline, during this 8-weeks period. The liver inflammation was reevaluated quantitatively. Serum IL-1β, IL-6 and tumor necrosis factor (TNF)-α levels were studied with commercial rat cytokine kits.

RESULTS: Supplementation with methionine and choline in (group 1 and group 2) resulted in healing of both steatosis and inflammation, independently of rosiglitazone treatment. Rosiglitazone lowered serum IL-1β, IL-6 and TNF-α and attenuated inflammation scores in group 4 as compared to group 3. The results were summarized in the table.

CONCLUSIONS: MCDD causes NASH. Supplementation with methionine and choline results in complete healing. Concomitant rosiglitazone

administration decreases inflammation component, which may be mediated through decreases in IL-1β, IL-6 and TNF-α levels. (Table. Inflammation scores and cytokine levels in all groups).

(Mean±SD	IL-1β (pg/mL)	IL-6 (pg/mL)	Tumor necrosis factor-α (pg/mL)	Inflammatory foci (n)	Total inflammatory cell (n)
Group 1 (n=6)	524±45	806±54	522±27	0 (0-0)	0 (0-0)
Group 2 (n=6)	501±29	808±55	557±53	0 (0-0)	0 (0-0)
Group 3 (n=7)	730±71	1075±151	564±46	3 (3–5)	55 (27–85)
Group 4 (n=7)	611±56	932±96	515±56	1 (1–4)	14 (5–64)
p (Kruskal -Wallis H)	<0.001	<0.001	0.013	<0.0001	<0.0001
p (3 vs 4)	<0.001	0.001	0.004	0.0379	0.0175

PP14
EXPRESSION OF ADHESION MOLECULES ON MATURE CHOLANGIOCYTES FROM CANALS OF HERING TO INTERLOBULAR BILE DUCTS IN PRIMARY BILIARY CIRRHOSIS

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BACKGROUND AND AIMS: The present study was designed to localize ICAM-1 and lymphocyte function-associated antigen-1 (LFA-1) expression from the interlobular lobular bile ducts to the canals of Hering (CoH) in relation to the autoimmune process of bile duct destruction in (PBC), using immunohistochemical and immunoelectron microscopic studies.

METHODS: We studied ten wedged liver biopsy samples of PBC (5 cases each of stage 2 and stage 3) and five control wedge biopsy specimens of normal portions of liver collected during surgical resection for metastatic liver carcinoma. Anti-ICAM-1 and anti-LFA-1 antibodies were used in immunohistochemistry, and anti-ICAM-1 antibody was used in Western blot. Human ICAM-1and LFA-1 peptide nucleic acid probes were used for in situ hybridization. Immunoelectron microscopy was conducted using immunoglobulin-gold and silver staining methods.

RESULTS: In PBC liver specimens, immunohistochemistry showed aberrant ICAM-1 expression on the plasma membrane of the epithelial cells lining interlobular bile ducts and bile ductules, but not on the hepatocytes in CoH. LFA-1-positive lymphocytes were closely associated with the epithelial cells in bile ductules. ICAM-1 expression at protein level was confirmed by Western blot. Messenger RNA expression of ICAM-1 was demonstrated in the bile ductules, while mRNA of LFA-1 was expressed in lymphocytes infiltrating the bile ductules. By immunoelectron microscopy, ICAM-1 was demonstrated on the basal surface of epithelial cells in the interlobular bile ducts and bile ductules and on the luminal surfaces of cholangiocytes in damaged CoH. In the CoH, some epithelial cells morphologically resembling progenitors were observed, but gold-labeled ICAM-1 and LFA-1 particles were not evident in close vicinity of these cells.

CONCLUSION: De novo expression of ICAM-1 was observed on mature cholangiocytes in the CoH and epithelial cells in the bile ductules in PBC, implying that autoimmune destruction may take place in the intrahepatic biliary system not only in the interlobular bile ducts but also upstream in the CoH, through direct binding of ICAM-1 around cholangiocytes and LFA-1 expressed on the activated lymphocytes.

PP15
CLINICAL UTILITY OF AFP-L3 GLYCOFORM IN RISK ASSESSMENT FOR HEPATOCELLULAR CARCINOMA (HCC) IN PATIENTS WITH CHRONIC HEPATITIS AND CIRRHOSIS

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Hepatocellular carcinoma (HCC) is a major public health concern worldwide largely due to epidemic of hepatitis B and C. Alpha-fetoprotein (AFP) has been used widely in assisting clinical diagnosis of HCC. However, AFP is not an effective tumor marker for early HCC. This is partly due to overlapping expression profiles of the AFP and fluctuating patterns of serum concentration of AFP in chronic hepatitis and cirrhosis. AFP has three glycoforms based on reactivity with lectin, *Lens culinaris* agglutinin (LCA), AFP-L1, L2, and L3. AFP-L1 is the major subspecies of AFP from inflammatory liver cells, AFP-L2 from germ cell tumor such as nonseminomatous testicular carcinoma, and AFP-L3 is the AFP glycoform from malignant liver cell. The structural difference between AFP-L1 and L3 is an additional alpha 1-6 fucose residue on AFP-L3. To determine clinical utility of AFP-L3 in early recognition of HCC in high risk patients, a four-year prospective study of AFP-L3 for risk assessment of HCC has been completed from 2000-2004 in seven major medical centers in North America. Data from 440 patients (89.1%) met criteria for further analysis. Among them, 39 (8.9%) had developed clinically verifiable HCC. The mean value of AFP-L3% was 17.3% compared to that of 3.5% in non-HCC group (n=401, P<0.0001). The risk of HCC given AFP-L3% being positive (≥10%) was 40.0% (95% CI: 26.4%-53.6%); in contrast, the risk of HCC given AFP-L3% being negative (<10%) was 4.9% (95% CI: 2.7%-7.0%). The relative risk for developing HCC in next 21 months after the AFP-L3 was elevated above 10% of total AFP was 8.2 (95% CI 4.7-14.3). It had average and median lead times of 205 and 130 days, respectively (ranging from 0-619 days) compared to imaging. In comparison, patients with AFP ≥10 ng/mL had a relative risk of 5.3 (95% CI 2.5-11.4). In summary, the AFP-L3% is useful marker for risk assessment of developing of HCC in high risk patients. A positive AFP-L3% assay offers a unique early warning for HCC in high risk patients.

PP16
ONCOGENIC KIT MUTATIONS IN GASTROINTESTINAL STROMAL TUMORS: DIFFERENCES IN SIGNAL TRANSDUCTION PATHWAYS UNRAVELED IN A CELLULAR MODEL

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Oncogenic mutations of the receptor tyrosine kinase KIT are encountered in myeloid leukemia and various solid tumors, including Gastro-Intestinal Stromal Tumors (GIST), the most frequent mesenchymal tumors in the GI tract. STI571 (Gleevec, Novartis), an inhibitor of the receptor tyrosine kinase KIT represents a breakthrough in their treatment. Signaling pathways and sensitivity to STI571 may vary among oncogenic (ligand independent activating) mutations of KIT. We have previously identified the oncogenic mutant KITK642E , a single AA substitution in the ATP binding

domain (tyrosine kinase 1 domain, TK1D) in a familial form of GIST (Isozaki K, Terris B et al. 2000 Am J Pathol 157:1581-1585). Murine KITWT and the murine homologues of human KIT oncogenic mutants, further referred to as KITK641E and KITdel559, a point deletion in the juxtamembrane domain (JMD) were stably expressed in IL-3 dependent Ba/F3 cells. Clones expressing similar levels of KIT exhibited comparable autonomous growth and chemotactism in vitro, both responses were abolished by 0.1-1 mM STI571. Signal transductions pathways, investigated with a panel of (phospho-)specific Abs revealed striking differences in the pathways activated by KITK641E and KITdel559 oncogenic mutants, namely for Akt/PKB, MAP kinases and Stats. Proteomics and microarray analysis also revealed important differences in gene and protein expression between JMD and TK1D mutants. Cellular models are valuable basic tools to investigate the effect of oncogenic KIT mutants in terms of cellular signaling and regulations and to elaborate novel strategies for tumors expressing KIT oncogenic mutants, individually tailored on specific cellular and molecular bases.

PP17
ORAL ANTICOAGULANTS AND SMALL INTESTINAL BACTERIAL OVERGROWTH

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As reported in the literature, intestinal flora produces vitamin K2 (menaquinone-n). The vitamin K antagonist warfarin acts lowering the number of γ-carboxyglutamyl residues in coagulation proteins causing an increase in prothrombin time. The therapeutic requirement of oral anticoagulants, necessary to obtain the same INR goal, widely differs among patients that introduce similar amount of vitamin K (phylloquinone) with diet. Drug interactions and genetic factors can only partially explain these differences, but in some cases no reason can be found at all. Intriguingly, experimental animals and patients with small intestinal bacterial overgrowth (SIBO) never develop hypoprothrombinemia. SIBO is often associated with predisposing conditions but has been shown to occur even in subjects without any favouring factor. The scope of our prospective study was to evaluate the result of H_2 and CH_4 lactulose breath test, used for diagnosing SIBO, among patients on therapy with different doses of warfarin. We consecutively enrolled 30 adult outpatients (15 females) on chronic oral anticoagulant therapy with stable INR within 2 and 3. Three inclusion groups were defined as follows: low dose (LD), 10 patients taking ≤17.5 mg/wk of warfarin; intermediate dose (ID), 10 patients taking warfarin within 26.5 and 43.75 mg/wk; high dose (HD), 10 patients taking ≥70 mg/wk of warfarin. Each patient underwent the lactulose breath test after having eaten no fermentable carbohydrates during the day before. No one had used antibiotics during the last 4 weeks before the test. In the HD group, 50% (n=5) of patients had an altered breath test suggesting SIBO, just 10% (n=1) in the ID and no patient in the LD group (P=0.01). No statistic association resulted between the dose of warfarin and potentially interacting drugs intake. In conclusion, this study seems to suggest the possible role of SIBO as a factor influencing the therapeutic dose of warfarin.

PP18
RANDOMIZED CONTROLLED TRIAL OF LIVE *LACTOBACILLUS ACIDOPHILUS* PLUS *BIFIDOBACTERIUM INFANTIS* IN TREATMENT OF INFANTILE ACUTE WATERY DIARRHEA

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BACKGROUND: Rota virus is the major cause of acute watery diarrhea (32%) in infancy group in Chulalongkorn hospital. The initial proper management decreases the morbidity and mortality of the infected infants. Drug which shortens duration of diarrhea and hospitalization day is cost effectiveness.

OBJECTIVE: To evaluate the effectiveness of live *Lactobacillus acidophilus* plus *Bifidobacterium infantis*.

DESIGN: Randomized controlled trial.

METHOD: 71 infants (aged 1-24 months) with acute watery diarrhea (<5 days) presented at Out Patient Unit of Pediatric Department, King Chulalongkorn Memorial Hospital, Bangkok were enrolled after parental's signed informed-consent. They were randomized into 2 groups, Study group (N=35) received: 2 day course of live lactobacillus plus bifidobacterium (3×10^9 CFU) bid and ORS and Control group (N=36) received ORS only. All infants received lactose-free milk as total feeding or adjunct to breast milk for standardization together with low osmolar oral resuscitation solution. Case record forms of basic data, daily monitoring with stool frequency, character, vomiting, appetite, general well being were completed for 5 days by mothers.

RESULT: 71 infants with acute watery diarrhea with complete follow up were recruited. Analysis by SPSS version 11 with ANOVA, Chi-square and T-test was performed. Both groups had no statistical differences in sex, age, birth weight, body weight, onset of diarrhea and dehydration status. After treatment the mean duration of diarrhea was 1.6±0.7 day in study group and 2.9±1.7 day in control group (p-value= 0.001). The stool frequency was 2.2±2 times/day in study group and 2.6±2 in control group (P=0.586); Hospitalization day in study group = 2.1±1.2 day and 2.6±1 day in control group (P=0.726). In patient with positive rota viral in stool, study group (N=15) had duration of diarrhea = 1.7±0.6 day and the control group (N=8) had 2.9±0.8 with strong statistical significance (P=0.007).

CONCLUSION: Live *Lactobacillus acidophilus* plus *Bifidobacterium infantis* is the successful treatment in acute watery diarrhea in infants and cost-effective by 2-days course of treatment can shorten the duration of diarrhea.

PP19
THE PREBIOTIC COMBINATION INULIN/OLIGOFRUCTOSE PREVENTS COLITIS IN HLA-B27 TRANSGENIC RATS ASSOCIATED WITH IMMUNOMODULATION AND CHANGES IN INTESTINAL MICROFLORA

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HLA-B27 transgenic (TG) rats develop spontaneous colitis under specific pathogen-free conditions (SPF) but germ-free rats remain disease-free, emphasizing a role for intestinal bacteria in the pathogenesis of the disease. Prebiotics are nutrients that affect the host by stimulating growth and/or activity of potentially health promoting (probiotic) bacteria.

AIM: The aims of this study were to investigate whether prebiotics can prevent colitis in SPF HLA-B27 rats, and secondly, to explore mechanisms of protection.

METHODS: SPF HLA-B27 TG rats received orally the prebiotic combination inulin/oligofructose, or not, prior to the development of clinically detectable colitis. After 7 weeks, the rats were killed, and cecal and colonic tissues were collected for gross cecal scores (GCS), histological inflammatory scores (scale 0-4), and mucosal cytokine measurement. Cecal and colonic contents were collected for PCR-denaturing gradient gel electrophoresis (PCR-DGGE) analysis of the gut microbiota, enumeration of selected bacterial populations by fluorescent in-situ hybridization (FISH) and assessment of short-chain fatty acid composition.

RESULTS: Prebiotic treatment significantly decreased GCS and inflammatory histological scores in the cecum and colon. Prebiotic treatment also decreased cecal IL-1β but increased cecal TGF-β concentrations. Inulin/oligofructose altered the cecal and colonic PCR-DGGE profiles, and FISH analysis showed significant increases in cecal *Bifidobacterium* populations after prebiotic treatment compared to water-treated rats. The prebiotic combination did not affect the composition of cecal or colonic short-chain fatty acid composition.

CONCLUSIONS: The prebiotic combination inulin/oligofructose partially prevented colitis in HLA-B27 TG rats, which was associated with alterations to the gut microbiota, decreased tissue pro-inflammatory cytokines and increased immunomodulatory molecules. These results show promise for prebiotics as a relatively cheap and easy to administer dietary therapy for chronic inflammatory bowel diseases.

WEDNESDAY, SEPTEMBER 14

PP20
EFFECTS OF *BOSWELLIA SERRATA* EXTRACT IN PATIENTS WITH COLLAGENOUS COLITIS: RESULTS OF A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER TRIAL

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BACKGROUND: Collagenous colitis is an idiopathic microscopic colitis characterized by chronic watery diarrhea, a typical subepithelial collagen layer, and lymphoplasmacellular infiltration. Due to their anti-inflammatory properties, *Boswellia serrata* extract (BSE) have been used in various inflammatory disorders such as bronchial asthma, chronic polyarthritis and inflammatory bowel diseases.

AIM: We investigated the effect of BSE on symptoms, quality of life and histology in patients with collagenous colitis in a randomized, double-blind, placebo-controlled multicenter trial.

METHODS: Patients with chronic diarrhea (≥5 times per day) and histologically proven collagenous colitis were randomized to receive either oral BSE 400 mg three times daily for 6 weeks or placebo. Complete colonoscopy was performed before and after treatment. Histopathology was assessed by a single pathologist blinded to the patients' treatment. Clinical symptoms and quality of life were assessed by standardized questionnaires and SF-36. Patients of the placebo group with persistent diarrhea received cross-over BSE therapy.

RESULTS: 31 patients (mean age 59 years, 26 female) were randomized; 25 patients were available for per protocol analysis. Four patients discontinued treatment due to protocol violation, one patient due to side effects. The rate of clinical remission (frequency of diarrhea <3 times per day) was higher in the BSE group than in the placebo group (per protocol 58,3% vs. 30,8%, respectively). Seven patients received cross-over BSE therapy, five of them showed complete remission after 6 weeks.

CONCLUSIONS: Oral BSE is clinically effective and safe for the treatment of patients with collagenous colitis. Long-term follow-up of these patients is necessary to investigate whether clinical remission is sustained.

PP21
POPULATION-BASED STUDY OF THE EPIDEMIOLOGY OF AND THE RISK FACTORS FOR MICROSCOPIC COLITIS

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BACKGROUND: Microscopic colitis (lymphocytic and collagenous colitis) is a common cause of watery diarrhea. Despite its importance, the epidemiology of microscopic colitis (MC) in a non-selected population has been poorly defined. The objective of this study was to identify the incidence of and risk factors for developing microscopic colitis.

METHODS: A population-based surveillance cohort study was conducted in the Calgary Health Region (CHR) between April 1, 2002 and March 31, 2004. All adult (>18 years) CHR residents were identified through the Calgary Laboratory Services' regionalized pathological database. Charts were reviewed to confirm the diagnosis and record risk factors for acquisition. Category-specific risks for developing MC were reported as relative risks (RR) with exact 95% confidence intervals.

RESULTS: One hundred sixty three residents of the CHR were identified with a new diagnosis of MC (58% collagenous colitis) for an annual incidence of 9.9 per 100,000 population. There was an increasing incidence of MC in association with advancing age. The mean age was 59 years and patients over the age of 65 were greater than five times more likely to develop MC (RR 5.6; 95% CI, 4.0-7.7; P<0.0001). Females were at a higher risk of acquiring MC as compared to males (RR 4.3; 95% CI, 2.8-6.5; P<0.0001) and this was demonstrated across all age groups. In addition to age and gender, a number of co-morbid illnesses were associated with a higher risk for developing MC including celiac disease (RR 7.9; 95% CI, 4.0-14.2; P<0.0001), patients with a history of malignancy (RR 7.2; 95% CI, 4.2-11.7; P<0.0001) and hypothyroidism (RR 6.1; 95% CI, 3.5-10.0; P<0.001).

CONCLUSIONS: This study provided important data on the burden of microscopic colitis in a North American population. This is the first study to quantify the risk of developing microscopic colitis in celiac patients and to demonstrate malignancy and hypothyroidism as risk factors for developing microscopic colitis.

PP22
MAGNIFIED NARROW BAND IMAGING IS USEFUL TO DETECT EARLY COLORECTAL CANCER

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AIM: The depth of cancer invasion is very important in order to determine the treatment for early gastrointestinal cancer. However, accurate diagnosis of the vertical cancer invasion is sometimes difficult to make. Narrow band imaging (NBI) is a new endoscopic technology visualizing micro-vascular patterns of gastrointestinal mucosa. Magnified NBI has been shown to be useful for determining the cancer depth in early esophageal and gastric cancers. An aim of this study is to evaluate the usefulness of magnified NBI in determining the cancer invasion of elevated-type early colorectal cancers.

PATIENTS AND METHODS: We found 9 lesions of elevated-type early colorectal cancer in 5,300 consecutive patients examined by colonoscopy between January 2004 and April 2005. Those lesions were observed using NBI system with an Olympus magnifying endoscope (magnified-NBI). After the magnified-NBI observation, 4 lesions were treated with endoscopic mucosal resection (EMR), and 5 lesions by surgery. The vascular patterns determined by magnified-NBI were classified and were compared with the histopathological diagnosis of cancer invasion.

RESULTS: Endoscopic appearances of those cancers were: type-IIa (1 patient), type-IIa+IIc (4 patients): and accumulated type-IIa (laterally spreading tumor: LST) (4 patients). The vascular patterns determined by magnified-NBI observations were regular (fine network or thin vascularity pattern) (5 patients): and irregular (thick vascularity) (4 patients). Pathological diagonosis of the vertical cancer invasion were sm-1 in 4 patients, sm-2 in 4 patients, and sm-3 in 1 patient. On magnified-NBI, all of sm-1 lesions showed regular vascular pattern, while 4 out of 5 (80%) of sm-2 or 3 lesions showed irregular vascular pattern.

CONCLUSION: The vascular pattern on magnified-NBI gives us information about the depth of cancer invasion of elevated-type early colorectal cancer. Lesions showing regular vascular patterns can be safely treated with EMR. But lesions showing irregular vascular patterns should be treated with surgery, because they have a good chance of distant metastasis.

PP23
CENTRAL NEUROPLASTICITY AND THE EFFECT OF TEGASEROD IN VISCERAL HYPERSENSITIVITY IN RATS FOLLOWING COLONIC INFLAMMATION

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Studies have shown that patients develop persistent symptoms of bowel dysfunction and altered visceral perception following resolution of an acute gastroenteritis, a condition referred to as post-infectious IBS (PI-IBS). It is postulated that changes in mucosal inflammation might induce visceral hypersensitivity by activating visceral afferent pathways. The purpose of this study was to investigate what neuroplastic changes occurred in visceral afferent pathways following colonic inflammation, and the effects of

tegaserod, a partial 5-HT4 agonist, in visceral hypersensitivity and the expression of substance P (SP) and calcitonin gene-related peptide (CGRP) in the colon and lumbarsacral spinal cord.

METHODS: Adult male Sprague-Dawley rats were randomly divided into experimental group and control group. Conlonic inflammation was induced in experimental rats by intraluminal administration of trinitrobenzenesulfonic acid (TNBS, 100mg•Kg^{-1} in 30% ethanol). Saline (0.5 mL) was intraluminally administered in the control rats. Abdominal contractions induced by inflation of a balloon (0-1.6 mL) colonically inserted were recorded in rats by implanting electrodes in the abdominal striated muscles. Immunohistochemistry method "ABC" was used to observe the responses of neurons and glial cells (astrocytes and microglias) in lumbarsacral spinal cord and medulla oblongata following colonic inflammation; Immunohistochemistry method "FITC" was used to further study the expression of N-methyl-D-aspartate receptor 1 and receptor 2A/B (NMDAR1 and NMDAR2A/B) in lumbarsacral spinal cord following colonic inflammation. Finally, tegaserod was intra-gastrically administered to study its effects on visceral sensitivity and the expression SP and CGRP in the colon and lumbarsacral spinal cord.

RESULTS: Colonic distension evoked a significant increase of abdominal contractions 3, 7 and 14 days after TNBS administration. Abdominal contractions were still increased significantly in two (2/7) experimental rats after recovery of colonic inflammation. Twenty-eight days after TNBS administration, the responses of astrocytes and microglias in the spinal cord and medulla oblongata as well as the activity of neurons in the medulla oblongata reduced significantly and became comparable to the control group (P>0.05). However, The activity of neurons in the spinal dorsal horn was still significantly increased in three (3/7) experimental rats. Twenty-eight days after TNBS administration, the number of NMDAR1-IR and NMDAR2A/B-IR neurons was still increased significantly in four (4/7) TNBS-treated rats compared with the saline-treated rats (P<0.05). Abdominal contractions induced by colonic distention decreased significantly after intra-gastric administration of tegaserod for 7 and 14 days. After intra-gastric administration of tegaserod for 7 days, the density of SP in the colon and lumbarsacral spinal dorsal horn reduced significantly (P<0.05). However, CGRP content in the colon and spinal dorsal horn did not significantly reduced in tegaserod-treated rats (P>0.05).

CONCLUSIONS: The persistent activation of neurons in the spinal dorsal horn after the remission of colonic inflammation may play an important role in the development of visceral hypersensitivity. Increased expression of NMDAR1 and NMDAR2A/B was associated with neuronal hyperexcitability in the spinal dorsal horn.

PP24
IS TEGASEROD EFFECTIVE AND SAFE FOR TREATMENT OF IRRITABLE BOWEL SYNDROME OR CHRONIC CONSTIPATION? A META-ANALYSIS OF RANDOMIZED TRIALS

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PURPOSE: To determine whether tegaserod compared to placebo improves patient satisfaction and quality of life at an acceptable level of risk in patients with irritable bowel syndrome (IBS) or chronic constipation (CC).

METHODS: A comprehensive search was undertaken to identify all published or unpublished randomized trials of tegaserod versus placebo in any language. Medline, Cochrane CENTRAL, Embase, and INAHTA databases were searched up to April 2005. To meet inclusion criteria, trials had to be randomized, with at least one pertinent clinical outcome. Two reviewers extracted data from each trial. The primary outcome was patient satisfaction with relief. Secondary outcomes included quality of life, satisfaction with bowel movements (BM), and any other clinically relevant indicators of efficacy or risk. Publication bias was explored through visual inspection of funnel plots for each outcome. Odds ratios (OR, 95%CI) were calculated for discrete outcomes, and weighted mean differences (WMD, 95%CI) were calculated for continuous outcomes.

RESULTS: A total of 10 randomized trials were identified, including 8576 patients (89.8% female). Seven, two and one trial(s) included constipation-predominant IBS, chronic constipation patients, and diarrhea-predominant IBS patients. The duration of each trial was 12 weeks. No trials of longer duration were found. At baseline, mean age was 43.8 vs 44.2y, and mean duration of disease was 14.4y vs 14.6y for tegaserod and placebo, respectively. Statistical heterogeneity was found for many endpoints. Clear evidence of publication bias was not found for any endpoint. Statistically significant, but clinically modest, improvement was found for patient global assessment of relief (1.41, 95% CI 1.17-1.70; P=0.0004), BM satisfaction score (WMD –0.30, 95% CI –0.37 to –0.23), and BM responders (OR 1.76, 95% CI 1.40-2.20; P<0.0001), abdominal bloating/distention score (WMD –0.18, 95% CI –0.32 to –0.03; P=0.02), mean BM weekly (WMD 0.73, 95% CI 0.50 to 0.96; P<0.0001), mean spontaneous BM weekly (WMD 0.82, 95% CI 0.55 to 1.09; P<0.0001), mean complete spontaneous BM weekly (OR 1.40, 95% CI 1.14 to 1.72; P=0.002) and laxative use (OR 0.64, 0.50-0.83; P=0.0006). Significant improvement was not found for straining score (WMD –0.13, 95% CI –0.27 to 0.01; P=0.06), and number of days with excess straining (WMD –0.13, 95% CI –0.31 to 0.06; P=0.18). Quality of life was not reported in any trial. While the overall incidence of side effects was not significantly increased (OR 1.01, 95% CI 0.90-1.14), tegaserod discontinuation due to adverse effects was significantly increased (OR 1.57, 95% CI 1.21-2.03, P=0.0006). The most common side effect was diarrhea (OR, 2.50, 95% CI 1.67-3.73; P<0.00001), but severe diarrhea was not increased (OR 2.96, 95% CI 0.35-24.64; P=0.3) and antidiarrheal use did not differ (OR 1.92, 95% CI 0.72-5.08; P=0.2). No difference was found for severe adverse events, headache, nasopharyngitis, ischemic colitis, abdominal surgery, and ECG changes.

CONCLUSION: Tegaserod has modest efficacy at 12 weeks for improving patient satisfaction and selected symptoms in constipation-predominant IBS and CC. It appears to be well-tolerated, except for increased incidence of non-severe diarrhea. There is urgent need for further studies to delineate the efficacy and safety of repeated courses and longterm sustained treatment with tegaserod beyond 12 weeks.

Funding: CCOHTA 2004 HTA Capacity Building Grants Program

PP25
STABLE TRANSFECTION OF ESTROGEN RECEPTOR BETA INTO HUMAN INTESTINAL CELLSβ: EFFECT ON PROLIFERATION

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BACKGROUND: There is growing evidence obtained by in vivo and in vitro studies supporting a protective role for estrogens in colorectal cancer. In postmenopausal women, estrogen plus progestin replacement significantly reduces the risk of colorectal cancer by 37%, as shown in a large, prospective, randomized controlled trial. In the multiple intestinal neoplasia (Min) mouse model, the number of intestinal adenomas increased by 77% following ovariectomy, but decreased significantly in mice with estrogen alone. Similarly, in two carcinogen-induced colon cancer models, estrogen alone protects ovariectomized animals against colon cancer. The main effects of estrogen are mediated by two nuclear receptors, ERα and ERβ. Upon estrogen activation, both receptors bind to estrogen response elements in the regulatory regions of target genes. However, major differences in tissue distribution, transcriptional activities and phenotype of corresponding knockout mice suggest distinct biological functions for ERα and ERβ. Importantly, ERβ immunoreactivity is significantly lower in colon cancer cells compared to normal colonic epithelial cells, and a progressive decline in ERβ expression parallels the loss of colonic cell differentiation. The role of ERβ in the colon may be important because ERβ is thought to be the predominant estrogen receptor. The purpose of this study was to investigate whether ERβ activation modulate intestinal cell growth.

METHODS: Studies were done in human fetal intestinal epithelial crypt cells (HIEC) which expressed low to moderate ERβ but undetectable ERα levels. HIEC were stably transfected with ERβ cDNA using lentivirus-mediated system. ERβ overexpression was detected by real-time RT-PCR, Western blot and immunofluorescence. Growth kinetic was measured in HIEC treated with vehicle, estradiol and tamoxifen for 2, 4, 6 and 8 days. Furthermore, (methyl-3H)-thymidine incorporation during DNA reinitiation was assessed in HIEC overexpressing ERβ.

RESULTS: HIEC depicts high lentivirus infection efficiency, as visualized

by fluorescence of pLenti-GFP infected cells. Real-time RT-PCR analysis confirms that stably transfected HIEC express high ERβ level (216 fold) relative to the parental cells. Furthermore, high level of ERβ protein expression was observed in stably transfected HIEC and immonofluorescence analysis demonstrates mainly nuclear localization of ERβ. In untransfected HIEC, therapeutic concentration of Tamoxifen (100 nM) were associated with reduced growth observable after 4 days of treatment. Physiological concentration of estradiol (10 nM) was associated with short term growth inhibition. In ERβ overexpressing HIEC, DNA-reinitiation was impaired by estradiol treatment in a dose-dependant manner and profondly reduce (more than 80%) by tamoxifen (10 nM).

CONCLUSION: The availablility of stable normal intestinal cell lines overexpressing ERβ will allows us to investigate the mechanism by which ERβ activation decreases intestinal cell proliferation.

PP26
THE DAVE (DIGITAL ATLAS OF VIDEO EDUCATION) PROJECT – GASTROENTEROLOGY: A PEER-REVIEWED, NON-PROFIT, FREE ACCESS INTERNET EDUCATIONAL TOOL FOR THE GASTROENTEROLOGY PHYSICIAN AND EDUCATOR

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INTRODUCTION: Advances in imaging technology have facilitated the production of high quality endoscopic videos and other teaching modules. Conventional publishing formats suffer from the inability to successfully deliver this new high technology medium as the volume of medical data grows so rapidly, standard text material becomes rapidly outdated. The recently created internet site, the DAVE Project–Gastroenterology fills this void via a new educational format.

OBJECTIVES: To create a peer-reviewed, non-profit, free-access internet learning tool for gastroenterology physicians, teachers, and students. This site includes a digital atlas of video endoscopy generated from a worldwide contributor base.

METHODS: The DAVE–GI internet site (http://dave1.mgh.harvard.edu/) is built on a dynamic software platform implementing HTML and a relational database that provides real-time results for any user query. The information files used in the DAVE Project are generated from several sources. Edited endoscopic video clips with narration from both diagnostic and therapeutic procedures are created in high resolution MPEG2 format with embedded audio narration. Clinical Grand Rounds and Clinical Journal Clubs from major academic institutions are digitally recorded and then formatted for internet viewing within minutes of the presentation. Whenever possible, auto-updating resources are employed such as the "smart search" National Library of Medicine, PubMed search feature written specifically for the DAVE Project. This search feature uses file keywords to automatically load targeted PubMed searches that auto-update. All the material on the site, including videos, pathology and radiology images, and PowerPoint presentations can be downloaded for nonprofit use for educational purposes. The internet site is free to use, non-profit and all its material is peer-reviewed.

SUMMARY: Advances in video software technology and broadband internet access now provide an opportunity to improve the process of acquiring and disseminating medical information for education and patient care purposes. The DAVE Project offers a variety of educational modules including a digital atlas of video endoscopy, clinical grand rounds, and journal clubs as well as key PubMed links. The DAVE Project represents the logical progression of educational technology and has been supported by an unrestricted educational grant from the Pentax Corp.

POSTERS OF DISTINCTION

MONDAY, SEPTEMBER 12

PD30
THE GASTROESOPHAGEAL REFLUX DISEASE: THE COMPARISON OF AMBULATORY 24-HOUR PH MONITORING WITH BARIUM STUDIES

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INTRODUCTION: Gastroesophageal reflux disease (GERD) is the most common esophageal disorder, the clinical manifestations of GERD, typical or atypical, result from the reflux of gastric contents into the esophagus. 24-hour esophageal ambulatory pH monitoring is considered as the gold standard for the diagnosis of GERD, however some experts, especially radiologists (Pan et al. 2003, Madsen et al. 2001), think that barium study is a suitable alternative or good supplement to 24-hour pH monitoring, above all in preoperative evaluation of patients undergoing fundoplication.

AIMS AND METHODS: We studied retrospectively a group of 48 patients who underwent both 24-hour pH monitoring and barium study in the period from March 2000 to March 2004. The aim of the study is to determine the correlation between pathologic acid reflux found in 24-hour pH monitoring and massive pathologic gastroesophageal reflux (GER) on barium studies. The radiologic reports were reviwed to determine the presence of a pathologic GER – patients with reflux to or above thoracic inlet either spontaneous or with provocative maneuvers in the recumbent position were classified as having pathologic GER. To assess pathologic GER in pH monitoring a combination of a few standardized pH-metric values (DeMeester Score, number and duration of acid refluxes, fraction time pH<4, number and duration of acid refluxes longer than 5 min) was used.

RESULTS: In the period from March 2000 to March 2004 a group of 48 patients underwent both 24-hour pH monitoring and barium study (27% of a total number of 176 24-hour pH monitoring studies in this period). 41 patients (85%) were examined in indication of typical GERD manifestation, in 7 patients (15%) the indication was an extraesophageal manifestation (noncardiac chest pain, respiratory, ear, nose and throat symptoms). The pathologic GER was found on 40 pH monitoring studies (83%) in comparation with only 21 patients (44%) having pathologic GER on barium studies. All 21 patients (100%) with massive reflux on barium studies had pathologic acid reflux on pH monitoring.

CONCLUSIONS: Ambulatory 24-hour pH monitoring remains the gold standard in investigation of pathologic GER, our experience in agreement with the majority of publications confirmed its high sensitivity. Barium study seems to be a suitable supplement of a complex of diagnostic methods (together with endoscopy and biopsy) in patients where complications of GERD or an anatomic abnormality (hiatal or paraoesophageal hernia) could be expected.

PD31
PHMETRY BEFORE LONG-TERM TREATMENT WITH PPI?

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BACKGROUND: Patients with gastroesophageal symptoms often have other gastrointestinal symptoms as well. PPI medication has effect on their reflux symptoms but not on other gastrointestinal problems, often IBS-related.

AIMS AND METHOD: Are there subgroups among patients with suspected GERD relevant to PPI treatment? 279 patients referred to a gastroenterological unit at a county hospital for 24h pHmetry and esophageal manometry (Medtronics) answered GSRS (gastrointestinal symptoms rating scale, with scores between 1=no symptoms at all and 7=very severe symptoms, for abdominal pain, reflux symptoms, indigestion, diarrhoea and constipation), questions about medication, past surgery and by the patient experienced difficulties in doing pHmetry and manometry 1-5 (1=very troublesome and 5=very easy). Upper endoscopy was done at the referring units and not in connection with the esophageal investigations.

RESULT: Patients on antidepressant medication, in most cases SSRI, had more abdominal pain, indigestion and constipation than patients without antidepressant medication. There were no difference in acid refluxes. Women had less pHmetric verified acid refluxes than men, but higher abdominal pain and constipation scores and used antidepressant medication more. The reflux scores did not differ. Reflux scores seem to be independently explained by acid refluxes verified by pHmetry, other gastrointestinal symptoms and sensitivity to esophageal investigations or age. Three groups with gastroesophageal reflux symptoms, high reflux scores with heartburn and acid regurgitation, were identified: Significant Spearman rank correlations (R values) between reflux score and other variables. Group 1: Reflux score are related to objective findings verified by more refluxes (pH<4 total time) R=.424 and more symptomatic refluxes (symptom index) at pHmetry R=.312. Group 2: Refluxscore related to other gastrointestinal symptoms, constipation R=.197, diarrhoea R=.258, abdominal pain R=.523 and indigestion R=.406, but not to pH variables or symtom index. Group 3: Refluxscore related to experience of the the investigations R=–.211 and age R=–.135, troublesome investigation and younger patient, but not to other symptoms and/or pH variables.

CONCLUSION: Since patients with GERD often have other gastrointestinal symptoms, maybe 24h pHmetry should be used more to identify patients in need for continous PPI medication to avoid unnecessary PPI treatment in patients with other relevant gastrointestinal symptoms not caused by acid refluxes.

PD32
USEFULNESS OF MAGNIFYING ENDOSCOPY FOR DIAGNOSIS OF NONEROSIVE REFLUX DISEASE

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BACKGROUND AND STUDY AIMS: This study was designed to assess the usefulness of magnifying endoscopy for diagnosis of nonerosive reflux disease.

PATIENTS AND METHODS: The subjects were 99 patients who had subjective symptoms of the neck, chest or abdomen but in whom no conventional endoscopic findings of reflux were obtained. Magnified endoscopic observation of the intrapapillary blood vessels just above the mucosa of the esophagogastric junction was carried out after conventional endoscopic observation in each patient. Visualized intrapapillary capillary loops (IPCL) were classified into the following three types: regular (R), dilated (D) and obscured (O). The relationship between magnifying endoscopic findings and reflux symptoms according to the Carlsson-Dent questionnaire was examined. Magnifying endoscopic findings were also evaluated from two histopathological parameters: basal cell layer thickness and length of papillae.

RESULTS: The morphology of the IPCL in the esophageal mucosa was R type in 46 subjects and D type in 49 subjects. Four subjects had O type. Of the subjects whose score in the Carlsson-Dent questionnaire was 4 or higher, the percentage of subjects with D type was significantly larger than the percentage of subjects with R type ($P<0.001$). The thickness of the basal cell layer in subjects with D type was significantly larger than that in subjects with R type ($P<0.01$). The length of papillae in subjects with D type was significantly larger than that in subjects with R type ($P<0.05$).

CONCLUSIONS: Magnifying endoscopic observation of IPCL may be useful for diagnosis of nonerosive reflux disease.

PD33
PANTOPRAZOLE 40 MG IS AT LEAST COMPARABLE TO ESOMEPRAZOLE 40 MG IN ACHIEVING ENDOSCOPICALLY CONFIRMED HEALING AND SYMPTOM RELIEF OF GASTROESOPHAGEAL REFLUX DISEASE (GERD) AFTER 4, 8 AND 12 WEEKS OF TREATMENT

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PURPOSE: To assess healing and symptom relief rates with the new validated reflux questionnaire ReQuest™ in patients with erosive gastroesophageal reflux disease (GERD) grade A-D (LA Classification) comparing pantoprazole 40 mg (PANTO) and esomeprazole 40 mg (ESO) for up to 12 weeks.

METHODS: A total of 581 patients (intention-to-treat population, ITT) were medically treated in this randomized, double-blind, multicenter, parallel-group comparison conducted in Germany. Patients with endoscopically confirmed GERD grade A-D received either PANTO (n=288) 40 mg or ESO (n=293) 40 mg once daily over a period of 4, 8, and 12 weeks. Healing of esophageal lesions was defined as no endoscopic findings. For assessment of GERD-symptomatology, patients completed the validated reflux questionnaire ReQuest™ daily. Symptom relief was achieved if the score of the subscale ReQuest™-GI (gastrointestinal; comprising acid complaints, upper abdominal/stomach and lower abdominal/digestive complaints, and nausea) fell below a predefined upper limit of a GERD symptom threshold. For the comparison of PANTO and ESO, the two-sided 95% confidence intervals (CI) according to the standard normal approximation (non-inferiority margin of –15%) were calculated for the differences in the healing and symptom relief rates.

RESULTS: PANTO showed superior results regarding healing rates after 12 weeks of treatment: 98.0% (PANTO) and 94.4% (ESO) (CI above 0 [0.02%; 7.27%]; per protocol, PP). Maximum symptom relief rates of 94.6% (PANTO) and 91.6% (ESO) were achieved after 12 weeks. In all cases, the lower limits of the 95% CI for the difference between the treatment groups were above the non-inferiority margin.

		Healing rate (%)	Healing rate (%)	Healing rate (%)	Symptom relief rate (%)	Symptom relief rate (%)	Symptom relief rate (%)
		4 weeks	8 weeks	12 weeks	4 weeks	8 weeks	12 weeks
ITT	PANTO	68.8	86.1	91.0	63.2	77.1	79.2
	ESO	68.6	83.3	87.7	64.2	75.4	77.1
PP	PANTO	75.0	94.1	98.0*	75.5	90.2	94.6
	ESO	74.8	89.7	94.4	77.6	89.3	91.6

**superiority (CI above 0 [0.02%; 7.27%])*

CONCLUSIONS: PANTO 40 mg is comparable to ESO 40 mg regarding symptom relief after 4, 8 and 12 weeks of treatment and regarding healing of esophageal lesions after 4 and 8 weeks of treatment, after 12 weeks of treatment, PANTO is superior to ESO.

This research was funded by the ALTANA Pharma AG, Konstanz, Germany

PD34
THE PHARMACOLOGICAL PROFILE OF THE NOVEL POTASSIUM-COMPETITIVE ACID BLOCKER AZD0865 IN HEIDENHAIN POUCH DOGS

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PURPOSE: AZD0865 is a novel potassium-competitive acid blocker (P-CAB) in development to improve the treatment of acid-related diseases. The pharmacological profile of AZD0865 was elucidated in Heidenhain pouch (HP) dogs.

METHODS: Four dogs with a cannulated Heidenhain pouch for the collection of histamine-stimulated gastric (pouch) secretions were used in each of the following studies with AZD0865. Gastric juice was collected in 30-min fractions, and acid output was calculated from titrated acidity and sample weight. In a dose-response study, AZD0865 was given (0.125-1 µmol/kg orally, and 0.25 µmol/kg iv) 1.5 h before starting a 6.5-h stimulation period. A similar protocol was used to assess antisecretory effects on the 1st, 4th, 8th and 14th day at 0.5 µmol/kg/day. The last 2 h of a single 3.5-h stimulation was used in experiments related to duration of effect; this period was centred 4, 10 and 24 h after single doses at 1 µmol/kg, 24 h after 5 days at 1 µmol/kg/day, and 24 h after single doses at 2-16 µmol/kg. The concentration of AZD0865 was determined in plasma (all studies) and in titrated samples of gastric juice (some studies).

RESULTS: Oral AZD0865 displayed dose-linear pharmacokinetics; C_{max} was seen 0.5-1.0 hrs after dose, and bioavailability was approximately 50%. Following the iv dose, $t_{1/2}$ was (mean±SE) 2.0±0.2 h, plasma clearance was 4.3±0.5 mL/kg/min and the volume of distribution was 0.64±0.04 L/kg.

AZD0865 pharmacokinetics were similar after single and repeated oral doses, both at 0.5 and 1 µmol/kg/day. AZD0865 inhibited stimulated acid secretion in a dose-dependent manner, with peak-level inhibition established approximately 3 h post dose. For the interval 3-5 h post dose, the oral ED_{50} (95% CI) was estimated at 0.25 (0.14-0.36) µmol/kg, and similar inhibition was produced by the oral 0.5 µmol/kg and the iv 0.25 µmol/kg doses (81±8% and 81±4%, respectively). In the repeated-dose study at 0.5 µmol/kg/day, the 3-5 h inhibition was 93±4% after the first dose and consistent inhibition was seen after 4, 8 and 14 doses. A low level of inhibition remained before the daily dose during repeated dosing, and the time to peak effect was shorter than after a single dose. The concentration of AZD0865 in gastric juice surpassed plasma levels approximately 2 h post dose, and remained quantifiable 24 h post dose in gastric juice but not in plasma. Duration of action studies (1 µmol/kg/day) showed 99±1% inhibition 4 h after single dose, with 41±5% and 45±3% remaining 24 h after single and repeated doses, respectively, when the drug was generally below the limit of quantification in plasma. After higher single doses, the 24-h inhibition was >90% when the plasma concentration remained higher than approximately 125 nmol/L.

CONCLUSIONS: AZD0865 provides potent inhibition of gastric acid secretion with a fast onset of effect, prolonged duration of effect and a predictable dose-response relationship. The pharmacokinetic C_{max} preceded the peak antisecretory effect, and duration of effect outlasted the time with quantifiable concentrations in plasma. The long duration of effect reflects super-concentration of AZD0865 at its site of action in the canaliculus of the parietal cell. The peak effect, the 24-h effect, and the pharmacokinetics of AZD0865 were consistent after single and repeated doses.

PD35
THE ANTISECRETORY EFFECT OF THE POTASSIUM-COMPETITIVE ACID BLOCKER AZD0865 IN THE RAT

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PURPOSE: AZD0865, a novel potassium-competitive acid blocker (P-CAB), is a substituted imidazopyridine in development to improve the treatment of acid-related diseases. This study determined the gastric acid antisecretory properties of AZD0865 in chronic fistula rats.

METHOD: Gastric acid secretion in response to a 2.5-h stimulation with pentagastrin+carbachol was assessed in groups of 8 chronic fistula rats. AZD0865 was given orally before the start of stimulation and collection of gastric juice in 30-min fractions. The antisecretory effect was evaluated from average secretory responses in a 2-h period centred at a different time after dose, depending on the type of study. The effect of escalating single doses (0.12-2 µmol/kg), and of repeated dosing (0.25 and 0.5 µmol/kg/day) was measured 3.5 h after dose. Duration of effect was estimated from responses recorded up to 96 h after single doses of 1, 10 and 50 µmol/kg, and 24 h after 5 days at 1 and 10 µmol/kg/day. In additional experiments (1 and 5 µmol/kg/day), the concentration of AZD0865 in plasma and gastric juice was determined.

RESULTS: Inhibition of stimulated acid output with AZD0865 was dose dependent, with ED_{50} estimated at 0.3 µmol/kg. Complete blockade was established within 2 h of administration at 1 µmol/kg. Almost complete inhibition (≥97%) was maintained for 4.5 and 9 h after treatment with 1 and 2 µmol/kg, respectively. On the first day of dosing at 0.25 and 0.5 µmol/kg, mean inhibition of acid output was 58% and 98% respectively. In both dose groups, inhibition on the first day was not significantly different from that on the 4th, 8th or 14th day. AZD0865 had a long duration of effect. Acid secretion was dose-dependently inhibited 24 h after single doses of 1, 10 and 50 µmol/kg (47, 95 and 100%, respectively), and returned to control levels by 36, 48 and 96 h, respectively. Inhibition 24 h after 5 days' dosing at 1 and 10 µmol/kg/day (49% and 93% respectively) was consistent with inhibition after single doses. In similar experiments, inhibition 24 h after single and 5-day repeated dosing was 37% and 21% for the 1 µmol/kg dose, and 78% and 82% for the 5 µmol/kg dose. The concentration of AZD0865 in gastric juice was similar 23-25 h after single and repeated doses at 1 (~30 nmol/L) and 5 (~190 nmol/L) µmol/kg. In addition, 25-h plasma concentrations were consistent after single and repeated doses: <20 nmol/L (below the LOQ) and ~65 nmol/L at 1 and 5 µmol/kg, respectively.

CONCLUSIONS: AZD0865 is a potent inhibitor of stimulated gastric acid secretion with a fast onset of action. AZD0865 provided consistent, dose-dependent inhibition of acid secretion over 24 h with either single or repeated dosing. There was no increase in the concentration of AZD0865 in plasma or gastric juice after repeated administration. The long duration of effect of AZD0865 is most likely due to concentration at its site of action in the parietal cell.

PD36
ENDOSCOPIC MUCOSAL LIGATION (WITHOUT RESECTION), NOVEL OPTION FOR ERADICATION OF SHORT SEGMENT BARRETT'S ESOPHAGUS. SECONDARY REPORT OF AN ONGOING STUDY

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BACKGROUND: BE is a recognized premalignant condition. Numerous attempts for eradication have been made.

OBJECTIVE: To evaluate feasibility and safety of EML in the removal of short segment Barrett's esophagus (SSBE), after band ligation.

METHODS: 30 pts in the treated group and 30 controls, with endoscopically and histologically proven SSBE, underwent a prospective, case controlled, study, comparing EML vs. endoscopic surveillance. Each therapeutic session consisted of: A) initial endoscopy for identification of BE, vital staining, biopsies and selecting areas to be treated. B) Second endoscopy for band shooting in previously selected sites. We used an Olympus GIF130 and a six band shooter in all the cases. Omeprasol 20 mg tid, permanently, in all pts, even the fundoplicated. Next sessions repeated every 3 weeks until endoscopical and histological absence of BE in the four quadrants. Follow up endoscopies planned to be done at 2, 6, 12 months and yearly. Control group: 30 historical pts from our database, in periodic BE surveillance. All data base images were examined by another endoscopist in a blinded fashion for changes in BE length. One blinded pathologist examined all the specimens.

RESULTS: 30 pts 14 male 16 female, mean age 46 years. Complete eradication of BE was achieved in 29/30pts (96%) and >95% of reduction 1 case. The mean was 3 sessions for total removal. Neither residual Barrett's epithelium nor buried glands were observed at 1 month of eradication in each case. Dysplasia was never seen. All the patients referred light chest discomfort and dysphagia for 2 days after each session. No major complications were seen in any patient, exception for temporary retroesternal pain in 2 pts. No patient developed permanent stricture even after 7 sessions. In the control (surveillance-database) group, partial length regression in 3 pt (4.7%) at 1 yr, and no changes were seen in the rest.

CONCLUSIONS: EML for removal of SSBE is a promising new technique that implies hermetical removal of BE, without large denudated areas for healing, but only small re-epithelization areas. This study shows a very low rate of complications, is easily reproducible and non expensive. A larger number of pts and a longer surveillance are needed in a controlled, clinical trial.

PD37
CLOSING OF NON-NEOPLASIC CHRONIC ACQUIRED ESOPHAGIC FISTULAE BY ENDOSCOPIC CAUTERIZATION

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The non-neoplasic acquired esophagic fistulae are relatively infrequent complications originated by a great number of agents to which the organ is exposed and it shows a high morbility. According to their anatomic with characteristics they clinically appear with symptoms and signs to the organ they communicate. Fistulae are difficult to manage clinically and therapeutically due to the complications which appear when they affect organs, like the lungs, pleura, mediastinum, making it necessary an evaluation for each case. With the objective of determining the effect of the endoscopic cauterization of the non-neoplasic acquired esophagic fistulae, using a sodium hydroxide solution at 20%, an experimental study was done with fifteen patients assited at the Institute of Gastroenterology in Havana,

Cuba, between 1995 and 2002. Each of the patients had a clinical chart with their personal data, ethiology, clinical picture, type and location as well as their evolution during the endoscopic therapy. The endoscopic cauterization method with sodium hydroxide at 20% consists of applying this solution, to the edges of the fistula orifice, usding a small hyssop-shapped held between the valves of the biopsy forceps, under endoscopic observation at intervals for seven to ten days. Seventy per cent (70%) of the patients had non-neoplasic acquired esophagic fistulae caused by esophagic perforation as a result of endoscopic procedures and surgical treatment. The most common clinical picture was the acquired esophagic fistula due to internal communication with respiratory symptons (60%), followed by due to external communication 30%. The most frequent localization of the fistulae in our patients was in the proximal esophagus 50%. This fistulae were diagnosed by endoscopy in 2.19% of the all treated patients. It was observed that the bigger the orifice's diameter is, the more cauterizations sessions the patient needs for the orifice cure. One hundred per cent of the 15 patients cauterized by endoscopy with sodium hydroxide at 20% were healed without any further complications. The methods of endoscopic cauterization with sodium hydroxide at 20%, should be more utilized in our daily practice due to its simplicity, innocuosness and low cost in order to improve the quality of life of our patients.

PD38
A NOVEL ANTREFLUX DEVICE BASED ON MAGNETS

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BACKGROUND: The problem of abolishing gastroesophageal reflux (GER) with simple, effective and devoid of unpleasant side effects procedures is still unresolved. We tried to settle this problem with a magnetic device that should be applied to the distal end of the esophagus.

MATERIAL AND METHODS: Two plastoferrite magnets of 2×4×0.5 cm with a force of 0.16 N/cm^2 at 7 mm of distance were applied to the opposite sides of a flaccid polyethylene tube mimicking the physical characteristics of the terminal esophagus, as the external diameter was 2.8 cm and the wall was thickened to 3.5 mm by means of a soft plastic material. The two magnets attracting themselves compressed the tube, creating an artificial high pressure zone of 2 cm in length that divided the tube in two segments. Both segments of the tube were connected to pressure transducers and a polygraph and one of them (A) was connected by means of a T tube to a hydraulic pump. The pressure was progressively increased in this segment up to a value sufficient to detach the magnets with consequent flowing of the water in the other segment of the tube (B).

RESULTS: When the progressive increase of the pressure in segment A reached an average value of 9.75±1.05 mmHg (mean±SD) the magnets detached allowing a free flow through them and the pressure in segment B started to increase. Once the pump was stopped and the drains cock opened, the intraluminal pressure decreased and the magnets adhered again closing the passage.

CONCLUSIONS: A couple of magnets clamping a tube with the characteristics of the distal esophagus is able to give rise to a high pressure zone of about 10 mmHg and 2 cm in length that is considered sufficient to prevent GER (NEJM 1982;302:1547) and does not block the circulation in the vascular bed of the esophageal wall. We believe that this magnetic device has the necessary requirements to deserve further "in vivo" studies and are convinced that it represents a novel promising approach to resolve the hoary problem of GER treatment.

PD39
COST-EFFECTIVENESS OF LAPAROSCOPIC VERSUS CONVENTIONAL NISSEN FUNDOPLICATION; A RANDOMIZED COMPARISON AND CONSECUTIVE UPDATE

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Laparoscopic Nissen fundoplication (LNF) has merely replaced the conventional procedure (CNF), because of proven equivalent short-term effectiveness with shorter postoperative hospital stay, higher quality of life and earlier return to work. Higher costs for the procedure itself are therefore considered acceptable. An economic evaluation of LNF in comparison to CNF based on prospective data with adequate follow-up is however lacking.

METHODS: Data from a multicenter randomized trial (n=57 LNF and n=46 CNF) were combined with a consecutive prospective cohort study on LNF, performed by the same surgeons (n=121 LNF). Outcome data were integrated using a decision-analytic model to determine incremental cost-effectiveness at one year postoperatively. Satisfactory decline of complaints was the primary outcome of clinical effectiveness. Quality of life was measured using the SF-20 and a direct rating scale. Costs were estimated from a social perspective and included costs associated with losses in productivity because of sick leave. The incremental costs per successfully operated patient were estimated. Furthermore, three parameters (operation costs, reoperation rate, hospitalisation costs) were evaluated in sensitivity analyses.

RESULTS: Mean operating time, reoperation rate and hospitalisation costs in the LNF group were considerably lower in the second series. In the initial RCT, overall hospital costs per patient averaged Euro9.126 for LNF and Euro6.989 for CNF at one year. In the second LNF series mean costs were Euro7.916. Higher direct medical costs for LNF were only partly compensated by lower costs of productivity loss and a reduction of operating time and reoperations. In the RCT, LNF was successful in 91.5% and CNF in 91.3%. The success rate of LNF was 90.2% in the second series. Regarding cost-effectiveness only, LNF resulted in higher costs and worse outcome, ie, CNF appeared the preferable strategy. The sensitivity analysis revealed that a cost reduction of the laparoscopic procedure by Euro998 would cancel out the cost advantage of CNF. Similarly, if the reoperation rate after LNF would drop from 0.05 to below 0.008 and/or if the mean number of sick leave days after LNF would be reduced from 67.2 to below 61.1 days, the procedure would become less expensive than CNF. Complications, reoperation rate and quality of life after operation were similar for both procedures.

CONCLUSION: Including reinterventions, the results after LNF and CNF were virtually similar at one year. However, initially LNF was approximately 10% more expensive. In a well organised and expert setting, this cost disadvantage may be neutralised especially when return to work is accelerated. Effectiveness and quality of life, however, remain similar.

PD40
OPTIMIZED MOTILIN AGONIST PROKINETICS

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There is a medical need for prokinetic agents useful in the treatment of GI motility disorders including gastroparesis and GERD. The motilin receptor is a clinically-validated target for prokinetic therapeutics; the archetypical motilin agonist erythromycin A (Ery) has demonstrated clinical efficacy in gastroparesis[1], GERD[2], and impaired gallbladder function[3]. However, chronic use is limited by its antibacterial activity and association with cardiovascular arrhythmias[4]. Several analogs of Ery with reduced antibacterial activity have been investigated in clinical trials. These compounds have shown reduced activity in multiple dosing regimens (tachyphylaxis)[5], high affinity for the hERG channel (linked to QT prolongation and torsades de pointes), and/or contain reactive chemical moieties. Our early Ery derivatives had dramatically reduced antibiotic activity, acceptable motilin agonist potency, reduced tachyphylaxis and lacked chemically-reactive moieties. However, their affinity for the hERG channel was similar to that of Ery. These compounds were used as scaffolds for structural optimization to reduce the hERG interaction and further reduce the potential for tachyphylaxis. Testing included evaluation in in vitro contractility models to assess potency and tachyphylaxis[6], MIC determinations of antibiotic activity and electrophysiological testing of hERG channel current inhibition. Stringent assay conditions were applied–MIC assays included two of the most erythromycin-sensitive strains known, *Strep. pneumoniae*

ATCC6301 and *Micrococcus luteus* ATCC9341. Similarly, hERG screening was performed using a patch clamp assay at 37°C, where inhibition by erythromycin derivatives is most pronounced[7]. The table below compares benchmark and leading candidates evaluated in our standard assays. Our lead compounds are 5-40 fold more potent than Ery, cause minimal tachyphylaxis, have negligible antibiotic activity, and are ~10-fold weaker than Ery in inhibiting hERG channel current. The compounds are orally bioavailable, with appropriate pharmacokinetic profiles in the dog. They all have been shown to accelerate gastric emptying in dogs. Additional studies are in progress to select the final clinical candidate.

	Drug	Agonist EC50 (nM)	Tachyphylaxis (% activity @ 4th dose)	Antibiotic MIC vs (ATCC6301) (ug/mL)	hERG nhibition @ 30 uM (%)	hERG inhibition @ 300 uM (%)
Benchmark	EryA	1200	72	0.03	27	90
	ABT-229	7.1	22	100	98	100 @ 100 uM
	GM 611	11	9	200	84	100 @ 50 uM
Optimized Leads	506Q	52	92	64	10	51
	511Q	220	96	>128	10	37
	29D	104	95	>128	7	41
	112F	58	85	64	8	34
	315G	31	82	128	23	60

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PD41

HELICOBACTER PYLORI GENOTYPING IN GASTRIC LOW-GRADE MALT LYMPHOMA AND ITS CORRELATION WITH CLINICAL OUTCOME

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BACKGROUND: *Helicobacter pylori* (HP) has different factors of pathogenicity which can be associated with diseases like peptic ulcer or gastric adenocarcinoma. Prevalence and influence of HP pathogenic factors in positive low-grade gastric MALT lymphoma and their potential influence on clinical outcome after eradication of HP have not been investigated so far.

AIM AND METHODS: Genotype of different HP for cagA, babA2, iceA1, vacAm, vacAs and JHP950 has been determined using paraffin wax embedded tissue from patients with HP positive MALT lymphoma. The different genotypes were correlated with time to complete remission after HP eradication. In addition, the lymphoma cell population was analysed for monoclonality and translocation t(11;18) to identify potential risk factors for an unfavourable clinical outcome. Patients with only partial remission 12 months after HP eradication where irradiated.

RESULTS: So far, 24 patients have been included for genotyping of HP. 22 (92%) were tested positive for ureA after DNA extraction from paraffin wax embedded tissue and could be further evaluated. During clinical follow up n=4 were drop outs, n=3 (17%) had to be irradiated because of no complete remission after 12 months. 50% of MALT lymphomas showed monoclonality, n=2 (1%) had translocation t(11;18). Genotyping revealed positive results for: cagA: 64%, babA2: 86%, iceA1: 50%, JHP950: 36%.

CONCLUSION: Percentage for babA2 and cagA were identical with former reported results. IceA1 and the new marker JHP950 (Lehours et al.) were less frequent than already published. Perhaps due to the small number of genotyped HP positive patients there is no correlation between an unfavourable outcome and a special genotype. Still more patients have to be investigated. The genetic markers for JHP1462, oipA and sabA on-off-status are in work at the moment. A concluding statement will follow.

PD42

MINIMALLY INVASIVE TREATMENTS FOR EARLY GASTRIC CANCER USING ENDOSCOPIC MUCOSAL RESECTION AND LAPAROSCOPIC SURGERY COMBINED WITH SENTINEL NODE NAVIGATION

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BACKGROUND: Recently, more than 70% of the gastric cancers at our institute are early gastric cancers. As lymph node metastasis was only observed in 2.1% of cases with mucosal cancer, a complete local resection without lymph node dissection can result in a curative treatment. On the other hand, it was observed in 13.7% of submucosal gastric cancer cases. Thus, a new strategy for detecting lymph node metastasis is required to enable limited treatments to be performed.

AIM: Minimally invasive treatments for early gastric cancer using endoscopic mucosal resection (EMR) and laparoscopic surgery combined with sentinel node navigation (SNN) were evaluated.

METHODS: Since 1988, we have been using a double-channel method of EMR to treat mucosal cancer. The curative indications for EMR in Japan were 1) mucosal cancer, 2) differentiated tubular adenocarcinoma, 3) superficial carcinomas less than 2 cm in diameter. We have developed laparoscopic wedge resection of the stomach since 1992. Our indications were 1) mucosal cancer, 2) superficial elevated lesions less than 25 mm and 3) superficial depressed lesions less than 15 mm without an ulcer lesion. Since 1999, we have conducted a feasibility study for intraoperative radioguided SN mapping for T1 or T2, N0 gastric cancer. The endoscopic injection of technetium-99m tin colloid (500 nm in size) was performed preoperatively, and radioactive SNs were identified using a gamma probe. Since 2000, we have applied SNN to a laparoscopy-assisted distal gastrectomy (LADG) with lymphatic basin dissection to expand the indications for submucosal gastric cancer.

RESULTS: A double-channel method of EMR was performed to treat 632 patients between 1988 and 2004. Almost of the patients underwent EMR during 2 or 3 days of hospital stay, and returned to their normal life style. Although local recurrence was observed in 13.5% (326 EMR: 1988-2001), the 44 patients have been rescued by additional endoscopic treatments (36 cases) or open surgery (8 cases). No deaths from gastric cancer have occurred. The survival rate after EMR was nearly the same as that for patients who underwent open surgery. We have developed laparoscopic wedge resection of the stomach for 100 patients between 1992 and 2000. The patients could start oral intake one to two days after surgery and were discharged during 5 to 8 days. Three local recurrences and 4 metachronal cancers have occurred in this series. No deaths from gastric cancer have occurred. SNs were identified in 97% of 320 patients. The average number of SNs was 4.1. The sensitivity and accuracy of the mapping were 93% and 99%, respectively. Fifty two patients underwent laparoscopic surgery (wedge resection of the stomach: 17 cases, LADG: 14 cases, pylorus-preserving gastrectomy or segmental resection of the stomach: 21 cases) combined with SNN under a suitable curability and a minimally invasive condition between 1999 and 2005.

CONCLUSION: Our endoscopic mucosal resection and laparoscopic surgery combined with sentinel node navigation for early gastric cancer have been resulted in a curative and minimally invasive treatment.

PD43

MOLECULAR ANALYSIS OF NOD2/CARD15 AND TP53 GENES IN *HELICOBACTOR PYLORI*-INFECTED PATIENTS WITH CHRONIC GASTRITIS, INTESTINAL METAPLASIA AND DYSPLASIA, AND INTESTINAL TYPE OF GASTRIC CANCER

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From 1430 patients with dyspepsia, group of 131 patients with chronic gastritis, intestinal metaplasia, dysplasia or intestinal type of gastric cancer and infected with *Helicobacter pylori* was selected. These patients and 13 patients with normal gastric muscosa without infection were subjected to molecular analysis of NOD2/CARD15 and TP53 genes. Studies have previously identified abnormalities of these genes in various gastrointestinal diseases. Genomic DNA samples were extracted from paraffin blocks of gastric mucosal biopsies that were histopathologically diagnosed. Using tissues and peripheral blood cells, we aimed to determine how frequently abnormalities occurred in studied group of patients from Western Poland. *Helicobactor pylori* infection was confirmed by histological analysis and urease test. One hundred thirty one *H. pylori*-infected patients were selected to analysis of 3020insC mutation, –802C>T (Pro268Ser) polymorphism in NOD2/CARD15 gene and most frequent mutations in TP53 gene. Screening procedures involved single strand conformational polymorphism and heteroduplex analysis. Samples indicating presence of aberrant DNA fragment were subjected to direct sequencing. Eight c248G>A, 6 c249G>A and 5 c250C>T mutations in TP53 gene were found (17%). 3020insC in NOD2/CARD15 was observed in 12% of patients. Further analysis of NOD2/CARD15 gene showed that frequency of allele T of –802C>T polymorphism was significantly higher in patients (33%) as compared to control group of healthy individuals (18%) with χ^2=13.59 and P=0.0002. Control group consisted of 13 patients without gastric mucosal changes and 100 persons from population group. Genotype CC was observed in 67 (51%), CT in 42 (32%) and TT in 22 (17%) patients while values for control group were 78 (69%), 29 (26%) and 6 (5%), respectively. Statistical analysis revealed that differences were statistically significant, χ^2=11.09 and P=0.0039. Observed frequencies of genotypes CT and TT increased with severity of changes in gastric mucosa. In healthy control group 23% of patients with genotypes CT and TT were observed, while in chronic gastritis group, dysplasia and intestinal type of gastric cancer CT and TT genotypes showed higher frequencies, 44%, 52% and 71%, respectively. Our findings suggest that polymorphism –802C>T is associated with changes in gastric mucosa and plays a significant role in the initiation and the progression of carcinogenesis. The number of observed mutations in gastric mucosa correlated with severity of disease.

PD44

SHORT MUCIN 6 ALLELES ARE ASSOCIATED WITH *HELICOBACTER PYLORI* INFECTION

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BACKGROUND: The mucus gel layer provides protection against acid, mechanical trauma, and pathogens. The most important components of this layer are large glycoproteins named mucins. The genes encoding for these mucins show a variable number tandem repeat (VNTR) polymorphisms resulting in mucins that substantially differ in length and number of oligosaccharide side chains. These differences may influence their protective properties and may therefore be related to susceptibility to *H. pylori* infection. Therefore the aim of this study was to investigate the relationship between mucin 6 VNTR length and *H. pylori* infection.

METHODS: Blood samples were collected from patients visiting the Can Tho General Hospital in Viet Nam for upper gastrointestinal endoscopy. DNA was isolated from whole blood, the repeated section was cut out with a restriction enzyme (P*vu*II) and the length of the allele fragments was determined by Southern blotting. *H. pylori* infection was diagnosed by ^{14}C urea breath test. For analyses, mucin 6 VNTR length was dichotomized as being either long (>13.5 kbp) or short (≤13.5 kbp) and patients were classified according to genotype (long-long [LL], long-short [LS], short-short [SS]).

RESULTS: 160 patients were studied (mean age 43 years, 36% male, 58% *H. pylori*-infected). Mucin 6 PvuII-restricted allele fragments lengths ranged from 7 to 19 kbp. Of the patients with the LL, LS, SS mucin 6 genotype 43% (24/56), 57% (25/58) and 76% (11/46) were infected with *H. pylori*, resp. (P=0.003).

CONCLUSION: Short mucin 6 alleles are associated with *H. pylori* infection. This may be explained by the antibiotic activity of mucin 6, which may be related to the number of side chains of the mucin 6 molecules.

PD45

SEROEPIDEMIOLOGY OF HEPATITIS D VIRUS INFECTION IN CHRONIC HBV CARRIERS IN SOUTH-WEST OF IRAN (KHOZESTAN PROVINCE)

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BACKGROUND AND AIMS: HBV infection is a major health problem in south-west of Iran. A preliminary report indicates that hepatitis D virus (HDV) infection exists in this area. However, its prevalence in different patients groups of chronic carriers of HBV have not been studied in detail. This study evaluates the prevalence of hepatitis D virus within these groups.

METHODS: This cross-sectional study was carried out between April 2003 to October 2004. Our study included 268 chronic HBV carriers (positive HBs Ag for more than six month) in whom we performed HDV (HDV Ab) serum marker by ELISA method (Dia-pro kits). The patients divided into three groups of inactive chronic carrier, chronic hepatitis and liver cirrhosis.

RESULTS: Analysis of serum markers indicated that 24.3% (65/286) of patients had evidence of HDV infection, Anti-HDV was found in 21 of 168 (11.3%) patients with inactive carriers, and in 10 of 28 (35.7%) patients with chronic hepatitis and 34 of 54 (63%) of cirrhotic patients. A significant difference (P<0.001) was noticed between the three groups.

CONCLUSIONS: The present study shows that delta virus infection is prevalent in south west of Iran and the HDV prevalence in chronic HBV carriers is related to severity of liver disease and HDV infection must be considered as one of main factors in progress to chronic hepatitis and cirrhosis in our community.

PD46

INDOMETHACIN TO REDUCE THE RATE OF ACUTE PANCREATITIS AFTER ENDOSCOPIC RETROGRADE CHOLANGIOPANCREATOGRAPHY: A RANDOMIZED CONTROLLED TRIAL

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AIMS: Our aim was to determine if prophylactic rectal indomethacin reduces the incidence of pancreatitis following therapeutic endoscopic retrograde cholangiopancreatography (ERCP).

METHODS: Patients who underwent ERCP were enrolled in a single-center, randomized, double-blind controlled trial. Thirty minutes before endoscopy, patients were given a suppository containing either 100 mg indomethacin or placebo. Serum amylase levels (after 2 hours) and clinical evaluation were performed in all patients. Patients were observed for at least 24 hours after ERCP. Serum amylase levels were re-checked in those

who developed abdominal pain. The presence of pancreatic-type pain at 24 hours in conjunction with an elevated serum amylase level more than three times normal was defined as pancreatitis.

RESULTS: A total of 130 patients (56 male and 74 female with a mean age of 58.0 ± 16.9 years) entered the trial, and 65 patients received rectal indomethacin. Pancreatitis was seen in 3 patients (4.6%) who received indomethacin and 5 patients (7.6%) who received placebo (P=0.7).

CONCLUSIONS: We did not find any significant difference between indomethacin and placebo in the prophylaxis against ERCP-induced pancreatitis. The use of NSAIDs before ERCP requires further investigation.

PD47
ANALYSIS OF ETIOLOGICAL FACTORS PREDISPOSING TO CHRONIC PANCREATITIS IN CHILDHOOD

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INTRODUCTION: Chronic pancreatitis (CP) is a rare disease in childhood. The pathogenesis of CP is poorly understood. The etiology of CP in children is varied and includes anatomic anomalies, gene mutations, metabolic disorders and others. However, the literature on the subject is conflicting because most of the information is found within individual case reports or small case series. The aim of our study was to evaluate etiological aspects of CP in children.

METHODS: Children with CP hospitalized since 1995 to 2005 were enrolled into the study. Clinical and epidemiological data were recorded and analyzed. All children were screened for gene mutations by direct DNA sequencing. Imaging studies (ERCP, MRCP, CT) were performed in all children. For patients under 15 years of age, factors predisposing to pancreatitis as alcohol consumption and smoking were excluded. The patients and parents were informed on the aims of the project and they signified their written agreement for clinical and molecular procedures to be used.

RESULTS: 108 children with CP were hospitalized (62 girls and 46 boys). Mean age was 8.87 years (range: 2.0 to 19.4 years). Gene mutations were found in 34 children (32%) (PRSS1 mutations in 14 children, CFTR in 9 patients, SPINK1 in 16 children). In 6 cases were found two gene mutations. Hyperlipemia was found in 19 patients (18.7%). 17 pts (16%) had anatomic anomalies (14: pancreas divisum, 2: ansa pancreatica, 1: two main pancreatic ducts). CP was associated with biliary disease in 10 patients (9.3%) (choledochocele, cholangitis scleroticans, choledocholithiasis). History of abdominal trauma was present in 5 cases (4.7%). In 13 children we found autoantibody (12%). In two patients CP was probably associated with neurological drugs, in 4 with lambliosis, in case with dermatomiositis, in 1 with colitis ulcerosa and in one patient with ascariasis. In 18 children we found more than one etiological factor (16.8%).

CONCLUSIONS: 1. The most common ethiological factors of CP are gene mutations, metabolic disorders and anatomic anomalies. 2. Our data demonstrate the need for genetic testing in children with CP. 3. We should be aware of coexisting etiologic factors causing CP in children, as gene mutations and anatomic anomalies.

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TUESDAY, SEPTEMBER 13

PD48
LIFESTYLE AND STOMACH CANCER IN IRAN: A POPULATION-BASED CASE CONTROL STUDY

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BACKGROUND: The incidence of stomach cancer has been gradually decreasing in the world; however, it is still the most common cancer in Iran with wide intra-country variation. Ardabil province in North West of Iran has been reported to have the highest incidence rate of stomach cancer in Iran with age standardized incidence rates of 49.1 and 25.4 per 100,000 in men and women, respectively. This is one of the highest reported incidences in the world. The aim of this study was to evaluate the influence of lifestyle on the risk of stomach cancer in this high risk area.

METHODOLOGY: To identify reasons for this high rate, a population-based case-control study was conducted in Ardabil province. 217 histopathologically confirmed incident cases of gastric cancer were recruited from Ardabil cancer registry. 394 controls were also randomly selected from residents of Ardabil province matched for five year age groups and gender. All subjects were interviewed face to face by health professionals using a pilot tested and structured questionnaire. Information on demographic characteristics; dietary habits; tobacco smoking, alcohol consumption; drug abuse; medical and occupational history were collected by this questionnaire. Meanwhile 10 mL blood specimen was collected for detection of IgG antibodies against *Helicobacter pylori* using ELISA test which was validated locally.

RESULTS: A significantly elevated risk of contracting stomach cancer was observed in drug abusers (OR: 2.50, 95% CI: 1.15 – 5.44) particularly in intestinal type (OR: 3.01, 95% CI: 1.25 – 7.26) without sub-site association for cardia and non-cardia. This association was attenuated after adjustment for main confounders but it was still significant. On the other hand no association was found between stomach cancer and cigarette smoking (OR: 1.17, 95% CI: 0.84 – 1.64) and alcoholic beverage drinking (OR: 1.26, 95% CI: 0.40 – 4.05). Furthermore in a sub sites analysis, although non-cardia gastric cancer tended to occur in smokers more than non smoker (OR: 1.44, 95% CI: 0.92 – 2.25), (OR: 0.91, 95% CI: 0.59 – 1.42) respectively, it was not significant. Meanwhile there was no difference between intestinal vs. diffuse type of gastric cancer among smokers. In addition, a higher odds of non filtered cigarettes smoking was seen among cases than controls (OR: 1.83, 95% CI: 0.71 – 4.76).

CONCLUSION: Our findings provide evidence that in Iran, drug abuse may play a carcinogenic role in the development of gastric cancer, and that smoking and alcohol drinking did not emerge as risk factors. An interaction effect was not found between the lifestyle habits.

PD49
NOD2/CARD15 BUT NOT TOLL-LIKE RECEPTOR 4 MUTATIONS ARE ASSOCIATED WITH CROHN'S DISEASE IN HUNGARIAN PATIENTS: PHENOTYPE-GENOTYPE CORRELATIONS

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AIM: Mutations of NOD2/CARD15 gene increase risk for Crohn's disease (CD) and are associated with fibrostenosing behaviour. Since

NOD2/CARD15 is involved in the recognition of bacterial antigens including the pathway of toll like receptor 4 (TLR4) functional D299G polymorphism of TLR4 may be an other genetic modifier for CD. In view of the large geographical differences in frequency of these genetic markers and absence of data in Central-European patients, common NOD2/CARD15 mutations and D299G-TLR4 polymorphism were determined in Hungarian CD patients.

PATIENTS AND METHODS: 527 unrelated patients with CD (m/f: 265/262, age: 37.1 (SD 7.6) years) and 200 healthy subjects were included. DNA was screened for possible NOD2/CARD15 mutations by denaturing-HPLC (confirmed by direct sequencing). TLR4-D299G was tested by PCR-RFLP. Comparisons between groups were made by χ^2 test.

RESULTS: NOD2/CARD15 mutations were found in 185 patients (35.1%) and in 33 controls (16.5%, P<0.0001). SNP8/R702W (10.8% vs. 6%, P=0.02), SNP13/3020insC (19.4% vs. 5%, P<0.0001) and exon4 R703C (2.1% vs. 0%, P=0.02) mutations were more frequent in CD, while the frequency of SNP12/G908R was not increased. The frequency of TLR4 D299G was not different in CD and controls (9.9% vs. 12.0%). TLR4 carriers tended to present at earlier age: age of onset in wt/TLR4 D299G carriers: 27.4 years vs. NOD2mut/TLR D299G: 23 years (P=0.06), in NOD2mut/wt: 26.4 years. The presence of variant NOD2/CARD15 allele was associated with an increased risk for CD (ORhet=1.71, 95%CI=1.12-2.6, P=0.0001, OR two-risk-alleles=25.2, 95%CI=4.37-oo, P<0.0001), younger disease onset (carrier: 26.4 vs. non-carrier: 29.8 years, P=0.0006), ileal disease (81.9% vs. 69.5%, OR=1.99, 95%CI=1.29-3.08, P=0.02, in presence of NOD2/CARD15 and TLR4: 86.7% vs. 64.8%), stricturing behavior (OR=1.69, 95%CI=1.13-2.55, P=0.026) and increased need for resection (OR=1.71,95%CI:1.13-2.62, P=0.01), but not with duration, extraintestinal manifestations, familial disease or smoking.

CONCLUSION: These results confirm in large cohorts of Hungarian CD patients the association of variant NOD2/CARD15 (R702W, R703C and 3020insC) alleles with younger disease onset, ileal disease, stricturing disease behavior. In contrast, presence of G908R or TLR4 D299G polymorphism was not different from controls.

PD50
COMPARATIVE STUDY OF REBAMIPIDE AND 5-AMINOSALICYLIC ACID AS AN ENEMA IN RAT ULCERATIVE COLITIS INDUCED WITH DEXTRAN SULFATE SODIUM

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OBJECTIVES: Rebamipide is an anti-gastric ulcer and anti-gastritis agent, having muco-protective, radical scavenging, anti-inflammatory, and wound-healing activities. Recently Makiyama et al. (2000) proposed the rebamipide enema as an alternative remedy in proctitis type ulcerative colitis patients, although the pharmacological characteristics remained to be elucidated. We investigated the therapeutic efficacies of rebamipide enema comparing with 5-aminosalicylic acid (5-ASA) in rat dextran sulfate sodium (DSS)-induced colitis model.

MATERIALS AND METHODS: Colitis was provoked by giving 3% DSS in male Sprague-Dawley rats, and maintained with 1% DSS for 15 other days. Bloody stool and the consistency of stool were blindly scored on 4-step units. Rebamipide (3 and 10 mg/kg) or 5-ASA (30, 100 and 300 mg/kg) was administered rectally once or twice daily for the initial 14 days of the colitis-maintaining phase. Colorectal mucosal lesion was measured as the area differentiated by alcian blue staining after fixation.

RESULTS: Twice daily treatment with 3 and 10 mg/kg rebamipide enema for 14 days significantly improved DSS-induced fecal bleeding and diarrhea in a dose-dependent manner. At 3 and 10 mg/kg, rebamipide significantly reduced the scores in stool consistency to 65% and 54% of control, respectively. The scores in bloody stool were preferentially reduced to 8% of control at 10 mg/kg, and the fecal bleeding disappeared in 12 of 15 rats. Although 3 of 15 rats died in the vehicle control group, no animal died in any rebamipide groups. The colorectal mucosal lesion was dose-dependently reduced, with the statistical significance at 10 mg/kg. Once daily treatment with rebamipide enema was also effective for fecal bleeding and diarrhea. However, 5-ASA enema, treated once daily, improved the fecal abnormalities only as higher doses of 100 and 300 mg/kg, without preventing the incidence of death. In a direct comparative study, 3 mg/kg rebamipide was the same or more effective to 100 mg/kg 5-ASA.

CONCLUSION: These results suggest that rebamipide enema should reveal good effectiveness, especially on hematochezia in colitis, and that rebamipide enema will provide a beneficial remedy for ulcerative colitis.

PD51
SHORT-TERM TREATMENT WITH ADALIMUMAB IMPROVES PATIENT-REPORTED OUTCOMES IN ACTIVE CROHN'S DISEASE

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PURPOSE: Crohn's disease is a debilitating long-term condition associated with negative impact on the physical, emotional and social function of patients throughout their productive years. The Inflammatory Bowel Disease Questionnaire (IBDQ) is a validated instrument designed to evaluate patient-reported outcomes in clinical trials for treatment of inflammatory bowel disease. This study evaluates the effect of adalimumab, a fully human monoclonal IgG1 antibody, on patient-reported outcomes in moderate to severely active Crohn's disease.

METHODS: In a 4-week multicenter, double-blind, placebo-controlled clinical trial, patients were randomized to receive placebo; adalimumab, 40 mg sc at Baseline and 20 mg sc at Week 2 (adalimumab 40/20); adalimumab, 80 mg sc at Baseline and 40 mg sc at Week 2 (adalimumab 80/40); or adalimumab, 160 mg sc at Baseline and 80 mg sc at Week 2 (adalimumab 160/80). Patient-reported outcomes were assessed at Baseline and at Weeks 1, 2, and 4 with self-administration of the IBDQ, consisting of 32 items with a total score ranging from 32 to 224, with higher scores reflecting greater well-being. Statistical analysis was conducted using ANCOVA model to compare mean change in IBDQ total scores from baseline at Week 4 for each treatment group versus placebo, and 4 IBDQ dimensional scores -systemic, bowel system, emotional function, and social function.

RESULTS: A total of 299 patients were randomized to receive placebo (n=74), adalimumab 40/20 (n=74), adalimumab 80/40 (n=75), or adalimumab 160/80 (n=76). At Week 4 (Table), patients randomized to the two higher doses of adalimumab had a significantly greater improvement in IBDQ total score from baseline compared to placebo (P<0.05). In the two higher-dose adalimumab groups (80/40; 160/80) at Week 4, changes in mean scores were significantly higher for 2 of the 4 IBDQ dimensions: bowel system (5.00±0.1, P<0.005; 5.05±0.1, P<0.001); and emotional function scores (4.95±0.1, P<0.05; 4.97±0.1, P<0.05), respectively, compared to placebo (4.58±0.1). Patients randomized to receive adalimumab 40/20 did not demonstrate greater mean IBDQ total score or dimensional scores compared with placebo at Week 4.

Mean Change from Baseline in IBDQ Total Score at Week 4 – LOCF

Dose	Mean change from Baseline (SD)	Difference from placebo (95% CI)	p-value
Placebo	19.49 (±3.5)	–	–
Adalimumab 40/20	18.05 (±3.5)	–1.44 (–11.3, 8.4)	0.7746
Adalimumab 80/40	31.90 (±3.5)	12.41 (2.6, 22.2)	0.0131
Adalimumab 160/80	32.35 (±3.5)	12.86 (3.1, 22.6)	0.0100

CONCLUSION: Adalimumab improves patient-reported outcomes in patients with moderate to severely active Crohn's disease within 4 weeks of treatment initiation, as measured by the IBDQ. This beneficial treatment effect was achieved with the highest doses of adalimumab – 80/40 and 160/80. The long-term impact of adalimumab on patient reported outcomes is currently under investigation.

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PD52
EXISULIND OF DUODENAL POLYPS IN PERSONS WITH FAMILIAL ADENOMATOUS POLYPOSIS

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INTRODUCTION: Duodenal adenomas are a major cause of death in persons with familial adenomatous polyposis FAP but current therapy is inadequate. Exisulind, the sulfone metabolite of sulindac, has no COX activity and has been shown to induce regression of rectal polyps in FAP by stimulating apoptosis by a phosphodiesterase (PDE)-dependent mechanism. The aim of this study was to determine if exisulind inhibits the growth of duodenal adenomas in persons with FAP.

METHODS: 155 persons with classical or attenuated FAP were screened and 101 were enrolled. Duodenoscopy was performed and a segment with 10 - 40 polyps less than 10 mm in diameter was mapped, photographed and marked with tattoos. Four index polyps adjacent to the tattoos were individually assessed at both procedures. Subjects were randomized to receive exisulind (450 mg daily) or placebo for one year and duodenoscopy was then repeated. Biopsies were obtained from polyps and mucosa at each procedure for histopathology, apoptosis by TUNEL assay and PDE expression.

RESULTS: Patient demographics were similar between the treatment groups.

	Placebo (n=51)			Exisulind (n=50)		
	Mean	Std.dev	Range	Mean	Std.dev	Range
Number of polyps	24.7	8.48	10-40	22.1	9.44	10-40
Mean polyp size, mm	2.35	1.05	1-5	2.22	0.93	1-5
Mean size of index polyps, mm	2.31	1.20	0.6-6	2.14	1.30	0.6-6.7

	Placebo (n=42)		Exisulind (n=40)			
	Mean	SEM	Mean	SEM	95% CI for diff	P-value
Percent increase in the number of polyps	46%	11%	47%	15%	(–36%, 37%)	0.73
Increase in mean size, mm	0.12	0.14	0.16	0.11	(–0.32, 0.40)	0.60
Increase in mean size of index polyps, mm	–0.31	0.17	0.08	0.16	(–0.09, 0.85)	0.04

There were no statistically significant differences between the apoptotic indices in either the adenomas or mucosa between the groups. PDE was over-expressed in both duodenal and rectal polyps.

CONCLUSIONS: 1. Exisulind therapy for one year does not inhibit the growth of duodenal adenomas; nor does it stimulate apoptosis in duodenal adenomas or mucosa in persons with FAP.

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PD53
CLINICOPATHOLOGICAL DETERMINANTS FOR MALIGNANT POTENTIAL IN COLORECTAL FLAT AND POLYPOID ADENOMAS: THE KASID MULTI-CENTER STUDY

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BACKGROUND: Colorectal flat adenomas have been a topic of debate in the view of malignant potential. The aims of this prospective study are to investigate the clinicopathological features of flat adenomas compared to that of polypoid adenoma and to identify the determinants for malignant transformation in colorectal flat and polypoid adenomas.

METHODS: This was a prospective, cross sectional study of 4,412 patients who had undergone total colonoscopy and polypectomy at 11 tertiary medical centers between July 2003 and July 2004. After colonoscopic polypectomy, each removed polyp was sent to a pathologist at each center for histopathologic examination. Of these patients 3,360 patients (mean age, 57.3 yrs; 2,383 males and 977 females) were diagnosed as adenomas. Demographic data and polyp-related variables including size, location, and gross morphology (flat or polypoid) of representative adenoma, were evaluated as determinants for malignant potential (high grade dysplasia or cancer) of colorectal adenomas. Potential risk factors for malignant transformation were analyzed.

RESULTS: Out of 3,360 adenomas, 207 (6.2%) were flat adenomas and 3,153 (93.8%) were polypoid adenomas. The patients with flat adenoma were older (59.6 vs. 57.1, P<0.001) than polypoid adenoma patients. The mean size of flat adenomas was lager than that of polypoid adenomas (10.6 mm vs. 9.2 mm, P=0.006). In addition, flat adenomas were more frequently located in the right colon than polypoid adenomas (49.3% vs. 32.0%, P<0.001). However, there were no significant differences in gender, body mass index, total number and distribution of accompanying adenomas, and villous histology between two groups. The incidence of high grade dysplasia or cancer in flat adenomas was similar to that of polypoid adenomas (5.4% vs. 4.6%, P=0.36). Multivariate analysis revealed that the adenoma size > 10 mm (OR 6.83; 95% CI 4.81–9.70) and adenoma location in left colon (OR 1.59; 95% CI 1.07–2.38) were significant determinants for malignant potential of colon adenoma.

CONCLUSION: Clinicopathological determinants for malignant potential in colorectal adenomas were not gross morphology of adenoma but adenoma size and location.

PD54

ONE-TIME SCREENING WITH AN IMMUNOCHROMATOGRAPHIC OCCULT BLOOD TEST PREDICTS THE DETECTION OF ADVANCED ADENOMA AND COLORECTAL CANCER IN THE AVERAGE RISK POPULATION

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AIM: To investigate the efficacy of one-time screening with an immunochromatographic fecal occult blood test (IFOBT) for advanced adenoma (AA) and CRC detection.

METHODS: 2502 individuals between 50-79 yo were selected by random. Exclusion criteria were regular consumption of non-steroidal antiinflamatory drugs or anticoagulants, recent CRC screening or digestive tract bleeding, a family or personal history of CRC, inflammatory bowel disease, or coagulopathy. All participants received two tests, IFOBT (OC-Light®) and GFOBT (Hemo-Fec®), and were offered a colonoscopy. AA was defined as an adenoma ≥10 mm in diameter, with high-grade dysplasia, or with significant (≥20%) villous component.

RESULTS: 587 individuals were excluded and 1915 (77%) were finally included. Among them, 1439 (75%) sampled and returned both tests. Positivity with any test was acknowledged in 10% (IFOBT 8.4%, GFOBT 3.7%). Colonoscopy was performed on 120/148 (80%) individuals with any positive test, and on 191/1291 (14.8%) with both tests negative. Colonoscopy on negative test-individuals disclosed AA in 5 (2.6%) cases, and CRC in none. However, 14 (12%) individuals with any test positivity were diagnosed with CRC, and 33 (28%) with AA. IFOBT was more sensitive than GFOBT for the detection of AA (51% vs 18%), CRC (100% vs 52%), or both (57% vs 22%). Specificity for AA, CRC or both was 97%, 93% and 95% with the IFOBT and 97%, 97% and 98% with the GFOBT respectively. As compared with subjects who had a negative test for FOBT, the relative risk of advanced colonic neoplasia (AA or CCR) in subjects who had a positive IFOBT was13 (CI: 6,1-27,7) and in those with a positive GFOBT was 3,17 (CI: 1,98-5,07)

CONCLUSIONS: One-time screening with the inmunochromatographic fecal occult blood predicted the detection of all CRC, and more than 50% AA. IFOBT showed a power for advanced neoplasm detection four times higher than GFOBT. These findings suggest that IFOBT should be the first choice FOBT for advanced colorectal neoplasm screening in the average-risk population.

PD55

PATIENT SURVEILLANCE AFTER CURATIVE-INTENT SURGERY FOR RECTAL CANCER

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PURPOSE: Follow-up of patients with rectal cancer after potentially curative primary therapy has significant financial and clinical implications for patients and society. The ideal monitoring regimen is unknown.

METHODS: We evaluated the self-reported practice patterns of a large group of experts. The 1,795 members of the American Society of Colon and Rectal Surgeons (ASCRS) were asked, via a detailed questionnaire, how often they request 14 discrete follow-up modalities (office visit, serum CEA level, CBC, liver function tests, sigmoidoscopy, colonoscopy, chest x-ray, intra-rectal ultrasound, abdomen/pelvis CT, chest CT, abdomen/pelvis MRI, positron-emission tomography, bone scan, and CEA scan) in their patients treated for cure with TNM stage I, II, or III rectal cancer over the first 5 post-treatment years.

RESULTS: Thirteen envelopes were returned unopened; 566 of the remaining 1,782 ASCRS members (32%) responded and 347 of these (61%) provided evaluable data. Members of the ASCRS often follow their own patients post-operatively rather than delegating this to others. Office visit is the most frequently requested item for each of the first 5 postoperative years (mean ± SD = 4.0 ± 2.8 visits in postoperative year 1 after radical surgery for stage III lesions, diminishing to 1.7 ± 1.2 visits in year 5). Colonoscopy is requested 0.9 ± 1.0 times in year 1 and 0.5 ± 0.6 times in year 5. Strategies for patients with stage I and II lesions are similar to those for stage III lesions.

CONCLUSIONS: There is substantial variation in follow-up intensity among these experts. The reported surveillance strategies rely most heavily on relatively simple and inexpensive tests, but endoscopy and imaging modalities are also used regularly. The observed variation in the intensity of post-operative monitoring is of concern; investigation of the source(s) of this variation is warranted.

PD56

MECHANISM FOR THE ONSET OF STEATOHEPATITIS IN HEPATOCYTE-SPECIFIC *Pten* DEFICIENT MICE, AN ANIMAL MODEL OF NONALCOHOLIC STEATOHEPATITIS

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PURPOSE: Hepatocyte-specific Pten deficient mice (Pten deficient mice) have the almost same hepatic lesions both pathologically and in natural course as human nonalcoholic steatohepatitis (NASH) that is characterized by hepatic steatosis, accumulations of lobular inflammatory cells and sinusoidal fibrosis. Although the mechanism of steatosis is becoming clear based on the analysis of gene mutated mice with fatty liver, the mechanism for hepatitis against the backdrop of steatosis is still unclear. We found that the increase of beta oxidation-related genes expression and hydrogen peroxide in Pten deficient mice livers and clarified that cytopathy caused by hyperoxidation of lipids that composed hepatocyte membrane was one of major causes of hepatitis in Pten deficient mice. Alcoholic steatohepatitis (ASH) is pathologically similar to NASH. An excessive uptake of alcohol causes the increased permeability of lipopolysaccharide (LPS) from intestinal mucosa resulting in the increased exposure of LPS to the livers via portal vein and the increased responsiveness of Kupffer cells to LPS. It is suggested that the increased exposure and responsiveness of LPS to Kupffer cells caused hepatitis in ASH. To study the possibility that hepatitis in NASH is induced by the increased responsiveness of the liver to LPS, we analyzed the sensitivity of Pten deficient mice to LPS.

METHOD: We injected LPS to 10-week-old Pten deficient mice and control mice from the tail vein and compared the contents described below before and after LPS injection; 1) The values of serum alanine aminotransferase (ALT), TNF-alpha, IL1-beta and IL6, 2) The degree of inflammatory cells infiltration in the livers by HE staining, 3) The frequency of hepatocytes apoptosis by TUNEL staining.

RESULTS: Serum ALT, TNF-alpha, IL1-beta and IL6 levels were significantly elevated in Pten deficient mice compared to control mice. Histopathologically, Pten deficient livers showed more severe inflammatory cells infiltration than control mice and the frequency of TUNEL-positive hepatocytes was also significantly increased in Pten deficient mice compared to control mice.

CONCLUSION: These results suggest that Pten deficient mice were more sensitive to LPS than control mice. We think that continuous stimulation of LPS derived from bacteria in the intestine via portal vein induces inflammation based on increased sensitivity of Pten deficient livers to LPS. Although Pten deficiency in Pten deficient mice brings about the change of its downstream genes expression in hepatocytes, those are not seen in Kupffer cells. Therefore, we propose the mechanism that the change of responsiveness to LPS of Pten deficient hepatocytes leads to the increased sensitivity of Kupffer cells to LPS via some kinds of secretory factors from hepatocytes, resulting in the induction of hepatitis based on the increase of inflammatory cytokines production from Kupffer cells.

PD57
LONG-TERM CONSUMPTION OF TRANS FATTY ACIDS IN RELATION TO RISK OF GALLSTONE DISEASE IN MEN

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BACKGROUND: The consumption of trans fatty acids adversely affects blood lipid levels. The relationship with the incidence of gallstone disease is unknown.

METHODS: We prospectively studied consumption of trans fatty acids in relation to the risk of gallstone disease in a cohort of 45,912 men. Trans fatty acid consumption was assessed using a validated semi-quantitative food frequency questionnaire. Newly diagnosed gallstone disease, by radiology or cholecystectomy, was ascertained biennially.

RESULTS: During 14 years of follow-up, we documented 2,356 new cases of symptomatic gallstones. After adjusting for age and other potential risk factors, compared with men in the lowest quintile of dietary intake of trans fatty acids, the relative risk (RR) of gallstone disease for those in the highest quintile was 1.23 (95% confidence interval (C.I.) 1.04-1.44, P for trend = 0.03). Among individual trans fatty acids, the RR for trans oleic fatty acid, when extreme quintiles were compared, was 1.24 (95% C.I. 1.06-1.45, P for trend = 0.02). Intakes of trans palmitoleic fatty acid (RR = 1.09, 95% C.I. 0.90-1.31), trans trans 18:2 fatty acid (RR = 1.14, 95% C.I. 0.96-1.34), and cis trans 18:2 fatty acid (RR = 1.00, 95% C.I. 0.86-1.16) were not significantly associated with the risk.

CONCLUSIONS: Our results suggest that a higher intake of trans fatty acids modestly increases risk of gallstone disease. This adds to the concern that the practice of partial hydrogenation of vegetable oils to form shortening and margarine can have adverse health effects.

PD58
DIAGNOSIS OF THE GRADE OF HISTOLOGICAL DIFFERENTIATION OF PANCREATIC CARCINOMA USING ULTRASOUND CONTRAST IMAGING

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INTRODUCTION: Recently, contrast-enhanced ultrasound (CE-US) has performed for diagnosing pancreatic diseases. And we have reported that it is possible for CE-US using the contrast agent to differentiating pancreatic carcinoma from other pancreatic mass lesions. However, some cases of pancreatic carcinoma show the different enhanced pattern from common pancreatic ductal carcinoma, that is, iso and hyper vascularity pattern.

AIMS AND METHODS: The aim of our study is to evaluate the various enhancement patterns of pancreatic carcinoma, especially to differentiate the histological diagnosis of pancreatic carcinoma by CE-US. The subjects were 53 patients with pancreatic carcinoma in our hospital. And the subjects diagnosed histologicaly by operation and biopsy were 38 cases (72%). The biopsy was undertaken by duodenoscopy, conventional ultrasound, and endoscopic ultrasonography-fine needle aspiration biopsy (EUS-FNAB). The ultrasound scanner was Sequoia 512 with Agent Detection Imaging (ADI) (Siemens Acuson, Los Angeles, CA). The microbubble contrast agent used was Levovist (Shering, Germany). 2.5g Levovist (concentration 300 mg/mL) was injected intra-venously at the speed of 1 mL/s. Then we observed the hemodynamics of the pancreatic carcinoma by the mode of vascular image at the frame rate of 5/sec for 60 sec and perfusion image of intermittent scanning (0.1~0.5 fps) up to 180 sec after injection. The vascular and perfusion image were classified into three categories in comparison with non-tumorous pancreatic area; hyper, iso, and hypo pattern.

RESULTS: All 53 pancreatic carcinomas were detected by conventional ultrasound: the size of these lesions were average 34.2 mm (12~60 mm). The 44 cases of 53 pancreatic carcinomas showed hypovascular and hypoperfusion imaging (83%). The 8 cases (15%) were heterogeneous isovascular and isoperfusion imaging, and the one case (2%) was heterogeneous hypervascular and hyperperfusion imaging. The 44 hypovascularity cases showed the dotted signal of vascular flow and peripheral enhansement of tumor in both vascular and perfusion imaging. The grade of histological differentiation of 38 cases diagnosed histologicaly were chiefly classified into 3 types. The 27 cases (71%) of 38 cases were well~moderately differentiated adenocarcinoma. The enhancement pattern by CE-US was hypovascular/hypoperfusion imaging. The 7 cases (18%) were poorly differentiated adenocarcinoma, and then they were divided into 2 scirrhous type and 5 medullary type. The enhancement pattern was hypovascular/hypoperfusion imaging in 2 scirrhous type and heterogeneous isovascular/isoperfusion imaging in 5 medullary type. The one case was papillary adenocarcinoma. The enhancement pattern was heterogeneous hypervacsular/hyperperfusion imaging. The histological details of 3 cases were unknown.

CONCLUSION: This study suggested that the enhancement pattern of pancreatic carcinoma in CE-US may reflect the grade of histological differentiation and the dosage of interstitial tissue, and it is useful for CE-US using the contrast agent to differentiating pancreatic carcinoma and, needless to say, other pancreatic mass lesions.

PD59
GENETIC POLYMORPHISMS OF HRAS1 VARIABLE NUMBER OF TANDEM REPEATS AND RISK OF COLORECTAL NEOPLASMS IN JAPAN

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As in Western countries, colorectal cancer has been become the main cause of cancer death in Japan. Colorectal neoplasm is a multifactorial disease, in which many factors contribute to its development including dietary, lifestyle habits and genetic predispositions. The multifarious molecular changes in cancer development frequently involve alterations on minisatellites as well as allelic deletion or loss of heterozygosity. The HRAS1 minisatellite is a variable number of tandem repeat (VNTR) locus located 1 kb downstream of the polyadenylation site, and this HRAS1 VNTR has been reported to be associated with risk of various cancers. To examine whether individuals with rare HRAS1 VNTR alleles are at increased risk of colorectal neoplasms, a total of 165 Japanese subjects were studied. All of the subjects have undergone total colonoscopy just before the enrollment. For genotyping of 108 patients with colorectal neoplasms (41 cancers and 67 adenomas) and 57 unaffected controls, we used a PCR-based long-gel electrophoresis assay that provides precise allele size discrimination, and rare alleles were differentiated from common alleles (a1, a2, a3, a4) by shifts in electrophoretic mobility. This study was approved by institutional review boards of Tottori University Faculty of Medicine. There was an evidence of a strong overall effect of the HRAS1 VNTR on colorectal neoplasm risk. The prevalence of the rare alleles in colorectal neoplasm cases was significantly different compared with controls (28.7 versus 8.8%, respectively). Compared to non-neoplasm subjects with 2 common alleles, the odds ratio (OR) for neoplasm subjects with more than 1 rare allele was 5.71 (95% CI = 3.4-13.7, $P < 0.001$). Repeating the analyses with cancer cases only (n = 41), the OR for subjects with at least 1 rare allele was 9.13 (95% CI = 3.4-24.9, $P < 0.001$). There were no differences based on other clinicopathological variables such as drinking, smoking and family-history of neoplasms. These results indicate that there is a strong association between rare alleles of the HRAS1 VNTR and colorectal neoplasms in Japan, and suggest that the HRAS1 VNTR rare allele(s) can be useful for identifying risk groups for colorectal neoplasms.

PD60
ALTERATIONS IN BETA-CATENIN, AXIN FAMILY AND APC GENES AND ABERRANT EXPRESSION OF APC PROTEIN IN HEPATOCELLULAR CARCINOMA

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BACKGROUND AND AIMS: Recent studies have shown that alterations in the Wnt signaling pathway, for example adenomatous polyposis coli (APC) gene, beta-catenin gene and Axin genes' mutations play

important roles in the carcinogenesis of various malignant tumors. In addition to mutations and loss of heterozygosity (LOH) of onco-suppressor genes, aberrant methylation of promoter regions have been identified as an important mechanism of transcriptional silencing of onco-suppressor genes. In this study, we focused on alterations in the Wnt signaling pathway in hepatocellular carcinoma (HCC). We investigated the expression of beta-catenin protein and the mutational status of the beta-catenin, APC, Axin 1 and Axin 2 genes. We also investigated the expression of APC protein and its relation with methylation of the APC promoter region.

METHODS: Beta-catenin immunohistochemistry was carried out on the 89 HCC samples. Mutations in beta-catenin, APC, Axin 1 and Axin 2 genes were determined by direct sequencing in 24 samples that showed positive beta-catenin staining. Furthermore, immunohistochemistry of APC and methylation-specific PCR for the APC promoter region were performed in those 24 samples.

RESULTS: Beta-catenin immunohistochemistry showed positive nuclear and cytoplasmic staining in 24 (27.0%) of the 89 HCC samples, indicating the existence of alterations in the Wnt signaling pathway in those 24 HCC samples. Mutations in beta-catenin, Axin 1 and Axin 2 genes were detected in 10, 13 and 9 of the 24 samples, respectively, but no mutation was detected in APC. Reduced expression level of APC protein was observed in 7 of the 24 samples in APC immunohistochemistry and hypermethylation of the APC promoter region was detected in 21 of the 24 samples in methylation-specific polymerase chain reaction.

CONCLUSIONS: In addition to mutations in beta-catenin, Axin 1 and Axin 2 genes, it is thought that reduced expression level of APC protein, which could be caused by transcriptional silencing of the promoter region by hypermethylation, results in alteration in the Wnt signaling pathway in HCC.

WEDNESDAY, SEPTEMBER 14

PD61
BENEFITS OF CENTRALIZED CARE OF PATIENTS WITH ACUTE UPPER GASTROINTESTINAL BLEEDING PROVIDED WITHIN THE TEACHING HOSPITAL SERVICES

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INTRODUCTION: Acute upper gastrointestinal bleeding is a life-threatening condition with substantial incidence and relatively high mortality. The fundamental principle of the care for such patients is not only the hospitalization with intensive monitoring of life functions, but especially the existence of multispecialty team, which must be the integrated unit in diagnostic and therapeutic procedure. For the sake of improving the quality of care of these patients it is necessary for such services to be centralized and organizationally supported by mandatory guidelines. Following these provisions, the 2nd Internal Clinics of the University Hospital Olomouc was authorized to provide care for patients with acute upper gastrointestinal bleeding.

OBJECTIVE: The evaluation of mortality and reduction of costs expended on treatment of patients with acute upper gastrointestinal bleeding in centralized care provided with health care centre within the catchment area of a region with 100 000 inhabitants.

PATIENT SET AND METHODS: The authors monitored in the group of 816 individuals admitted into University Hospital Olomouc with signs of acute upper GI bleeding during six-year period, whether the integration of the centralized care for these patients resulted in the shortening of duration of hospitalization, thereby in the reduction of economical burden and mortality.

RESULTS: The mortality in 2002 decreased by more than 2% (5.6% vs 3.5%) after the centralization of treatment and introduction of guidelines of integrated care for these patients. This difference is statistically non-significant. The duration of treatment period decreased by almost 2 days and the demand for blood transfers was reduced by 0,8 transfusion units, this difference is statistically significant. The results were statistically processed on 5% level of importance using the Epilufo programme (χ^2 independence test).

CONCLUSION: For better organization and higher quality of services it is suitable to centralize the care of patients with acute upper GI bleeding within one department of the health centre, where these patients can be provided with comprehensive health services. Considering the project results we can assume that the centralized care can bring reduction of mortality as well as of costs of the treatment.

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PD62
DIAGNOSIS OF VARICEAL BLEEDING AND ITS CONTROL IN CIRRHOSIS

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METHODS: 365 cirrhotic patients admitted in emergency for a complication of liver cirrhosis – variceal bleeding, ascites, jaundice or encephalopathy – were prospectively included into 3 groups: controls without bleeding (n=163), variceal bleeding treated by endoscopic therapy only (n=99) or with early vapreotide followed by endoscopic therapy (n=103). The 1st aim was to determine the independent predictors of bleeding. Baseline variables were compared between bleeding and control groups: 11 variables independently predicted bleeding group with diagnostic accuracy (DA)=92.3% and AUROC: 0.968. No hemodynamic variable was selected and hemoglobin (Hb) was selected at the second step. The same study was performed by excluding patients with no significant bleeding, ie, ≤2 blood units (BU); 9 variables independtly predicted significant bleeding with DA=95.8% and AUROC=0.982. No hemodynamic variable was selected and Hb was selected at the first step. The prediction of bleeding population at 6 hr by binary logistic regression with adjustment on beta-blockers provided the following 7 independent variables with DA=86.7%: decreased Child-Pugh score, previous bleeding, increased heart rate (HR), increased systolic arterial pressure (SAP), decreased hematocrit (Ht), delay admission/inclusion, and BU. The same analysis at 48 hr provided the same independent variables, except without HR, with DA=86.4%. The 2nd aim was to evaluate the specificity of Baveno criteria. In a 1st step, the composite variables of Baveno criteria defining control of bleeding were studied as crude (quantitative) variables at 6 and 48 hr by comparing the 3 groups. Discriminant variables (in univariate analysis) were at 6 hr: HR, Ht and BU; at 48 hr: HR, SAP, Ht and BU. Then in a 2nd step, we considered the Baveno definition of failure to control bleeding as well as its composite criteria (quantitative variables transformed in binary variables), the significant differences between the 3 groups were observed for the following variables at 6 hr: HR (≥100/min) and overall failure; from 6 hr to 48 hr: HR (≥100/min), BU (≥2) and overall failure. The 3rd aim was to discriminate the independent predictors of failure to control bleeding. In a 1st step, at 6 hr HR ≥ 100/min was the only significant independent variable with DA=99%. In a 2nd step, we excluded the composite variables of failure criteria, failure was independently predicted by HR and BU with DA=98,7%.

CONCLUSION: At baseline, hemodynamic parameters (HR, SAP) are not specific and very discriminant to diagnose bleeding with actual recommended treatment (early vaso-active drug followed by endoscopic treatment); hematological parameters (BU, Ht) are very specific and discriminant. The only independent predictor of failure, as defined by Baveno criteria, at 6 or 48 hr is HR >100 suggesting that other criteria of Baveno have no interest. Since HR is not predictive of bleeding, this suggests that all the composite variables of Baveno definition of failure have no interest. Therefore, we propose new criteria like Adjusted Blood Requirement Index (ABRI)=BU/(final Ht – initial Ht).

PD63
A SYSTEMATIC REVIEW ON EFFICACY AND SAFETY OF PROPOFOL SEDATION IN OUTPATIENT COLONOSCOPY

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BACKGROUND: Very few patients can tolerate colonoscopy without

sedation. Standard sedative regimens for routine colonoscopy result in prolonged recovery time post colonoscopy and can overwhelm recovery room capacity. This in turn can adversely affect patient waiting list for colonoscopy.

OBJECTIVES: To review efficacy and safety of PROPOFOL sedation in outpatient colonoscopy as an alternative to usual care.

SEARCH STRATEGY: MEDLINE, EMBASE, CINAHL, Cochrane Controlled Trails, DARE, LILACS, Web of Science, PubMed, advanced Google Scholar, OCLC conference proceedings and OCLC papers first were searched. In addition, reference lists of primary papers and review articles were evaluated.

SELECTION CRITERIA: Randomized controlled trials, which included outpatient colonoscopy comparing PROPOFOL sedation with usual care, were included. The primary outcome evaluated was recovery time. The secondary outcomes were procedure time, patient satisfaction, pain score, adverse events and cost analysis. The studies were assessed for methodological quality by concealment of allocation and Jadad criteria.

DATA COLLECTION AND ANALYSIS: Two reviewers independently extracted data from all included studies. Due to heterogeneity of included studies, statistical pooling of recovery time was not possible. Instead, we reported qualitative effect. Procedure time, patient satisfaction and pain score were analyzed by quantitative methods. Adverse events and cost analysis were analyzed by descriptive methods.

MAIN RESULTS: Nine studies were included in this review. The studies were heterogeneous in terms of interventions, controls, assessment tools for outcome measures, and blinding of outcome assessors. Five studies reported recovery time and there was a trend favoring shorter recovery time in the PROPOFOL group. Seven studies reported procedure time and there was no difference between groups. Four studies reported patient satisfaction and there was a trend towards higher level of satisfaction in the PROPOFOL group. Five studies reported pain scores and there was no difference between the two groups. Five studies reported adverse events and there was a statistically significant increase in the proportion of hypotension in the control vs PROPOFOL group (28% vs 4%, $P<0.05$) in one study. The remaining four studies did not demonstrate a significant difference in the adverse events between groups.

REVIEWERS' CONCLUSIONS: There is a trend favoring shorter recovery time and higher patient satisfaction for colonoscopy when PROPOFOL sedation was employed compared with usual care. However, no differences were identified in procedure time, pain score and adverse events between the two groups. More research is needed before definitive conclusion can be drawn.

PD64
A NOVEL ENDOSCOPIC IMAGING USING INFRARED FLUORESCENCE AND LABELED MONOCLONAL ANTIBODY FOR DETECTING DIGESTIVE TRACT CANCER

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BACKGROUND: According to micro-cancer in the digestive tract, it is desirable to reflect histopathological properties in endoscopic images. For establishing this system, antibody labeled with a detectable substance under endoscopy is necessary. We produced indocyanine green (ICG) derivative that can bind to antibody and various ICG derivative-labeled antibodies, which emit fluorescence (807 nm) when excited by near-infrared rays (768 nm). In this study, the possibility for a new diagnostic method was evaluated.

METHODS: The infrared fluorescence observation system consists of an infrared fiberscope, an exciter filter (transmitting wavelengths of 710-790 nm) and a barrier filter (transmitting wavelengths of 810-920 nm), an intensified charge-coupled device camera, an image capturing device and a light source. The light source is equipped with an infrared cut-off filter and an excitation filter, so that normal observation with white light and fluorescence observation with excitation light are possible. Anti-CEA antibody (CHEMICON INTERNATIONAL Inc, CA) was labeled with ICG derivative, and the labeled antibody was reacted with freshly resected specimen with gastric cancer, and immunofluorescent images observed by infrared fluorescent endoscopy were evaluated.

RESULTS: Immunofluorescence was obtained in freshly resected specimen with gastric cancer and no fluorescence was seen except cancer lesions. Referring to paraffin sections of the specimen, ordinary avidin-biotinylated peroxidase complex method with native anti-CEA antibody showed oxidized 3, 3-diaminobendizine-positive sites, which were well matched with the endoscopic fluorescence sites.

CONCLUSIONS: In the ultraviolet region, background artifacts such as auto fluorescence affect images, and adverse effects for the living body are apprehended. To solve this problem, infrared and labeled antibodies produced using ICG groups that can be administered into body were used. Binding of an antibody with high tissue specificity to an ICG derivative and administration under optimal conditions may provide endoscopic images that reflect histopathological characteristics.

PD65
A NOVEL ANTI-ADHESION GEL FOR BOWEL SURGERY, OXIPLEX®/AP GEL, DOES NOT INHIBIT NORMAL WOUND HEALING IN RABBITS

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PURPOSE: This study was designed to determine the affect of Oxiplex®/AP Gel on bowel healing following surgery in a rabbit model consisting of resection and anastomosis of the ascending colon.

METHODS: Rabbits were divided into four groups of 8 animals each. All animals had surgery. One-half was treated with Oxiplex®/AP Gel and one-half served as surgical controls (no gel). Two groups were necropsied at 7 days, one treated and one control. Two groups were necropsied at 21 days, one treated and one control. Bursting strength of the anastomosed section of bowel removed at necropsy was determined by submerging it in saline and increasing the transluminal pressure with air until bursting, observed by noting air leakage.

RESULTS: At 7 days, the means for the bursting strength were: Control: 124.3 ± 8.1 mmHg and Oxiplex®/AP Gel: 125.7 ± 11.9 mmHg. In addition, the incidence of adhesions was from 7 of 8 animals in the control group and 1 of 7 animals in the treated group. At 21 days, the means for the bursting strength were: Control: 125.0 ± 4.2 mmHg and Oxiplex®/AP Gel: 120.0 ± 2.7 mmHg. The P-values for all comparisons were greater than 0.05 (no significant difference between observations). The quality of the healing of incision sites and anastomotic sites was also assessed histologically. The parameters evaluated included inflammatory cell infiltration, fibroblast density, blood vessel formation and collagen maturity. The administration of Oxiplex®/AP Gel did not affect the healing of the bowel or the muscle incision sites in rabbits at 7 or 21 days post surgery

CONCLUSION: The use of Oxiplex®/AP Gel in a rabbit model of bowel anastomotic healing reduced adhesions to the surgical and closure sites and did not result in any difference in wound healing as evidenced by bowel bursting strength between treated and untreated animals.

This research was funded in part by FzioMed, Inc., San Luis Obispo, CA, USA

PD66
BURDEN OF IRRITABLE BOWEL SYNDROME WITH CONSTIPATION ON HEALTH CARE RESOURCE UTILIZATION, WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT AND QUALITY OF LIFE

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PURPOSE: Irritable bowel syndrome with constipation (IBS-C) is a chronic and episodic gastrointestinal motility and sensory disorder characterized by abdominal pain or discomfort associated with constipation. The objective of this study was to assess health care utilization, productivity loss and quality of life (QOL) in subjects with IBS-C compared with subjects without IBS-C.

METHODS: The study population consisted of respondents to the 2004 US National Health and Wellness Survey (NHWS). This survey is an annual cross-sectional survey of a nationally representative sample of the

adult US population (≥18 years) that covers a broad range of health topics. Eligible respondents completed a questionnaire on the internet regarding symptom burden, health care utilization, the general health version of the Work Productivity and Activity Impairment Questionnaire, general health version (WPAI:GH) and the SF-8 QoL questionnaire. A multivariate analysis was performed controlling for age, gender and number of physical comorbidities.

RESULTS: Of the 40,730 respondents, 3,895 (9.6%) reported being diagnosed with IBS-C or having IBS-C symptoms (abdominal pain, bloating and constipation). 78.5% of subjects with IBS-C or IBS symptoms were female. The mean age was 43 years. The IBS-C population had greater health care utilization: 7 physicians' visits per subject in the previous 6 months vs. 4 visits for the non-IBS-C population, and 0.4 emergency room visits vs. 0.2 for the non-IBS-C population. Subjects with IBS-C reported 0.6 mean hospital days during the past 6 months vs. 0.3 days for non-IBS-C subjects. All the differences were statistically significant (P values <0.005). 24,150 respondents completed the WPAI:GH: 2,187 with IBS-C and 21,963 without IBS-C. Subjects with IBS-C reported 9.9% absenteeism (missed work time) vs. 3.5% in the non-IBS-C population. Presenteeism (impairment at work) was 28.3% and 12.6%, respectively, for subjects with IBS-C and without IBS-C. The overall work productivity loss (absenteeism plus presenteeism) was greater for those with IBS-C than for those without IBS-C (30.8% vs. 13.7% P value <0.001). Moreover, impairment in performing daily activities was also significantly higher for IBS-C subjects than for subjects without IBS-C (42% vs. 20.8%; P values <0.001). Patients with IBS-C reported a significantly poorer QoL compared with patients without the disease. The SF-8 mental and physical component summary scores were 43 and 43.2, respectively for the IBS-C population compared with 50.6 and 48.9, respectively for the non-IBS-C subjects.

CONCLUSIONS: Patients with IBS-C had greater utilization in health care resources, experienced higher work productivity loss and activity impairment, and had a worse quality of life than those patients without IBS-C.

Sponsored by Novartis Pharma AG

PD67
PHLOROGLUCINOL (SPASFON) IN IRRITABLE BOWEL SYNDROME

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OBJECTIVE: To determine the efficacy and tolerability of phloroglucinol (Spasfon), an antispasmodic agent in the treatment of Irritable Bowel Syndrome (IBS).

METHODS: An open label (quasi interventional) study. One hundred patients coming to the gastroenterology clinics of Aga Khan University Hospital with IBS as defined by the Rome II criteria were enrolled between February 2004 and September 2004 to participate in the trial and were treated as outpatients. Spasfon 50 mg orally three times daily was given for two months. Symptoms were assessed before and during treatment using a questionnaire.

RESULTS: One hundred patients were enrolled in the study. Of them 61% (61/100) were males and 39% (39/100) were females. Their mean age was 41±14 years. Sixty-eight patients completed the study and 32 dropped out. On Spasfon treatment there was an overall statistically significant improvement in abdominal pain P<0.001, frequency of stool per day P<0.001, urgency P<0.001, passage of mucus per rectum P<0.001, sense of incomplete defecation P<0.001 and bloating P=0.001. However, no response was seen in the feature of straining in both genders P=0.676. The difference in response to treatment according to gender separately showed statistically significant improvement in the sense of incomplete defecation in females alone with P=0.003.

CONCLUSION: Spasfon in a dose of 50 mg three times daily is effective and well tolerated by the IBS patients. It relieves most of the symptoms of IBS.

PD68
RECOVERY OF MUCOSAL BARRIER FUNCTION IN ISCHEMIC PORCINE ILEUM AND COLON IS STIMULATED BY A NOVEL AGONIST OF THE CLC-2 CHLORIDE CHANNEL, LUBIPROSTONE

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Our previous studies demonstrate that PGE_2 stimulates recovery of barrier function in ischemia-injured porcine ileum by a mechanism that is dependant upon Cl^- secretion mediated solely through ClC-2 Cl^- channels. We therefore postulated that the selective ClC-2 agonist, lubiprostone (SPI-0211, Sucampo Pharmaceuticals, Inc.), would restore barrier function in injured intestinal tissues. Segments of porcine ileum and ascending colon subjected to ischemia for 45 minutes were mounted in Ussing chambers and bathed in Ringer's containing indomethacin (5 μM) to prevent endogenous prostanoid stimulation of Cl^- secretory channels. Recovery of barrier function was determined by measuring transepithelial electrical resistance [TER] and mucosal-to-serosal fluxes of ^3H-mannitol in injured tissues. Statistical analyses of data collected over a 180-minute time course included 2-way ANOVA for the effects of time and treatment on indices of barrier function. Application of 0.1-1 μM lubiprostone to ischemia-injured ileum induced dose-dependent increases in recovery of TER, with 1 μM lubiprostone stimulating a 2-fold increase in TER (TER=26 $\Omega \cdot cm^2$, P<0.01). This effect was preceded by a sharp and significant increase in short circuit current (I_{sc}=32 $\mu A/cm^2$, P<0.01), an indicator of Cl^- secretion in these tissues. In ischemic colonic tissue, 1 μM lubiprostone stimulated rapid elevations in TER (TER=67 $\Omega \cdot cm^2$, P<0.01) that were associated with a significant peak in I_{sc} (I_{sc}=10 $\mu A/cm^2$, P<0.01). Furthermore, lubiprostone induced significant (P<0.05) reductions in mucosal-to-serosal fluxes of mannitol to levels comparable to those of normal control tissues in both ischemic ileum and colon, indicating recovery of barrier function under the influence of this agent. ClC-2 was expressed as a 97 kDa protein in ileal and colonic mucosa. Densitometric analysis revealed a significant (P<0.05) increase in ClC-2 protein expression in ischemic ileum compared with control tissues whereas no change was detected in ClC-2 expression in injured and normal colonic tissue. Given results of parallel studies indicating localization of ClC-2 to epithelial tight junctions, we speculate that ClC-2 induces a conformational change in the tight junction that results in recovery of barrier function. Selective agonists of ClC-2 may provide a novel pharmacological means of hastening recovery of acutely injured intestine without inducing non-specific secretory pathways that could induce diarrhea.

This research was funded by Sucampo Pharmaceuticals Inc, Bethesda, Maryland, USA

PD69
EUS-GUIDED THERAPY FOR PANCREATIC PSEUDOCYSTS AND PANCREATIC NECROSIS: AN EXPERIENCE OF 19 CASES

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INTRODUCTION: EUS-guided pseudocyst drainage is a promising but evolving technique. Major concerns are diameter of the cystogastrostomy and adequacy of the drainage procedure to remove solid debris within the cyst cavity. We present our experience in 19 patients with pancreatic pseudocysts or pancreatic necrosis wherein EUS guided therapy was used.

PATIENTS: From July 2004 to January 2005, 19 patients with pancreatic pseudocysts were subjected to EUS guided drainage. Seventeen patients had cysts following acute pancreatitis while 2 after chronic pancreatitis (CP). Eight patients had simple cysts (clear contents) whereas 11 had complicated cysts (multiloculated, thick fluid, necrotic debris in floor). Seven patients (all complicated cysts) had recurrent cysts (Surgical cystogastrostomy – 2, ERP + transpapillary drainage – 2, repeated USG guided aspiration – 2, EUS + transgastric stenting – 1). Associated sepsis was seen in 7 patients.

METHODS: All patients underwent diagnostic EUS using a convex linear array echoendoscope followed by drainage of the collection in same sitting. Five patients with small cysts (volume <50 mL) required only aspiration of cyst using a 19 or 22G FNA needle. EUS guided needleknife puncture followed by guidewire placement into the cyst cavity was performed in 13 patients. In one patient with a thick cyst wall, puncture was done by a 19G FNA needle followed by guidewire placement through the needle. Dilatation of the tract up to 18 mm was then performed using an esophageal dilator balloon over the guidewire. In patients with clear cyst contents, a 7 Fr. Double pigtail stent was placed across the fistula into the cavity. In patients with complicated cysts, a gastroscope was passed transgastrically into the cyst cavity (Cystendoscopy). Using a polypectomy snare, septae were broken, loose necrotic debris was removed from the cavity by cold snaring technique (Endoscopic necrosectomy). A 7 Fr. Stent and a 7 Fr. Nasocystic catheter were placed in the cavity and sterile saline irrigation was performed. Procedure was repeated every 3 days until the wall looked healthy, USG/CT scan showed no residual necrosis/collection or cyst cavity had collapsed. Additional ERP was performed in 7 patients where ductal disruption was suspected (rapid refilling of the cyst, recurrent cysts). Ductal disruption was seen in 2, unsuspected early CP in 4, classical CP in one patient. Appropriate endotherapy was performed. Follow up USG was performed at 2 weeks and later as required. Stents were removed at 8 weeks. USG was repeated at 12 weeks after stent removal.

RESULTS: EUS-guided drainage was achieved in all 19 patients. Complete regression was seen in 8 patients (simple cysts) at 2 weeks, and in 17 at 8 weeks. Therapy failed in one patient who required surgical necrosectomy. Complications occurred in two patients (bleeding – 1, death – 1). Bleeding from the fistula site in one patient after balloon dilatation was arrested using hemoclips. One patient died of pulmonary embolism 2 weeks after drainage. No recurrences on USG at 12 weeks.

CONCLUSIONS: EUS guided therapy is a satisfactory method to treat pancreatic pseudocysts. Necrotic debris or multiple loculations are not contraindications for endoscopic therapy. An aggressive approach using balloon dilatation and cystendoscopy is necessary to achieve results comparable to surgery.

PD70
PANCREATIC CANCER DIAGNOSIS AND SURGERY IN THE ERA OF ENDOSCOPIC ULTRASOUND: A LONGITUDINAL CONTINUOUS COMPREHENSIVE SINGLE-CENTER EVALUATION

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AIM: to critically evaluate experience at one hospital in the diagnosis and treatment of patients with pancreatic cancer (PCA). In a similar study four years ago, evaluating years 1997-2001, the impact and positive value of EUS was demonstrated. Those patients staged by EUS were found to be significantly more accurately chosen for curative vs. palliative surgical procedures, and for surgical vs. non-surgical oncological therapy. The current study compares 2001-4 management of PCA to that in the four previous years.

METHODS: Chart review was undertaken regarding every patient presenting with PCA during the years 2001-2004. 72 patients on the Oncology Gastroenterology and Pathology department combined computerized files, had pancreatic cancers.

RESULTS: Of 72 cases, eight different types of tumors were identified, including adenocarcinoma, 2 neuroendocrine tumors, 2 metastatic tumors to the pancreas, and one each of pancreatic lymphoma, gastrointestinal stromal tumor, pseudopapillary tumor, adenosquamous tumor, and undifferentiated cancer. From 2001-4, 24% of PCA patients underwent surgery; less than during 1997-2001, when 28 of 62 (45%) underwent surgery, P<0.01. From 2001-4, 47% patients were staged before surgery by EUS, more than during 1997-2001, during which only 20 of 62 (32%) underwent EUS evaluations, P=0.056. In 94% of all cases, the EUS successfully identified the tumor. In 78% of cases, cytologic EUS-guided FNA sampling was diagnostic for PCA. There were no EUS complications in this series. PET-FDG scans, and MRI , two new and relatively expensive modalities for diagnosis and staging, were not applied for any of these patients. ERCP was performed for 29% of PCA patients, and stenting was used in 5 cases. 7% per cent of patients had CT scans read as normal at the time of EUS diagnosis of PCA, as had 50% of patients with transabdominal ultrasounds. The average time from the time of first relevant symptoms until the diagnosis of pancreatic cancer, was seven months. 29% of patients were smokers. Ca19-9 was measured in 66%, and found elevated in 50%, CEA was measured in 62%,and found elevated in 24% of all cases. EUS was of most impact in two situations: 1- when patients with negative transabdominal ultrasound and/or CT scans but suspicious clinical presentations were found on EUS to have tumors; these tumors were found to be most likely to be resectable for cure, and 2- when EUS staging of PCA identified advanced unresectable stages, sparing the patients futile operations.

DISCUSSION: PCA is optimally collaboratively treated by a broad multidisciplinary medical staff. Increased utilization of EUS and EUS-guided FNA cytology was found to be associated with decreased numbers of futile operative procedures. Based on the current local accuracy of EUS, when judiciously utilized, there is little if any need for adding MRI and/or PET FDG to the staging regimen for these patients.

CONCLUSIONS: Increased use of EUS succeeded in decreasing the frequency of futile surgery on patients with pancreatic cancer. Continued utilization of EUS for pancreatic tumors seems likely, based on these data, to spare unnecessary and futile and high-risk procedures, and to direct patients with pancreatic tumors toward optimal therapy.

PD71
USEFULNESS OF CONTRAST ENHANCEMENT FOR DIAGNOSIS OF PANCREATIC DISEASES BY TRANSABDOMINAL US AND EUS

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BACKGROUND: Intraveneous infusion of a microbubble contrast agent enables the visualization of slow flow in fine vessels1. Our purpose is to assess usefulness of contrast-enhanced harmonic US (CE-US) and contrast-enhanced power Doppler EUS (CE-EUS) for depiction and differential diagnosis of pancreatic tumors particularly of 2cm or less in size, as compared with fundamental B mode US (B-US) and contrast-enhanced CT (CE-CT).

SUBJECTS AND METHODS: Between 2001 Mar and 2005 Jan, consecutive 93 patients with suspicious pancreatic tumors received CE-CT, EUS, B-US and CE-US in our hospital. Coded phase-inversion harmonic mode (GE Logiq 9) which depicts signals from bubbles in fine vessels was used for CE-US. Power Doppler mode was used for CE-EUS (OLYMPUS GF-UC-240P AL5, ALOKA ProSound SSD 5500). Levovist was employed as the ultrasound contrast agent for CE-US and CE-EUS. CE-CT (Toshiba Aquillion) was imaged 30 and 180 seconds after the injection of contrast media. With respect to tumors of 2 cm or less in size, sensitivities in depicting tumors, sensitivies and specificities in differetiating ductal carcinomas from the other tumors were compared between the 4 modalities.

RESULTS: Values for sensitivity in depicting all tumors of the pancreas by CE-CT, EUS, B-US and CE-US were 90%, 98%, 90% and 96%, respectively. There existed 22 cases with tumors of 2 cm or less in size. Values for sensitivity in depicting those small pancreatic tumors by CE-CT, EUS, B-US and CE-US were 66%, 95%, 73% and 91%, respectively. The sensitivities on CE-US and EUS were significantly higher than that on CE-CT. When hypovascular nodules relative to their surrounding tissue were defined as ductal carcinomas, values for sensitivity in diagnosing ductal carcinomas were 54% on CE-CT, 85% on CE-US and 85% on CE-EUS. Three of 6 tumors that the fundamental B-mode US failed to depict were clearly depicted by the subsequent contrast-enhanced US. Although a subabnormality such as stenosis of the main pancreatic of the pancreas had been demonstrated on the B-US, the tumor was unclear in those three patients. The subsequent CE-US clearly demonstrated the outline of the tumor. EUS depicted 6 ductal carcinomas that CE-CT failed to depict, 5 of which were hypovascular on CE-EUS.

CONCLUSION: CE-US and EUS may be useful for differential diagnosis of small nodules of the pancreas which the other modalities failed to depict. In order to find pancreatic cancers on an early stage, CE-US and EUS should be performed when US or CE-CT detect the indirect findings

such as dilatation of pancreatic duct. Since EUS is superior to any other modalities with respect to the depiction of small pancreatic nodules, the invention of the technology of contrast-enhanced harmonic EUS would further improve the detection rate of small tumors.

PD72
INTERVENTIONAL ENDOSCOPIC ULTRASOUND CHOLANGIOGRAPHY (IEUC): MID-TERM FOLLOW-UP OF 18 CASES

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BACKGROUND: Endoscopic retrograde cholangiopancreatography with drainage is the procedure of choice for palliation of biliary obstruction. However, in 3-10% of cases, biliary access cannot be achieved. The development of interventional endoscopic ultrasonography has allowed access and subsequent decompression of dilated biliary systems in cases where standard drainage is unsuccessful. We report the mid-term results of 18 cases where EUS cholangiography was successfully performed after failed ERCP.

METHODS: Using EUS-guided fine needle technology, access to the left intrahepatic bile duct by EUS-guided transhepatic cholangiography (ETC) or to the extrahepatic bile duct by either a transduodenal or transgastric approach was achieved. Subsequent injection of contrast for cholangiography was performed. A guide wire was then advanced through the EUS needle and out the ampulla in an antegrade fashion. Once access was achieved with a guide wire, ERCP was then performed successfully.

RESULTS: EUS-guided cholangiography was successful in all 18 patients (10 male, 8 female) with mean age 61±12 yo (range: 36-81). Biliary decompression with stent placement was achieved in 15/17 patients. In 2 cases, the guide wire was unable to be advanced in a transampullary fashion and in one case the cholangiogram was normal and decompression was not needed. Complications occurred in 2 patients, one had bile peritonitis treated nonsurgically after transgastric approach, and the other had pneumoperitoneum, treated conservatively after transbulbar approach. On the other hand, no complications occurred in patients undergoing ETC. None of the patients died as a result of the procedure. After a mean follow-up of 9.4 months, 4 patients died secondary to their malignancy and one died secondary to complications after a Whipple resection.

CONCLUSION: Mid-term evaluation of IEUC confirms its efficacy in patients in whom ERCP is unsuccessful and is evolving as an attractive alternative to percutaneous drainage. EUS-guided transhepatic access to the biliary system appears safer than the extrahepatic approach.

Rendezvous access	Etiology of jaundice	Complications	Successful decompression
Transhepatic (ETC)	5 cancers, 2 surgical strictures, 2 cholangitis	None	8/9
Transgastric or transduodenal	6 cancers, 2 cholangitis, 1 benign stricture, 1 bile leak, 1 pneumoperitoneum		7/8

PD73
PROSPECTIVE STUDY ON THE ACCURACY OF IMMEDIATE CYTOLOGIC ANALYSIS OF PUNCTURE BY EUS OPERATORS

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The best accuracy of EUS-FNA is obtained with an attendant cytopathologist. However it is impossible in many centers and the EUS operators increase the number of pass.

AIM: We conducted a prospective monocentric study to evaluate the accuracy of EUS operator to determine the cellularity of the sample immediately after the FNA of a solid mass and the potential impact on final procedure.

PATIENTS AND METHODS: 100 consecutive patients with indications of FNA for solid masses of pancreas, lymph node, or mediastinum were included. Two passes had to be done for each target unless a technical problem occurred. One glass slide per pass was colorated with toluidine blue by the EUS operator. The cellularity was estimated before coloration and then confirmed with the microscope. The difficulty of judgment was noted. Immediately after the first pass the EUS operator had to precise if he would consider the specimen adequate enough to stop in a non experimental context. If cellularity was absent after two passes, complementary passes had to be performed until presence of cellularity or unusable needle. Cell block were done with the remaining material when possible. The whole samples were then evaluated by a cytopathologist. The appreciation of cellularity by the EUS operators was compared with the cytopathologist. EUS accuracy was compared to the final diagnosis obtained by surgery or follow-up for pancreatic and mediastinal masses.

RESULTS: Between 10/2003 and 06/2004, 100 patients (60 males, mean age 65,3) were included. 112 targets (mean diameter 27 mm (6-60)) were punctured (73 pancreas, 34 lymph nodes, 5 mediastinal masses). 220 passes were done leading to 597 slides and 147 cellblocks. The evaluation of cellularity by EUS before and after the coloration was 70,1% and 80% respectively. It was correlated in 80% of cases with the cellularity estimated by the cytopathologist. In case of errors we had noted a difficulty of interpretation in 65,1% of the cases. Final accuracy of EUS-FNA procedures for malignancy of pancreatic and mediatinal masses was 86%. A single pass would have been done in an "out protocol" setting in 42 patients. In this group, accuracy of the first pass was 86% for a final accuracy of 89%.

CONCLUSION: The evaluation of the cellularity of the slides by the EUS operators has a good concordance with the cytopathologist assessment. When the cellularity is considered sufficient after the first pass, further passes might not be needed.

PD74
REPROCESSING OF ENDOSCOPES: RESULTS OF AN OMED-OMGE SURVEY

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INTRODUCTION: Reprocessing of endoscopes represents one of the major concerns in daily endoscopy practice. Although several practice guidelines were established by different professional societies, a standard of reprocessing seems not yet achieved. OMED has initialized an international survey aiming to study the current reprocessing standards in different countries.

MATERIALS AND METHODS: A questionnaire was sent to physicians practicing GIT endoscopy in three countries. Endoscopists working in university referral centers, public hospitals and private clinics participated in the survey. Endoscopists in the three countries (n=78) answered the questionnaire in an individual anonymous manner. Results were analyzed by an independent third party.

RESULTS: 46% of participating endoscopists worked in university hospitals, 43% in private clinics and 11% in a regional or local hospital. Reprocessing process was usually performed in the endoscopy room in 59% of centers, in a special designated room in 28%, and in a central "sterilization" supply department in 13%. 79% used manual cleaning and reprocessing while 21% used automatic reprocessing devices after manual cleaning. 66% had dedicated personnel for the reprocessing procedure. 34% had the reprocessing process done by a nurse or by the endoscopist himself. 76% used an established disinfection protocol or practice guidelines. 91% usually did suction of water/detergent immediately after endoscopy. 88% manually cleaned the endoscopes after that. 73% reprocessed valves separately. 82% immersed the scope in disinfectant (average time 5 min). 56% used glutaraldehyde as a disinfectant. 6% used peracetic acid, 10% used hydrogen peroxide, 4% used other products. 85% rinsed the endoscopes after disinfectant immersion. 29% used alcohol rinsing. 71% forced air after the disinfection procedure to facilitate drying. 82% stored the endoscopes hanging upright. 46% had a dedicated storage

room, 43% stored their endoscopes in the procedure room, 11% stored them in the cleaning room. 65% said that they always had their endoscope highly disinfected before ERCP procedures. 21% didn't answer this question. Only 43% had a hospital committee overseeing the reprocessing of endoscopes. 47% had established monitoring guidelines. 21% did routine cultures of endoscopes to monitor adequacy of reprocessing. 19% said that they would review their reprocessing procedure if they had a positive culture, 19% would first identify the source of contamination, 4% would change their system or their practice, 11% would just inform the staff and 1% would take no action. 14% of endoscopists had previously encountered endoscopic transmitted infection.

CONCLUSION: Endoscopic reprocessing process remains center-dependant even in the same country. The majority of centers still rely on manual cleaning. A wide variation in the procedural steps was found among different centers though 3/4th of endoscopists affirmed following practice guide lines. Is standardization of the process, especially for manual disinfection, difficult or impractical? Would the reasons be rather financial? Would strict monitoring of the process help to achieve a standard practice? Is it the role of the endoscopist or the hospital administration or professional societies? Finally, can standard guide lines be established in a way that they could adapt to the variable national economies without undermining the basic standards? Many questions remain to be answered.

PD75
CDX2-DEPENDENT REGULATION OF LIPOPOLYSACCHARIDE-BINDING PROTEIN IN INTESTINAL EPITHELIAL CELLS

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INTRODUCTION: Lipopolysaccharide-binding protein (LBP) is an acute phase protein modulating the host's response to endotoxin. In intestinal epithelial cells, LBP is induced in response to cytokines and differentiation status. We thus investigated the role of CDX2, a transcription factor involved in intestinal epithelial cell differentiation, in the regulation of LBP expression in response to IL-1.

METHODS: Gene expression from IEC-6 rat intestinal epithelial cells expressing CDX2 was assessed by microarray analysis. LBP expression was analysed by Northern and Western blot. CDX2 transactivation potential was determined by transient transfection and luciferase assays in Caco-2/15 and IEC-6/CDX2 cells with luciferase constructs containing 1500 bp of the murine LBP promoter. CDX2-responsive elements were determined by mutagenesis and by electrophoretic mobility shift assays.

RESULTS: 1) Microarray data showed a 5.5-fold induction of LBP in IEC-6/CDX2 expressing cells. 2) LBP mRNA and protein levels were increased both by CDX2 and IL-1 in IEC-6 cells, and during differentiation of Caco-2/15 cells, as determined by Northern and Western blot. 3) CDX2 induced more than 5-fold LBP promoter-luciferase activity, as assessed by transient transfection assays. 4) A CDX-2-responsive element was identified between nt-1191 and -1185 of the LBP promoter by mutagenesis studies and electrophoretic mobility shift assays. 5) LBP was expressed in villus cells, as determined by Western blot analysis of protein extracts from crypt-to-villus human epithelial cell fractions.

CONCLUSION: CDX2 regulates LBP expression in intestinal epithelial cells. CDX2-dependent regulation of LBP may be involved in the differential response of intestinal epithelial cells along the crypt-to-villus axis, to endotoxins.

PD76
ROLE OF TRANSCRIPTION FACTORS IN THE CONVERSION OF FIBROBLASTIC TO INTESTINAL EPITHELIAL CELL LINEAGES

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INTRODUCTION: The molecular mechanisms involved in intestinal epithelial cell determination are poorly understood. Identification of the molecular pathways responsible for the maintenance of the intestinal epithelial phenotype is required to better characterize cellular fate during the initiation of pathologies such as colorectal cancer. We have previously described the role of Cdx2 and GATA-4 transcription factors in the regulation of specific intestinal epithelial genes. Recently, HNF-4alpha transcription factor has been demonstrated to play a major role in the hepatic epithelium maintenance.

OBJECTIVE: To determine the combinatory action of Cdx2, GATA-4 and HNF-4alpha transcription factors during intestinal epithelial cell determination.

METHODS AND RESULTS: We used the fibroblastic cell line NIH-3T3 to generate stable clones that express Cdx2, GATA-4 and HNF-4apha alone or in combination. A metallothionein zinc inducible promoter was utilized for both Cdx2 and GATA-4 constructs whereas a retroviral construct was designed for HNF-4alpha expression. Clones that showed the best controlled level of Cdx2 and GATA-4 protein induction were further utilized for the study. NIH-3T3 Cdx2/GATA-4/HNF-4alpha cells were plated on plastic or matrigel and supplemented or not with zinc during 30 days. Control cells derived from integration of empty vectors were also utilized in parallel. Total protein and RNA samples were prepared for each condition. Western blot analysis identified intestinal epithelial targets such as Hic-5 and pparγ up-regulated in the NIH-3T3 Cdx2/GATA-4/HNF4alpha cell line. RT-PCR confirmed the induction of intestinal fatty acid binding protein, intestinal trefoil factor 3, apoliprotein C3 and AIV gene expression in these cells. Electronic microscopy revealed the emergence of microvilli on the NIH-3T3 Cdx2/GATA-4/HNF-4alpha cells as compared to the control cells.

CONCLUSION: Our results suggest that the ectopic combination of HNF-4alpha, Cdx2 and GATA-4 can initiate a program of intestinal epithelial cell determination within a mesenchymal context. Further studies will be necessary to document the molecular targets of these transcription factors during the acquisition of the intestinal epithelial phenotype.

PD77
DUAL MODULATION BY HYDROGEN SULFIDE, A NOVEL ENDOGENOUS GASOMESSENGER, OF THE TENSION IN RAT GASTRIC ARTERY

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Hydrogen sulfide (H_2S) is now considered a gasomessenger/gasotransmitter in the circulatory system and central nervous system. H_2S can be synthesized from L-cysteine by cystathionine-γ-lyase (CSE) in the peripheral tissues and by cystathionine-β-synthase (CBS) in the brain. Previous evidence indicates that H_2S relaxes rat aorta through activation of ATP-sensitive potassium (K^+_{ATP}) channels. In the present study, we investigated the contractile/relaxant activity of sodium hydrosulfide (NaHS), a H_2S donor, in isolated rat gastric arterial rings, as compared with rat aortic tissues. The ring preparations of the gastric artery and aorta were prepared from male Wistar rats (7-10 weeks old). The segments were allowed to equilibrate for about 30 min (gastric artery) or 1 h (aorta) under a resting tension of 5 mN (gastric artery) or 10 mN (aorta) in Krebs-Henseleit solution maintained at 37°C and bubbled with 95% O_2/5% CO_2, and isometric tension was recorded through a force-displacement transducer. NaHS, when applied cumulatively, caused contraction at low concentrations and relaxation at high concentrations in both endothelium-intact aorta and gastric artery precontracted with phenylephrine, although it was inactive in the resting preparations. The contractile and relaxant effects of NaHS at low and high concentrations were enhanced and partially blocked, respectively, by the K^+_{ATP} channel blocker glibenclamide in the aorta. In the gastric artery, glibenclamide unaffected the contractile effect of NaHS at low concentrations, but blocked the relaxant effect of NaHS at a high concentration, which was even reversed to a contractile effect. In gastric and aortic tissues precontracted with high concentrations of KCl, NaHS at low and high concentrations produced glibenclamide-resistant contraction and relaxation, respectively. Removal of the endothelium largely inhibited the contraction, but not relaxation, in response to NaHS in both the precontracted gastric and aortic rings. Taken together, our data demonstrate that NaHS causes endothelium-independent relaxation through both K^+_{ATP} channel-dependent and -independent mechanisms, and also produces endothelium-dependent contraction in the precontracted rat gastric artery as well as aorta. The present evidence might predict a possible role of H_2S in regulation of gastric microcirculation.

PD78
THE EXPRESSION OF ERYTHROPOIETIN RECEPTOR AND THE PROLIFERATION IN THE CULTURED GASTRIC EPITHELIAL CELLS

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INTRODUCTION: Most of hemodialysis patients have gastric mucosal lesions (GML), which markedly improve after the administration of erythropoietin (Epo). Oxygen supply to gastric mucosa is the key factor in the genesis of these lesions. Using cultured microvascular endothelial cells of gastric mucosa, we demonstrated that Epo directly potentiates the vascularization in the mucosa. However, Epo may effect on the other cells constructing gastric mucosa. The aim of the present study was to determine the expression of Epo Receptor (EpoR) in the cultured gastric epithelial cells and the possibility that Epo directly stimulate the growth of these cells.

MATERIALS AND METHODS: Epithelial cells were isolated from porcine gastric mucosa and maintained in culture. RT-PCR and Western blots were performed in an attempt to identify a specific erythropoietin receptor (EpoR) in them. They were exposed to rHuEpo under various experimental conditions: 1) Medium, 2) Medium with 1 μg/mL Epo, 3) Medium with 1 μg/mL Epo + 1 mg/mL anti-Epo antibody, 4) Medium with 1 μg/mL Epo + 1 mg/mL Rabbit IgG, and cell proliferation index was measured by BrdU assay method.

RESULTS AND DISCUSSION: The expression EpoR gene was detected clearly in the cultured gastric mucosal epithelial cells by RT-PCR. In addition, the band corresponding to EpoR was confirmed in these cells by Western blotting. Epo accelerated the proliferation of gastric epithelial cells in a dose dependent manner. In the Epo group, significant exacerbation of cell proliferation as compared to the medium group was observed. This proliferation was inhibited selectively by addition of the anti-Epo antibody. In the Epo + anti-Epo antibody group, the values were significant lower than those in the Epo + Rabbit IgG group, the antibody negative control group.

CONCLUSION: These results suggest that Epo plays an important role in the repair of gastric mucosa through the direct effect on the epithelial cells as well as the endothelial cells, and leads to the improvement of gastric lesions found in the hemodialysis patients.

PD79
THE RELATIONSHIP BETWEEN UTILIZATION OF GASTROPROTECTIVE STRATEGIES BY PHYSICIANS AND THEIR ABILITY TO ACCURATELY ESTIMATE THE RISK OF NSAID ASSOCIATED UPPER GI COMPLICATIONS

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INTRODUCTION: The risk of gastrointestinal (GI) complications secondary to chronic NSAID use can be mitigated through the use of gastroprotective (GP) strategies, which include concomitant prescription of a proton pump inhibitor or misoprostol, or substitution of a COX-2 inhibitor for a traditional NSAID. Because of the high cost of GP strategies and their associated side effects, the use of GP strategies is only recommended for chronic NSAID users with risk factors for NSAID related GI complications. Previous studies have demonstrated that GP strategies are often over utilized in low-risk patients, and occasionally underprescribed for patients at high risk for NSAID related GI complications. The factors which promote inappropriate recommendation of GP strategies are not well characterized. Therefore, we sought to determine if the physician's decision to use or not use a GP strategy for an NSAID user is related to the accuracy of the physician's ability to assess a subject's risk of developing NSAID-related GI complications.

METHODS: We distributed a questionnaire to all family physicians and general internists licensed to practice in Manitoba. The questionnaire was composed of two clinical vignettes of NSAID users, one representing a patient at 1-2% annual risk of GI complications ("low-risk"), and the other describing a subject at 5-10% annual risk of GI complications ("high risk"). For each case, respondents were asked whether they would use a GP strategy and which GP strategy they would use. Respondents were also asked to estimate each hypothetical subject's annual risk of an NSAID related GI complication, Respondents were separated into three tertiles ("low-estimators", "average estimators", or "high-estimators") based upon their estimation of each hypothetical subject's annual risk of developing an NSAID related GI complication.

RESULTS: We distributed 1400 questionnaires, and received completed questionnaires from 201 respondents on the initial mail-out (second mail-out pending). The range of estimates for the risk of developing an NSAID related GI complication ranged from 0.08-80% for the "low risk" case (IQR: 2-10%, median 5%), and 0.5-100% for the "high-risk" case (IQR 5-20%, median 10%). 26% of physicians estimated the risk of GI complications was over 10%/yr for the low risk case, and 29% of physicians believed that the high risk subjects had a risk of bleeding over 20%/yr. High-estimators were significantly more likely to recommend a GP strategy for the "low risk" case than low-estimators (47% vs 16%, P=0.0004). High-estimators were also significantly more likely to opt for multiple GP strategies or avoid NSAID use altogether in the "high risk" case than low-estimators (67% vs 42%, P=0.019).

CONCLUSIONS: A substantial proportion of physicians significantly overestimate the risk of GI complications for both low- and high-risk patients. High risk estimation by physicians is associated with an increased likelihood of inappropriate GP strategy utilization for low-risk subjects, and of using multiple GP strategies in combination for high risk subjects. Improving the ability of physicians to accurately assess the risk of NSAID-related GI complications may promote the more appropriate utilization of GP strategies.

WCOG 2005 Reviewers

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